CARCINOID/NEUROENDOCRINE TUMORS

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/19208248

The term "carcinoid" is a misnomer: the evidence based on local invasion.

Citation
Journal of Experimental & Clinical Cancer Research, 2009, 28:15.

Authors
Soga, J.

Abstract
BACKGROUND: Since Oberndorfer proposed the term "carcinoid" in 1907, over 100 years have passed. This attractive term was initially proposed for 6 cases of his own experience with 12 submucosal lesions in the small intestine. Oberndorfer summarized the characteristic features of these lesions as follows: (1) small in size and often multiple, (2) histologically undifferentiated with a suggestion of gland-formation, (3) well-defined without any tendency to infiltrate the surroundings, (4) no metastases, and (5) apparently slow-growing reaching no significant size with a seemingly harmless nature. REVIEW: This article stresses the malignant nature of "carcinoid" on the basis of local invasion prior to metastases in the first two sessions, (1) with Oberndorfer's original diagram, and (2) with an experimental observation on extraglandular microcarcinoid in a form of "budding". Next, (3) a statistical comparison between a carcinoid group and a non-carcinoid ordinary carcinoma group is introduced on metastasis rates at an early stage with two prescribed factors of the depth of invasion restricted within the submucosa (sm-lesion) and a small tumor size category of 1 cm to 2 cm: the carcinoid group exhibited metastasis rates higher than those in the ordinary carcinoma group when calculated in the stomach and rectum. In the author's experience, "carcinoids" are malignant not only in the gastrointestinal tract but also in the other sites on the basis of local invasion. Lastly, (4) discussion on the terminology of "carcinoid" as a misnomer is carried out. Adequate terms referring to the entity of this malignant tumor group are discussed. One of the most adequate and brief terms for "carcinoid" that is included now in neuroendocrine tumor group would be "endocrinocarcinoma" as per the author's proposal, followed by NEC (neuroendocrinocarcinoma) or GEC (gut endocrinocarcinoma). CONCLUSION: The term "carcinoid" is a misnomer that can be confirmed on the basis of local invasion prior to metastases. "No metastases without local invasion" is not of a negligible importance.

http://www.ncbi.nlm.nih.gov/pubmed/19091780
Carcinoid tumors.
Citation
Oncologist, 2008, 13(12): 1255-1269.

Authors
Pinchot, S.N., Holen, K., Sippel, R.S., & Chen, H.
Abstract
Carcinoid tumors are rare, slow-growing neuroendocrine tumors arising from the enterochromaffin cells disseminated throughout the gastrointestinal and bronchopulmonary systems. Though they have been traditionally classified based on embryologic site of origin,

morphologic pattern, and silver affinity, newer classification systems have been developed to emphasize the considerable clinical and histopathologic variability of carcinoid tumors found within each embryologic site of origin. These neoplasms pose a diagnostic challenge because they are often innocuous at the time of presentation, emphasizing the need for a multidisciplinary diagnostic approach using biochemical analysis, standard cross-sectional imaging, and newer advances in nuclear medicine. Similarly, treatment of both primary and disseminated carcinoid disease reflects the need for a multidisciplinary approach, with surgery remaining the only curative modality. The prognosis for patients with these tumors is generally favorable; however, it can be quite variable and is related to the location of the primary tumor, extent of metastatic disease at initial presentation, and time of diagnosis.

http://www.unicornfoundation.org.au/documents/Gastroenteropancreatic%20NET%20%28GEP-NET%29.1.pdf

Gastroenteropancreatic neuroendocrine tumours.

Citation
Lancet Oncology, 2008, 9: 61-72.

Authors
Modlin, I.M., Oberg, K., Chung, D.C., Jensen, R.T., de Herder, W.W., Thaker, R.V., Caplin, M., Delle Fave, G., Kaltsas, G.A., Krenning, E.P., Moss, S.F., Nilsson, O., Rindi, G., Salazar, R., Ruszniewski, P, & Sundin, A.

Abstract
Gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) are fairly rare neoplasms that present many clinical challenges. They secrete peptides and neuroamines that cause distinct clinical syndromes, including carcinoid syndrome. However, many are clinically silent until late presentation with mass effects. Investigation and management should be highly individualised for a patient, taking into consideration the likely natural history of the tumour and general health of the patient. Management strategies include surgery for cure (which is achieved rarely) or for cytoreduction, radiological intervention (by chemoembolisation and radiofrequency ablation), chemotherapy, and somatostatin analogues to control symptoms that result from release of peptides and neuroamines. New biological agents and somatostatin-tagged radionuclides are under investigation. The complexity, heterogeneity, and rarity of GEP NETs have contributed to a paucity of relevant randomised trials and little or no survival increase over the past 30 years. To improve outcome from GEP NETs, a better understanding of their biology is needed, with emphasis on molecular genetics and disease modeling. More-reliable serum markers, better tumour localisation and identification of small lesions, and histological grading systems and classifications with prognostic application are needed. Comparison between treatments is currently very difficult. Progress is unlikely to occur without development of centers of excellence, with dedicated combined clinical teams to coordinate multicentre studies, maintain clinical and tissue databases, and refine molecularly targeted therapeutics.

EPIDEMIOLGY

http://www.ncbi.nlm.nih.gov/pubmed/20237925

Epidemiology of Small Bowel Carcinoids in a Defined Population.

Citation
World Journal of Surgery, 2010, Mar 17. [Epub ahead of print]

Authors
Landerholm, K., Falkmer, S., & Järhult, J.

Abstract

BACKGROUND: This retrospective study describes the epidemiology of small bowel carcinoids in a geographically defined population, with no other selection bias. METHODS: All patients (n = 145) resident in Jönköping County when diagnosed with carcinoid in the jejunum or ileum from 1960 to 2005 were included. Medical records were reviewed in detail, and tumor specimens were histopathologically and immunohistochemically reexamined when required (n = 44). RESULTS: The annual age-adjusted incidence of small bowel carcinoids was 1.12 (95% confidence interval 0.95-1.31) per 100,000 persons. Median age at diagnosis was 69 years. The predominating presenting symptom was uncharacteristic abdominal pain (50%), whereas a smaller number suffered from typical flushes (13%). Surprisingly, 14% presented with overt gastrointestinal hemorrhage. Most of the patients diagnosed based on their symptoms had metastases at diagnosis (44% regional, 40% distant). Metastasized tumors by definition belong to World Health Organization (WHO) histopathologic group 2; and when reexamined, most (83%) of the localized tumors were also found to belong to WHO group 2. CONCLUSIONS: In comparison to previous reports, a higher age-adjusted incidence of small bowel carcinoids was observed, and the patients were clearly older at the time of diagnosis. Even with metastatic disease, the presenting symptoms were usually uncharacteristic, and the carcinoid syndrome was infrequently seen.

http://www.ncbi.nlm.nih.gov/pubmed/20139156

Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE).

Citation
Annals of Oncology, 2010 Feb 5. [Epub ahead of print]

Authors

Garcia-Carbonero, R., Capdevila, J., Crespo-Herro, G., Diaz-Pérez, J.A., Martinez Del Prado, M.P., Alonso Orduña, V., Sevilla-Gracia, I., Villabona-Artero, C., Beguristain-Gómex, A., Llanos-Muñoz, M., Marazuela, M., Alvarez-Escola, C., Castellano, D., Vilar, E., Jiménez-Fonseca, P., Teulé, A., Sastre-Valera, J., Benavent-Viñelas, M., Mondelon, A., & Salazar, R.

Abstract

BACKGROUND: Neuroendocrine tumors (NETs) are an unusual family of neoplasms with a wide and complex spectrum of clinical behavior. Here, we present the first report of a National Cancer Registry of gastroenteropancreatic neuroendocrine tumors from a Southern European country. PATIENTS AND METHODS: Data was provided online at www.retegep.net by participating centers and assessed for internal consistency by external independent reviewers. RESULTS: The study cohort comprised 907 tumors. The most common tumor types were carcinoids (55%), pancreatic nonfunctional tumors (20%), metastatic NETs of unknown primary (9%), insulinomas (8%) and gastrinomas (4%). Forty-four percent presented with distant disease at diagnosis, most often those from small intestine (65%), colon (48%), rectum (40%) and pancreas (38%), being most unusual in appendix primaries (1.3%). Stage at diagnosis varied significantly according to sex, localization of primary tumor, tumor type and grade. Overall 5-year survival was 75.4% (95% confidence

interval 71.3% to 79.5%) and was significantly greater in women, younger patients and patients with hormonal syndrome and early stage or lower grade tumors. Prognosis also differed according to tumor type and primary tumor site. However, stage and Ki-67 index were the only independent predictors for survival. CONCLUSION: This national database reveals relevant information regarding epidemiology, current clinical practices and prognosis of NETs in Spain, providing valuable insights that may contribute to understand regional disparities in the incidence, patterns of care and survival of this heterogeneous disease across different continents and countries.

http://www.ncbi.nlm.nih.gov/pubmed/19582519

An analysis of trends and growth factor receptor expression of GI carcinoid tumors.

Citation
Journal of Gastrointestinal Surgery, 2009, 13(10): 1773-1780.

Authors
Bowen, K.A., Silva, S.R., Johnson, J.N., Doan, H.Q., Jackson, L. N., Gulhati, P., Qui, S., Riall, T.S., & Evers, B.M.

Abstract
INTRODUCTION: The purpose of our study was twofold: (1) to determine the incidence, patient and tumor characteristics, and outcome of patients with gastrointestinal carcinoid tumors using the Surveillance, Epidemiology and End Results (SEER) database, and (2) to delineate the expression pattern of growth factor receptors (GFRs) in carcinoid tumors. MATERIALS AND METHODS: The SEER database search provided information on patients diagnosed with carcinoid tumors from 1990 to 2002. Carcinoid tumor sections (n = 46) were stained for the GFRs: epidermal growth factor receptor, insulin-like growth factor receptor (IGFR), vascular endothelial growth factor receptor (VEGFR), and HER-2/neu. RESULTS: Over the 12-year analysis period, 18,180 patients were identified with carcinoid tumors of the foregut, midgut, and hindgut; the incidence of carcinoid tumors increased approximately 2-fold during this time period. Of the patients with carcinoid tumors, there was a trend of increased expression of VEGFR and IGFR, particularly in the foregut and midgut carcinoids. Analysis of the SEER database confirms that the incidence of carcinoid tumors is increasing with an approximate doubling in the number of carcinoid cases from 1990 to 2002. Furthermore, an increase in VEGFR and IGFR expression suggests that GFR inhibitors may be effective adjuvant therapy for carcinoid cancer.

http://www.ncbi.nlm.nih.gov/pubmed/18565894

One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States.

Citation
Journal of Clinical Oncology, 2008, 26(18): 3063-3072.

Authors
Yao, J.C., Hassan, M., Phan, A., Dagohoy, C., Leary, C., Mares, J.E., Abdalla, E.K., Fleming, J.B., Vauthery, J-N., Rashid, A., & Evans, D.B.

Abstract
PURPOSE Neuroendocrine tumors (NETs) are considered rare tumors and can produce a

variety of hormones. In this study, we examined the epidemiology of and prognostic factors for NETs, because a thorough examination of neither had previously been performed. METHODS The Surveillance, Epidemiology, and End Results (SEER) Program registries were searched to identify NET cases from 1973 to 2004. Associated population data were used for incidence and prevalence analyses. Results We identified 35,618 patients with NETs. We observed a significant increase in the reported annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000). Using the SEER 9 registry data, we estimated the 29-year limited-duration prevalence of NETs on January 1, 2004, to be 9,263. Also, the estimated 29-year limited-duration prevalence in the United States on that date was 103,312 cases (35/100,000). The most common primary tumor site varied by race, with the lung being the most common in white patients, and the rectum being the most common in Asian/Pacific Islander, American Indian/Alaskan Native, and African American patients. Additionally, survival duration varied by histologic grade. In multivariate analysis of patients with well-differentiated to moderately differentiated NETs, disease stage, primary tumor site, histologic grade, sex, race, age, and year of diagnosis were predictors of outcome (P < .001). CONCLUSION We observed increased reported incidence of NETs and increased survival durations over time, suggesting that NETs are more prevalent than previously reported. Clinicians need to be become familiar with the natural history and patterns of disease progression, which are characteristic of these tumors.

http://www.ncbi.nlm.nih.gov.ezproxy1.library.arizona.edu/pubmed/18853416

Neuroendocrine tumor epidemiology: contrasting Norway and North America.

Citation
Cancer, 2008, 113(10): 2655-2664.

Authors
Hauso, O., Gustafsson, B. I., Kidd, M.,Waldum, H.L. Drozdov, I. Chan, A.K., & Modlin, I.M.

Abstract

BACKGROUND: The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program has proven to be a significant resource in US neuroendocrine tumor (NET) epidemiology. Norway also holds a robust and detailed cancer registry: the Norwegian Registry of Cancer (NRC). METHODS: SEER NET data were compared with corresponding NRC data in the time period 1993 to 2004 to determine whether there are differences in NET epidemiology between Norway and the United States. RESULTS: The SEER and NRC reported 17,312 and 2030 NETs, respectively. The overall Caucasian SEER NET incidence was 4.44, compared with 3.24 in the NRC. In the SEER white subset, bronchopulmonary NETs were the most common (incidence = 1.42; 32% of all NETs), compared with small intestinal NETs in the NRC (0.81; 26%). A marked increase in SEER NET incidence (37%-40%) was observed in the period 2000 to 2004, compared with 1993 to 1997; an even more pronounced increase (72%) was seen in the NRC. African Americans exhibited a remarkably high overall NET incidence of 6.50; furthermore, among African Americans, rectal NETs were most common (1.65; 27%). Small intestinal NET incidence was approximately 30% higher in men compared with women in all populations. The highest 5-year survival rates were for rectal NETs (74%-88%) in both databases, whereas prostatic NETs had the worst outcome (0%-23%). At diagnosis, NETs were localized in 27% to 46% of patients. CONCLUSIONS: NET incidence in the US Caucasian population and in Norway is similar, but considerably higher (approximately 50%) among African Americans. NETs have been regarded as indolent tumors; however, the 5-year survival is only approximately 55%.

http://www.ncbi.nlm.nih.gov/pubmed/17429568

7201 carcinoids: increasing incidence overall and disproportionate mortality in the elderly.

Citation
World Journal of Surgery, 2007, 31(5): 1022-1030.

Authors

Perez, E.A., Koniaris, L.G., Snell, S.E., Gutierrez, J.C., Sumner, W.E.3rd., Lee, D.J., Hodgson, N.C., Livingstone, A.S., & Franceschi, D.

Abstract
INTRODUCTION: The aim of the study was to determine outcomes for respiratory and gastrointestinal carcinoid tumors utilizing a large cancer registry. METHODS: Cases of respiratory and gastrointestinal carcinoid from the Florida Cancer Data System (FCDS) from 1981 to 2001 were reviewed. Descriptive statistics, age-adjusted tumor incidence, and survival rates were determined. RESULTS: A total of 7201 cases of malignant carcinoid were identified. Pulmonary and gastrointestinal carcinoid tumors comprised 82% of all carcinoids encountered. The mean age was 64.4 +/- 0.15 years. Stratified by location, there were 3000 (51.4%) foregut carcinoids (including those found in the respiratory tree-2325 in the lung), 2130 (36.5%) midgut carcinoids, and 712 (12.2%) hindgut carcinoids. Second, distinct malignancies were observed in 23% of cases. The total age-adjusted incidence rate has increased from 0.62 per 100,000 in 1980 to 5.17 per 100,000 in 2000. Overall median survival was 21.97 months. The median survival was 19.0 months for foregut carcinoids (excluding those arising in the respiratory tract); 33.9 months for midgut tumors; and 22.7 months for hindgut carcinoids. There was a statistically significant better survival for those with midgut tumors than for those in the other groups (P < 0.001). Age < 60 years, white race, and female sex were all associated with better survival (P < 0.01). CONCLUSIONS: The incidence of pulmonary and gastrointestinal carcinoids has dramatically increased since 1981. Tumor location and age > or = 60 years are the strongest predictors of mortality.

http://www.ncbi.nlm.nih.gov/pubmed/17391319

A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress.

Citation
American Journal of Gastroenterology, 2007, 102(7): 1464-1473.

Authors
Modlin, I.M., Champaneria, M.C., Chan, A.K., & Kidd, M.

Abstract
OBJECTIVES: Small intestinal neuroendocrine tumors (SI-NETs) are the most common gastrointestinal neuroendocrine tumor, but their natural history and outcome remain poorly defined, which hinders both the prediction of disease progression and appropriate therapeutic options. We examined patterns, incidence, prognosis, and outcomes of these tumors over a 30-yr period. METHODS: Data were extracted from the NCI's SEER registry (1973-2002). Incidence rates, distribution, and 5-yr survival rates were analyzed and adjusted (U.S. decennial census data). RESULTS: Of the 18,641 NETs, 3,911 (21.0%) were SI-NETs, of which 1,953 (49.6%) were ileal. Since 1973, both SI-NET and its ileal variant have increased annually by 3.8% and 2.1%, respectively. Ileal tumors, as a percentage of SI tumors, have increased

from 52% to 63.6%. The age-adjusted incidence of ileal, small intestinal, and digestive system NETs has increased 225%, 460%, and 720% over 30 yr. Ileal tumors have specifically increased in prevalence in white (274%) and black (500%) men and women (213% and 286%, respectively); an overall increase of fourfold in blacks and 2.4-fold in whites. Although 83.3% of SI-NETs were staged, 83.7% were histologically ungraded. Five-year survival rates for SI-NETs were 62.6 +/- 1% (all stages), 73.8% (localized), 72% (regional), and 43.2% (distant). These have not significantly altered since 1973 (P= 0.11). CONCLUSIONS: SI-NETs have increased, particularly in men and in the black population, which may be due to in vivo changes, increased clinical and pathological awareness, or increased detection of tumors. SI-NETs are malignant, diagnosed late, and survival rates have remained unchanged over 30 yr.

http://www.ncbi.nlm.nih.gov/pubmed/17201794

Epidemiology of non-gastroenteropancreatic (neuro)endocrine tumours.

Citation
Clinical Endocrinology (Oxford), 2007, 66(1): 1-6.

Authors
Ferolla, P., Faggiano, A., Avenia, N., Milone, F., Masone, S., Giampaglia, F., Puma, F., Daddi, G., Angeletti, G., Lombardi, G., Santeusanio, F., & Colao, A.

Abstract
The widespread availability and reliability of immunohistochemical techniques in the last three decades have allowed researchers to identify cells with common neuroendocrine markers in virtually every organ. As a whole, these neuroendocrine cells form the so-called diffuse neuroendocrine system. Tumours arising from the cells of the diffuse neuroendocrine system are defined as (neuro)endocrine tumours (NETs). NETs have been increasingly described in recent years. However, despite the increase in the number of published papers focused on NET, we still lack adequate epidemiological data, particularly for non-gastroenteropancreatic (GEP) NETs. Furthermore, the real incidence of neuroendocrine differentiation for most sites is not completely known and is probably underestimated. As a consequence, data on the clinical features of many NET subgroups are not well known or confusing. For all of these reasons, we have attempted to evaluate the epidemiology of non-GEP NETs, reviewing the limited data available in the literature.

http://www.ncbi.nlm.nih.gov/pubmed/17066609

Carcinoid tumours in the gastrointestinal tract--a population-based study from Western Norway.

Citation
Scandinavian Journal of Surgery, 2006, 95(3): 158-161.

Authors
Helland, S,K., Prøsch, A.M., & Vista, A.

Abstract
OBJECTIVE: To analyze population-based incidence, anatomic distribution and patient characteristics of gastrointestinal carcinoid tumours. BACKGROUND: Neuroendocrine carcinomas (NE, carcinoid tumours) arise from neuroendocrine cells and are most commonly found in gastrointestinal tract and lungs. Previous studies on carcinoids report varying

incidence rates, location of tumours and patient survival rates. METHODS: Retrospective study. 88 patients were diagnosed with carcinoids located in the gastrointestinal tract in the period 1983-2003 in the Norwegian counties Hordaland and Sogn og Fjordane. Patient and tumour characteristics, treatment and survival were analyzed in a sub-group of 51 patients treated at Haukeland University Hospital. RESULTS: Incidence of carcinoids was 0.8 when analyzed from the counties Hordaland and Sogn og Fjordane as well as when analyzed from Haukeland University Hospital. There were 26 men and 25 women. Median age at surgery was 61 years (range 17-87 years). The tumours were located in the small bowel in 53%, appendix 18%, colon 4%, rectum 4%, stomach 8% and duodenum 10%. Five-year survival rate was 50% in stomach, 80% in duodenum, 43% in the small bowel, 100% for tumours in appendix, 40% in colon and 100% in rectum. CONCLUSION: Carcinoid tumours are relatively uncommon neoplasms and most of them are found in the small bowel. Carcinoids in the ileum tend to be more aggressive and carry a poorer prognosis than carcinoids at other locations. Tumours in the appendix are found at lower age and in an early stage. They rarely metastasize and have an excellent prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/15213627

Updated population-based review of carcinoid tumors.

Citation

Annals of Surgery, 2004, 240(1): 117–122.

Authors

Maggard, M.A., O'Connell, J. B., & Ko, C.Y.

Abstract

OBJECTIVE: To determine the population-based incidence, anatomic distribution, and survival rates of gastrointestinal carcinoid tumors. BACKGROUND: Carcinoid tumors arise from neuroendocrine cells and may develop in almost any organ. Many textbooks and articles represent single institution studies and report varying incidence rates, anatomic distribution of tumors, and patient survival rates. Population-based statistics remain largely unknown. METHODS: Data was obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results program (1973 to 1997). Incidence rates, distribution, and 5-year survival rates were analyzed. Multivariate Cox regression was used to identify predictors of survival using age, race/ethnicity, gender, and tumor characteristics (size, lymph node status, and stage). RESULTS: Of the 11,427 cases analyzed, the average age was 60.9 years, and 54.2% were female. The overall incidence rates for carcinoid tumors have increased significantly over the past 25 years, although rates for some sites have decreased (eg, appendix). The gastrointestinal tract accounted for 54.5% of the tumors. Within the gastrointestinal tract, the small intestine was the most common site (44.7%), followed by the rectum (19.6%), appendix (16.7%), colon (10.6%), and stomach (7.2%). The 5-year survival rates for the most common gastrointestinal sites were stomach (75.1%), small intestine (76.1%), appendix (76.3%), and rectum (87.5%). CONCLUSIONS: Using national, population-based cancer registry data, this study demonstrates that (1) incidence rates for carcinoid tumors have changed, (2) the most common gastrointestinal site is not the appendix (as is often quoted), but the small intestine, followed in frequency by the rectum, and (3) survival rates differ between individual anatomic sites.

http://www.ncbi.nlm.nih.gov/pubmed/15477707

Epidemiology of Neuroendocrine Tumours.

Citation
Neuroendocrinology, 2004, 80(Suppl. 1): 3-7.

Authors
Taal, B.G., & Visser, O.

Abstract
Neuroendocrine tumours account for only 0.5% of all malignancies. The incidence is approximately 2/100,000 with a female preponderance under the age of 50 years due to appendiceal location. The main primary sites are the gastrointestinal tract (62-67%) and the lung (22-27%). Presentation with metastatic disease accounts for 12-22%. In the last decades, the incidence has been rising. This might be due to more awareness, improved diagnostic tools or a change in definition. Most neuroendocrine tumours are mainly sporadic, but association with the multiple endocrine neoplasia type 1 syndrome and clustering within families is known. Also an increased risk of secondary cancers has been reported, but numbers are small. The 5-year survival is mainly associated with stage: 93% in local disease, 74% in regional disease and 19% in metastatic disease. In metastatic disease, survival increased since 1992, when treatment with octreotide became largely available in the Netherlands.

http://gut.bmj.com/content/53/4/549.abstract

Incidence and management of malignant digestive endocrine tumours in a well defined French population.

Citation
Gut, 2004, 53: 549-553.

Authors
Lepage, C., Phelip, J.M., Hatem, C., Vernet, C., & Faivre, J.

Abstract
Background and aims: Little is known about the epidemiology of malignant digestive endocrine tumours. The aim of this study was to report on their incidence and management in a well defined population. Methods: Data were obtained from the population based Digestive Cancer Registry of Burgundy (France) over a 24 year period. Incidence rates were calculated by sex, age groups, and period of diagnosis. Treatment and stage at diagnosis were also investigated. Prognosis was determined using crude and relative survival rates. A multivariate relative survival analysis was performed. Results: Between 1976 and 1999, 229 cases were recorded. Age standardised incidence rates were 0.76/100 000 for men and 0.50/100 000 for women. They increased over time in both sexes. The resectability rate was 74.1%. Among recorded cases, 26.6% did not extend beyond the organ, 20% had lymph node metastases, and 53.3% had visceral metastases or were unresectable. There was no improvement in the resection rate or in the stage at diagnosis over the study period. The overall relative survival rate was 66.9% at one year, 50.4% at five years, and 40.6% at 10 years. Stage at diagnosis, age at diagnosis, and subsite were independent significant prognostic factors. Conclusions: Although their incidence is increasing, malignant digestive endocrine tumours remain a rare cancer, representing 1% of digestive cancers. Stage at diagnosis and prognosis at a population level are worse than those reported in hospital series. In the short term, new therapeutic possibilities represent the best way to improve their prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/14687136

A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem?

Citation
American Journal of Gastroenteology, 2004, 99(1): 23-32.

Authors
Modlin, I.M., Lye, K.D., & Kidd, M.

Abstract
OBJECTIVES: Interest in gastric carcinoid tumors has amplified considerably given the biological establishment of their relationship to gastrin and advances in the elucidation of the pathobiology of such lesions. The recognized propensity of acid-suppressing agents such as the proton pump inhibitor class of drugs to increase plasma gastrin levels has been proposed as a causal relationship in the apparent increase in the identification of such lesions although the increased prevalence of endoscopy and the enhanced awareness of pathologists have also been considered as contributory factors. We sought to examine if there has been an increase in gastric carcinoid incidence time correlative with these parameters. METHODS: Carcinoid tumor cases from the End Results Group (1950-1969) and the Third National Cancer Survey (TNCS) (1969-1971) databases were combined with the most recent release of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry (1973-1999); these three datasets revealed 13715 carcinoid cases, of which 562 were gastric in origin. Age-adjusted analyses as well as population-based gender and race correction ratios were completed in conjunction with United States decennial census data. To allow a finer granularity in incidence trends, the SEER database was divided into early (1973-1991) and late (1991-1999) subsets. RESULTS Since 1950, the percentage of gastric carcinoids among all gastric malignancies has increased from 0.3% to 1.77%. Since 1969, the proportion of gastric carcinoids among all enteric carcinoid lesions has increased from 2.4% to 8.7%. Age-adjusted incidence rates among male, female, black, and white population subsets have all increased since the TNCS time period, with the greatest increase (800%) noted in white females. The male:female ratio has fallen from 0.90 to 0.54. The occurrence of synchronous or metachronous noncarcinoid tumors with gastric carcinoid tumors has decreased by 26% during the course of SEER data collection. The 5-yr survival rate for gastric carcinoids overall has risen from 51% to 63% during the same time period. CONCLUSIONS: Gastric carcinoids have increased in incidence over the last 50 yr. Differential increases in predominance across gender and race subdivisions may reflect genetic-based propensities (or protection) for gastric carcinoid tumors among certain ethnic populations. Increased endoscopic surveillance and associated sophisticated pathological evaluation of gastric biopsies undoubtedly are responsible for some of the observed increase in the incidence of gastric carcinoid tumors. These data allow no specific role to be assigned to the effects of acid-suppressive medications. Nevertheless the role of such agents cannot be discounted at this time since the time frame of the increased incidence is somewhat comparable to the introduction of these agents as is the known biological effect of gastrin on ECL cell proliferation.

http://www.ncbi.nlm.nih.gov./pubmed/12569593

A 5-decade analysis of 13,715 carcinoid tumors.

Citation

Cancer, 2003, 97(4): 934–959.

Authors

Modlin I.M, Lye K.D., & Kidd, M.

Abstract
BACKGROUND: Carcinoid tumors represent an unusual and complex disease spectrum with protean clinical manifestations. This compilation of several large United States-based databases comprising patients from 1950 to 1999 examines 13,715 carcinoid tumors and provides epidemiologic information regarding the natural history and evolution of the detection and diagnosis of this entity. METHODS: The authors evaluated 10,878 carcinoid tumors that were identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) from 1973 to 1999 in addition to 2837 carcinoid tumors that were registered previously by two earlier NCI programs. To the authors' knowledge, this represents the largest current epidemiology series addressing carcinoid tumors to date. RESULTS: Specific trends in incidence for carcinoid tumors of certain sites were identified. Among the most recently collected subset of data, sites that demonstrated the greatest incidence of carcinoids were the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%). Within the gastrointestinal tract, most carcinoid tumors occurred in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%). For all sites, age-adjusted incidence rates were highest in black males (4.48 per 100,000 population per year). Associated noncarcinoid tumors were frequent in conjunction with small intestinal (29.0%), gastric (20.5%), colonic (20.0%), and appendiceal (18.2%) carcinoids. The highest percentages of nonlocalized lesions were noted for cecal (81.5-83.2%) and pancreatic (71.9-81.3%) carcinoids, whereas the highest percentage of localized disease was found among rectal (81.7%), gastric (67.5%), and bronchopulmonary (65.4%) carcinoids. The best 5-year survival rates were recorded for patients with rectal (88.3%), bronchopulmonary (73.5%), and appendiceal (71.0%) carcinoids; these tumors exhibited invasive growth or metastatic spread in 3.9%, 27.5%, and 38.8% of patients, respectively. CONCLUSIONS: Carcinoids appear to have increased in overall incidence over the past 30 years; for some sites, this trend has been evident for nearly half a century. Recent marked increases in gastric and rectal carcinoids and a concomitant decrease in appendiceal carcinoid incidence may be due in part to varying rules of registration among the compiled databases examined in this report or to improvements in diagnostic technology; increased awareness of and about carcinoid tumors also may play a significant role. In 12.9% of all patients with carcinoid, distant metastases already were evident at the time of diagnosis; the overall 5-year survival rate for all carcinoid tumors, regardless of site, was 67.2%. These findings bring into question the widely promulgated relative benignity of carcinoid disease. Certain carcinoid tumors, such as those of the rectum, appear to be over-represented among the black and Asian populations within the United States, suggesting the role of genetics in the development of this intriguing disease.

http://cat.inist.fr/?aModele=afficheN&cpsidt=15503786
Carcinoids and their variant endocrinomas. An analysis of 11842 reported cases.
Citation
Journal of Experimental & Clinical Cancer Research, 2003, 22: 517-530.

Authors
Soga, J.

Abstract
Endocrinocarcinomas consisting of carcinoids and their variant carcinomas with endocrine features are neoplasms of relatively rare occurrence but have often been reported in many countries and regions of the world. The largest series of 13715 cases from the United States

was published in 2003. A total number of 11842 reported cases of endocrinocarcinomas from the Niigata Registry were divided into two groups: the carcinoid group (n=10804) with the typical (n=9430) and the atypical (n=1374) series and the variant group (n=1038). These cases came from 64 countries and reports were written in 17 different languages. They were statistically evaluated for comparison between the two groups or series in various aspects, including gender and age, tumor-size, rate of metastases, immunohistochemistry, and survival after curative resection. In the carcinoid group, more frequent cases were found in the digestive system (64.2%) than in the extradigestive system (35.8%). Organ distribution of carcinoid cases exhibited the most frequent site to be the respiratory system (19.8%), followed by the rectum (15.0%), jejunoileum (12.0%), stomach (11.4%), appendix (9.6%) and duodenum (8.3%). An extremely small number of cases (less than 0.7%) were found in the middle ear, testicle, kidney, and several others. The highest rate of metastases was noted in the ileocecum (75.3%), followed by the jejunoileum (65.2%), pancreas (64.2%), and larynx (61.4%). Small carcinoids with invasion confined to the mucosa and submucosa, indicated an unexpectedly high metastasis rate of 13.8% for lesions 20 mm or less, and 10.0% for those 10 mm or less, and 6.1% for those 5 mm or less. The carcinoid syndrome was found to occur at the rate of 7.7% of overall 11057 cases reported between 1953 and 2002, with the highest incidence of 28.8% in the 5-year period between 1963 and 1967, gradually decreasing down to 3.7 % in the last 5 years. The 5-year survival rate after curative resection of lesions showed a significant difference between the carcinoid group and the variant group (82.0% vs 41.8%: P <0.0001). In the former group, the 5-year survival rate showed a significant difference between cases with or without metastases (61.4% vs 95.7%: P <0.0001). In the latter group, the 5-year survival rate was 74.5% for cases without metastases and 24.1% for those with metastases (P<0.0001). The highest 5-year survival rate in the carcinoid group was noted in the ovary (93.6%), followed by the liver (92.6%), the respiratory system (89.7%), the appendix (89.5%.), and the rectum (85.4%), while poor 5-year survival rates were recorded in the pancreas (43.2%), the esophagus (43.5%) and the larynx (47.6%). It should be emphasized that there is a significant statistical difference in many aspects between the carcinoid group and the variant group. The present study confirms that the malignant nature of these endocrine tumors is well reflected in their metastasis rates, even in small lesions with submucosal invasion, resulting in the 5-year survival rates of a significant difference among the groups or series.

http://www.lungcancerjournal.info/article/S0169-5002%2802%2900080-6/abstract

Pulmonary neuroendocrine tumors: Incidence and prognosis of histological subtypes. A population-based study in Denmark.

Citation
Lung Cancer, 2002, 37(2): 127-135.

Authors
Skuladottira, H., Hirsch, F.R., Hansenc, H.H., & Olsen, J.H.

Abstract

Pulmonary neuroendocrine tumors are currently considered to consist of three grades of malignancy, ranging from typical and atypical carcinoids to large-cell neuroendocrine carcinoma and small-cell carcinoma. The study reported here is the first population-based study of the demographics of patients with neuroendocrine tumors grouped by histological subtype. A cancer registry-based analysis of patients in Denmark in whom bronchial neuroendocrine tumor was diagnosed in 1978–97 was performed and the patients were

followed up to 31 December 1999. Typical carcinoid was diagnosed in 105 patients, atypical carcinoid in 192, large-cell neuroendocrine carcinoma in 50 and small-cell carcinoma in 11□998. The recorded incidence of neuroendocrine tumors other than small-cell carcinoma increased by twofold among men (from 0.24 to 0.53 per 100□000 inhabitants per year) and by threefold in women (from 0.14 to 0.41 per 100□000 inhabitants per year) during the study period, while the incidence of small-cell carcinoma decreased among men and levelled off among women. The prognosis of patients with bronchial neuroendocrine tumors varied with the degree of malignancy; the 5-year survival rate ranged from 87% for patients with typical carcinoids, to 44, 15 and 2% for patients with atypical carcinoids, large-cell neuroendocrine carcinoma and small-cell carcinoma, respectively. In Denmark, the incidence of neuroendocrine tumours is increasing. Our findings support the pathological categorization of neuroendocrine tumors into three grades of malignancy. More research is needed to establish the etiological factors in the development of pulmonary neuroendocrine tumors

http://www.ncbi.nlm.nih.gov/pubmed/11596039

Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden.

Citation
Cancer, 2001, 92(8): 2204-2210.

Authors
Hemminki, K., & Li, X.

Abstract
BACKGROUND: Carcinoids are rare indolent neuroendocrine tumors, mainly located in bowel, stomach, and lung. Their etiology is virtually unknown although a family history is a minor cause. METHODS: Site specific incidence trends and several risk factors of carcinoid tumors were studied based on the nationwide Swedish Family-Cancer Database of 10.2 million individuals and their more than 1 million tumors. Data on a total of 5184 carcinoid tumors were retrieved from the Cancer Registry covering years 1958-1998. RESULTS: The overall age-adjusted incidence rates were 2.0 for men and 2.4/100,000 for women in 1983-1998. Appendix was the main site for women whereas small intestine was the main site for men. The incidence of all carcinoids, including those at the main sites increased during the follow-up period but appeared to plateau in the middle of the 1980s. Appendiceal carcinoids showed an unusually early onset with a maximum incidence at age 15-19 years for women and 20-29 years for men. Among women, parity was not related to the age specific incidence of carcinoid tumors. A Poisson regression analysis showed that family history of carcinoids in first-degree relatives (relative risk, 3.6), well educated social background (relative risk for professionals, 2.8), and birth in large cities were risk factors. CONCLUSIONS: The data suggest that the increase in carcinoid tumors may be largely ascribed to the application of advanced medical viewing techniques that detect asymptomatic tumors. However, the difference in incidence between men and women in appendiceal tumor may be real and independent of parity.

http://www.ncbi.nlm.nih.gov/pubmed/11697843

Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients.

Citation
Annals of Oncology, 2001, 12(9): 1295-1300.

Authors
Quaedvlieg, P.F., Visser, O., Lamers, C.B., Janssen-Heijen, ML. & Taal, B.G.

Abstract
BACKGROUND: Carcinoid tumours are rare malignant neuroendocrine tumours. In 1992 octreotide was introduced in the Netherlands as a palliative treatment for the carcinoid syndrome in metastatic carcinoid disease. The aims of this epidemiological study were to evaluate epidemiological data and the impact of octreotide on survival in metastatic carcinoid disease. PATIENTS AND METHODS: Between 1989 and 1996, 2391 patients with carcinoid disease were diagnosed in the Netherlands. Survival data from two Registries were available in 619 patients, diagnosed between 1980 and 1997. RESULTS: Between 1989 1996, incidence was 1.95/100,000. Under the age of 50 years a significant female predominance was observed. Under the age of 35 years, appendiceal carcinoid was the most frequently diagnosed primary site. Incidence of distant metastases at diagnosis for appendix and lung primary sites was 1.6% and 5.5%, compared to 40%, in the other primary sites. Multivariate analysis of 619 patients revealed that age, stage and appendix localisation predicted survival. In metastatic disease, however, only year of diagnosis after 1992 independently predicted survival (P = 0.012). CONCLUSIONS: The female predominance found under the age of 50 years suggests hormonal influence. Improved survival in metastatic carcinoid disease might relate to the use of octreotide.

RISK FACTORS

http://www.ncbi.nlm.nih.gov/pubmed/18491401

Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study.

Citation
International Journal of Cancer, 2008, 123(4), 867-873.

Authors
Hassan, M.M., Phan, A., Li, D., Dagohay, C.G., Leary, C., & Yao, J.C.

Abstract
Carcinoids are rare neuroendocrine tumors (NETs); however, their incidence has significantly increased in the United States over the past 30 years. Little is known about the epidemiology of these cancers and their associated risk factors. We evaluated the independent effects of multiple risk factors associated with NETs arising at 5 disease sites (small intestine, stomach, lung, pancreas and rectum). We conducted a retrospective, hospital-based, case-control study involving 740 patients with histologically confirmed NETs and 924 healthy controls. Information on different risk factors was collected, and unconditional logistic regression analysis was used to determine adjusted odds ratios (AORs) and 95% confidence interval (CI) by the maximum-likelihood method. Smoking and alcohol consumption were not associated with NETs development in either men or women. However, a family history of cancer was a significant risk factor for all NETs. A long-term history of diabetes mellitus was a significant risk factor for gastric NETs (AOR = 5.6; 95% CI, 2.1-14.5), particularly in women (AOR = 8.4;

95% CI, 1.9-38.1). Diabetes modified the risk among women with a positive family history of cancer for the development of gastric NETs (AOR = 52.2; 95% CI, 5.5-491.5). Our results suggest that the risk of NETs may mostly explained by genetic factors. The increased risk of gastric NETs in women with both diabetes and a positive family history of cancer suggest that women may have a greater genetic susceptibility to NETs than men.

http://www.ncbi.nlm.nih.gov/pubmed/12085477

Occupational risk factors for small bowel carcinoid tumor.

Citation

Journal of Occupational and Environmental Medicine, 2002, 44(6): 516-522.

Authors

Kaerlev, L.,Teglbjaerg, P.S., Sabroe, S., Kolsad, H.A., Ahrens, W., Eriksson, M., Guénel, P., Hardell, L., Cyr, D., Ballard, T., Zambon, P., Morales Suárez-Varela, M., Stang, A., & Olsen, J.

Abstract

Small bowel carcinoid tumor (SBC) is a rare disease of unknown etiology but with an age-, sex-, and place-specific occurrence that may indicate an occupational origin. A European multicenter population-based case-control study was conducted from 1995 through 1997. Incident SBC cases between 35 and 69 years of age (n = 101) were identified, together with 3335 controls sampled from the catchment area of the cases. Histological review performed by a reference pathologist left 99 cases for study; 84 cases and 2070 population controls were interviewed. The industries most closely associated (a twofold or more odds ratio [OR]) with SBC, taking into account a 10-year time lag after exposure were, among women, employment in wholesale industry of food and beverages (OR, 8.2; 95% confidence interval [CI], 1.9 to 34.9]) and among men, manufacture of motor vehicle bodies (OR, 5.2; 95% CI, 1.2 to 22.4), footwear (OR, 3.9; 95% CI, 0.9 to 16.1), and metal structures (OR, 3.3; 95% CI, 1.0 to 10.4). The identified high-risk occupations with an OR above 2 were shoemakers, structural metal preparers, construction painters and other construction workers, bookkeepers, machine fitters, and welders (men). The OR for regular occupational use of organic solvents for at least half a year was 2.0 (95% CI, 1.0 to 4.2). Exposure to rust-preventive paint containing lead was suggested as another potential occupational exposure (OR, 9.1; 95% CI, 0.8 to 107). This explorative study suggests an association between certain occupational exposures and SBC, but some of these associations could be attributable to chance. All findings should be regarded as tentative.

RACE

http://gut.bmj.com.ezproxy1.library.arizona.edu/content/55/7/1051.2.full

The site distribution of gastrointestinal carcinoids differs between races.

Citation

Gut, 2006, 55: 1051–1052.

Authors

Konishi, T., Watanabe, T., Muto, T., Kotake, K., & Nagawa, H.

Abstract

We read with great interest the guideline for gastroenteropancreatic neuroendocrine (including carcinoid) tumours by Ramage, *et. al* (Gut, 2005, 54 (suppl 4): iv1-16. In these

excellent guidelines, they reported that the appendix is the most frequent site of gastrointestinal primary endocrine tumours (35% of the total number of tumours) while colon and rectal carcinoids comprise only 7% and 10%, respectively. One important aspect not mentioned however was the fact that site distribution of gastrointestinal carcinoids differs among races. Modlin *et al* previously reported a marked predominance of carcinoids of the colon and appendix in the White Caucasian population based on nationwide surveillance in the USA.[1] In contrast, the incidence of rectal carcinoids was 3–4-fold higher in African - Americans than in White Caucasians. Accordingly, the site distribution of colorectal carcinoids markedly differs among these two races. Regarding carcinoids in the Asian population, there have been few reports based on a large database. In order to provide such evidence, we analysed colorectal carcinoids in the Japanese population using "the Multi-Institutional Registry of Large Bowel Cancers in Japan", a nationwide database which covers approximately 10% of the Japanese population, from 1984 to 1998.[2] Among 90 057 cases of colorectal tumours registered during this period, 345 cases of colorectal carcinoids were identified. All cases were in the Asian population. Site distribution was: the ileum, three cases (0.9%); appendix, eight cases (2.3%); colon, 28 cases (8.2%); and rectum, 304 cases (88.6%). Thus carcinoids in the Japanese population exhibited a much higher distribution in the rectum than in the colon or appendix. This overrepresentation of rectal carcinoids is compatible with a previous report from Taiwan in which 33 (89.2%) of 37 colorectal carcinoids originated from the rectum. Differences in the distribution of colorectal carcinoids among races suggest that race related genetic factors play an important role in the development of gastrointestinal carcinoids. Hence racial disparity should be considered in the diagnosis of carcinoids, and further investigation using a larger database is needed to clarify these points.

FAMILY HISTORY

http://www.ncbi.nlm.nih.gov/pubmed/18398037

Family history of cancer and associated risk of developing neuroendocrine tumors: a case-control study.

Citation
Cancer Epidemiology, Biomarkers & Prevention, 2008, 17(4): 959-965.

Authors
Hassan, M.M., Phan, A., Li, D., Dagohoy, C.G., Leary, C., & Yao, J.C.

Abstract
BACKGROUND: Carcinoids are rare neuroendocrine tumors (NET). Familial clusterings of NETs are rarely reported, except for a small proportion associated with multiple endocrine neoplasia syndrome type 1. We evaluated the effect of positive family history of NET as well as other cancers on the development of NETs arising at five different locations. METHODS: We conducted a retrospective, hospital-based, case-control study involving 740 patients with histologically confirmed NETs and 924 healthy controls. Information on family history of cancer was collected, and unconditional logistic regression analysis was used to determine adjusted odds ratios (AOR) and 95% confidence intervals (CI). RESULTS: The authors observed a significant relationship between first-degree relatives with cancers and the development of NETs arising at the small intestine, stomach, lung, and pancreas; AORs (95%

CI) were 1.6 (1.1-2.4), 2.5 (1.1-6.3), 2.6 (1.5-4.5), and 1.8 (1.1-3.1), respectively. A first-degree family history of esophageal cancer was significantly associated with pancreatic NETs; AOR, 5.6 (95% CI, 1.1-29.6). There was a 70% and 130% increased risk of developing small intestinal NETs among subjects with family histories of colorectal cancer and prostate cancer, respectively. Moreover, individuals with a family history of lung cancer had a 2-fold increase in risk of developing pulmonary NETs. CONCLUSIONS: Having a first-degree relative with any cancer in general, and NET in particular, was a risk factor for NETs. The elevated risk of developing NETs extended to individuals with a family history of other cancers (not NETs) among first-degree relatives. These results suggested that risk of NETs may be partially explained by genetic factors.

http://www.ncbi.nlm.nih.gov/pubmed/16773283

Familial rectal carcinoid: report of two first-degree relatives with rectal carcinoid and review of the literature.

Citation
Techniques in Coloproctology, 2006, 10(2): 143-146.

Authors
Katare, M.V., Fichera, A., & Heimann, T.M.

Abstract

Two brothers with familial carcinoid tumors of the rectum are presented. A few cases documenting the occurrence of carcinoid tumors in first-degree relatives in the absence of the multiple endocrine neoplasia (MEN) syndromes have been reported in the literature. Consistent with these previous reports, in this case both patients had gastrointestinal carcinoid tumors that are located in identical anatomic locations. The current literature on carcinoid tumors outside the setting of any known genetic syndrome is reviewed. Clinical relevance and screening recommendations are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/11745428

Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden.

Citation
International Journal of Cancer, 2001, 94(3):444-448.

Authors
Hemminki, K., & Li, X.

Abstract
Carcinoids are rare neuroendocrine tumors, mainly located in the bowel, stomach and lung. Familial risks in carcinoid tumours are not well known apart from multiple endocrine neoplasia 1 (MEN1). We used the nation-wide Swedish Family-Cancer Database on 10.1 million individuals for assessment. Carcinoid tumors were retrieved from the Cancer Registry covering the years 1958-1998. The offspring generation, aged 0-66 years, accumulated 190 million person-years at risk. The age-adjusted incidence rates were 0.76 for men and 1.29/100,000 for women. Standardized incidence ratios (SIRs) were calculated for offspring when their parents had a carcinoid or any other cancer. When parents presented with carcinoids, SIRs for offspring were 4.35 (n = 8, 95% CI 1.86-7.89) for small intestinal and 4.65

(n = 4, 95% CI 1.21-10.32) for colon carcinoids. If both offspring and parents presented with small intestinal carcinoids, the SIR was 12.31 (n = 4, 95% CI 3.20-27.34). Offspring carcinoids were also increased if parents presented with bladder and endocrine gland tumors, the latter association probably partially due to MEN1. Risks for second cancers were increased, particularly at sites where familial risks were found, including carcinoids in the small intestine

http://www.ncbi.nlm.nih.gov/pubmed/11391591

Familial pulmonary carcinoid tumors

Citation
Cancer, 2001, 91(11):2104-2109.

Authors
Oliveira, A.M., Tazelaar, H.D., Wentzlaff, K.A., Kosugi, N.S., Hai, N., Benson, A., Miller, D.L., & Yang, P.

Abstract
BACKGROUND: Pulmonary carcinoid tumors are rare and usually occur sporadically. Infrequently, they arise in association with multiple endocrine neoplasia type 1 (MEN1). Familial pulmonary carcinoid tumors not associated with MEN1 have not been described. METHODS: Two sets of first-degree relatives diagnosed with primary pulmonary carcinoid tumors with no clinical features of MEN1 were identified in a pair of siblings and in a mother and daughter. Mutations in the MEN1 gene were sought using polymerase chain reaction analysis on paraffin embedded tissue from two members of one of the families. RESULTS: Histopathologic and immunohistochemical studies confirmed the diagnoses of carcinoid tumors. None of these patients and no family members had features of MEN1. DNA analysis did not detect germline mutations in the MEN1 gene. CONCLUSIONS: The occurrence of familial pulmonary carcinoid tumors in the absence of MEN1 suggests a novel, rare germline mutation specific to the development of pulmonary carcinoids.

http://www.ncbi.nlm.nih.gov/pubmed/10744132

Familial occurrence of carcinoid tumors and association with other malignant neoplasms.

Citation
Cancer Epidemiology, Biomarkers, & Prevention, 1999, 8(8): 715-719.

Authors
Babovic-Vuksanovic, D., Constantinou, C.L., Rubin, J., Rowland, C.M., Schaid, D.J., & Karnes, P.S.

Abstract
Carcinoid tumors are generally thought to be sporadic, except for a small proportion that occur as a part of multiple endocrine neoplasia syndromes. Data regarding the familial occurrence of carcinoid as well as its potential association with other neoplasms are limited. A chart review was conducted on patients indexed for malignant carcinoid tumor of the gastrointestinal tract seen at the Mayo Clinic between 1988 and 1996. A survey of family history of malignancies and personal history of other tumors was mailed to all eligible patients. Data for 245 patients were analyzed. Observed rates of carcinoids and other malignancies were compared with Surveillance, Epidemiology, and End Results data.

Estimates of the cumulative probability for first-degree relatives developing a carcinoid tumor were calculated. Nine (3.7%) patients with carcinoid tumor had at least one first-degree relative with the same malignancy. The rate of carcinoid tumor in first-degree relatives of probands was higher ($P < 0.0001$) than expected based on the Surveillance, Epidemiology, and End Results population data. Cumulative probability in a first-degree relative for developing a carcinoid was calculated to be 1.5% at age 80. There was an increased risk for developing a carcinoid tumor among first-degree relatives of patients with carcinoid. Neither patients with carcinoid nor their first-degree relatives had an increased incidence of other malignancies

HEREDITARY DISEASES

http://www.ncbi.nlm.nih.gov/pubmed/20300877

Periampullary and duodenal neoplasms in neurofibromatosis type 1: two cases and an updated 20-year review of the literature yielding 76 cases.

Citation
Journal of Gastrointestinal Surgery, 2010, 14(6): 1052-1061.

Authors
Relles, D., Baek, J., Witkiewicz, A., & Yeo, C.J.

Abstract
BACKGROUND: Patients with neurofibromatosis type 1 (NF1) are at increased risk to develop tumors throughout the gastrointestinal tract, including neuromas, gastrointestinal stromal tumors (GIST), and periampullary somatostatin-rich carcinoids. Here, we briefly describe two male patients with NF1 and review the recent literature on this topic. METHODS: Databases for PubMed and MEDLINE were searched for English-language articles since 1989 using a list of keywords, as well as references from review articles. RESULTS: The results generated by the search yielded 50 articles and 74 cases. Patients most commonly presented with jaundice, weight loss, GI bleeding, or anemia. The mean age at presentation was 47.9 years, with 59% of patients being female. Mean tumor size was 3.8 cm (range 0.9-27 cm). Tumor location was the duodenum (60%), ampulla (31%), pancreas (5%), or bile duct/gallbladder (4%). Tumor type was reported as somatostatinoma (40%), GIST (34%), adenocarcinoma (8%), carcinoid (6%), neurofibroma (5%), schwannoma (4%), or gangliocytic paraganglioma (3%). Treatment included classic Whipple procedure (42%), local excision (25%), pylorus-preserving pancreaticoduodenectomy (17%), and other resection (6%). Mean follow-up was 31 months postresection (range 0-99 months): 75% of patients were alive with no evidence of disease. CONCLUSIONS: These results underscore the importance of a thorough evaluation for tumors in NF1 patients with gastrointestinal symptoms, as well as subsequent surgical management when findings suggest a tumor in the periampullary region, as resection remains the mainstay of treatment.

http://cme.medscape.com/medline/abstract/18978035

Are neuroendocrine tumours a feature of tuberous sclerosis? A systematic review.

Citation

Endocrine Related Cancer, 2009, 16(1): 45-58.

Authors
Dworakowska, D., & Grossman, A.B.

Abstract
Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder characterised by the development of multiple hamartomas in numerous organs. It is caused by mutations of two tumour suppressor genes, TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13.3, which encode for hamartin and tuberin respectively. The interaction between these two proteins, the tuberin-hamartin complex, has been shown to be critical to multiple intracellular signalling pathways, especially those controlling cell growth and proliferation. TSC may affect skin, central nervous system, kidneys, heart, eyes, blood vessels, lung, bone and gastrointestinal tract. Small series and case reports have documented that in tuberous sclerosis patients many endocrine system alterations might occur, affecting the function of the pituitary, parathyroid and other neuroendocrine tissue. There have been scattered reports of the involvement of such tissue in the pathological process of TSC, but no systematic review as to whether this is a true association. We have therefore systematically assessed all available published literature in this area. We conclude that there may be an association with pituitary and parathyroid tumours, and two recent descriptions of Cushing's disease are especially intriguing. However, the evidence seems more firm in the case of islet cell tumours, particularly insulinomas. As these latter may cause changes in mental state that may be confused with the cerebral manifestations of TSC per se, it is particularly important for physicians working with these patients to be aware of the putative and indeed likely association.

http://cme.medscape.com/medline/abstract/17684762

Hereditary neuroendocrine tumors of the gastroenteropancreatic system.

Citation
Virchows Archiv, 2007, 451 (Suppl 1): S29-S38.

Authors
Anlauf, M., Garbrecht, N., Bauersfeld, J., Schmitt, A., Henopp, T., Komminoth, P., Heitz, P.U., Perren, A., & Klöppel, G.

Abstract
Approximately 5-10% of neuroendocrine tumors (NETs) of the gastroenteropancreatic system (GEP) have a hereditary background. The known inherited syndromes include multiple endocrine neoplasia type 1, neurofibromatosis type 1, von Hippel-Lindau disease, and the tuberous sclerosis complex. This review discusses for each of these syndromes the: (1) involved genes and specific types of mutations, (2) disease prevalence and penetrance, (3) affected neuroendocrine tissues and related clinical syndromes, (4) special morphological features of NETs and their putative precursor lesions. In addition, GEP-NETs clustering in individual families or associated with other malignancies without known genetic background are discussed.

http://cme.medscape.com/medline/abstract/18063061

Clinical, genetic and radiographic analysis of 108 patients with von Hippel-

Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs).

Citation
Surgery, 2007, 142(6): 814-818.

Authors
Blansfield, J.A., Choyke, L., Morito, S.Y., Choyke, P.L., Pingpank, J.F., Alexander, H.R., Seidel, G., Shutack, Y., Yuldasheva, N., Eugeni, M.,Bartlett, D. L., Glenn, G. M., Middelton, L., Linehan,W.M., & Libutti, S.K.

Abstract
BACKGROUND: von Hippel-Lindau (vHL) disease is an autosomal dominant syndrome associated with neoplasms in multiple organs, which includes the pancreas. Here, we report the greatest single center experience in patients with vHL pancreatic endocrine neoplasm (PNETs). METHODS: Between December 1998 and November 2006, 633 patients with vHL were evaluated and those with PNETs were enrolled on a prospective protocol. RESULTS: Overall, 108 vHL patients had PNETs (17%). Nine patients had metastatic disease (8.3%) from their PNET. Patients with lesions greater than 3 cm (n = 25) were more likely to develop metastases than patients with lesions less than 3 cm (n = 83) (P < .005). Thirty-nine patients underwent resection. Germline sequencing showed that 78% of patients with metastases (7/9) had exon 3 mutations compared with 46% of patients without metastases (32/98; P < .01). Tumor doubling time was calculated for the largest PNET. The group with metastases had an average tumor doubling time of 337 days (range, 180-463 days) compared with 2630 days (range, 103-9614 days) for those without metastases (P < .0001). CONCLUSIONS: By implementing a system of selective operative resection based on defined criteria, vHL patients with PNETs can be managed safely. For patients with small primary lesions (<3 cm), without a mutation of exon 3 and slow tumor doubling time (>500 days), a nonoperative approach may be appropriate for these nonfunctional neoplasms.

http://www.ncbi.nlm.nih.gov/pubmed/15713725

Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series.

Citation
Journal of Clinical Endocrinology & Metabolism, 2005, 90(5): 2603-2609.

Authors
Ferolla, P., Falchetti, A., Filosso, P., Tomassetti, P., Tamburrano, G., Avenia, N., Daddi, G., Puma, F., Ribacchi, R., Santeusanio, F., Angeletti, G., & Brandi, M.L.

Abstract
Neuroendocrine tumors may occur in the setting of multiple endocrine neoplasia type 1 (MEN1) syndrome. Among these, a probably underestimated prevalence of well differentiated neuroendocrine thymic carcinoma (carcinoid), a neoplasm characterized by very aggressive behavior, has been described. We report characterization of the seven Italian cases in which this association occurred among a series of 221 MEN1 patients (41 sporadic and 180 familial cases; prevalence, 3.1%). All of the patients were male, and six of seven (85%) were heavy smokers. No associated hormonal hypersecretion was detected. The first diagnosis was between the second and fifth decades. Familial clusters were present in three of seven (42.8%). No genotype-phenotype correlation was found. All seven cases were associated with

hyperparathyroidism. In one patient, prophylactic thymectomy revealed a small nodular lesion suggestive of a thymic carcinoid, providing evidence that preventive thymectomy might prevent additional growth of an occult thymic carcinoid. These findings confirm that thymic carcinoids are associated with a very high lethality, with a near-total prevalence in smoker males. Therefore, prophylactic thymectomy should be considered at neck surgery for primary hyperparathyroidism in MEN1 male patients, especially for smokers, and, due to the frequent familial clusters distribution of this pathology, in subjects with affected relatives presenting this feature. Thus, we recommend screening every patient affected with a neuroendocrine thymic neoplasm for MEN1 syndrome.3

http://ajp.amjpathol.org/cgi/reprint/154/2/429.pdf

Mutations and Allelic Deletions of the *MEN1* Gene Are Associated with a Subset of Sporadic Endocrine Pancreatic and Neuroendocrine Tumors and Not Restricted to Foregut Neoplasms.

Citation

American Journal of Pathology, 1999, 154(2), 429:436.

Authors
Görtz, B., Jürgen, R., Krahenmann, A., de Krijger, R.R., Muletta-Feurer, S., Rütimann, K., Saremaslani, P., Speel, E.J., Heitz, P.U. & Komminoth, P.

Abstract
Endocrine pancreatic tumors (EPT) and neuroendocrine tumors (NET) occur sporadically and rarely in association with multiple endocrine neoplasia type 1 (MEN1). We analyzed the frequency of allelic deletions and mutations of the recently identified *MEN1* gene in 53 sporadic tumors including 30 EPT and 23 NET (carcinoids) of different locations and types. Allelic deletion of the *MEN1* locus was identified in 18/49 (36.7%) tumors (13/30, 43.3% in EPT and 5/19, 26.3% in NET) and mutations of the *MEN1* gene were present in 8/52 (15.3%) tumors (4/30 (13.3%) EPT and 4/22 (18.1%) NET). The somatic mutations were clustered in the 5* region of the coding sequence and most frequently encompassed missense mutations. All tumors with mutations exhibited a loss of the other allele and a wild-type sequence of the *MEN1* gene in nontumorous DNA. In one additional patient with a NET of the lung and no clinical signs or history of MEN1, a 5178–9G3A splice donor site mutation in intron 4 was identified in both the tumor and blood DNA, indicating the presence of a thus far unknown MEN1 syndrome. In most tumor groups the frequency of allelic deletions at 11q13 was 2 to 3 times higher than the frequency of identified *MEN1* gene mutations. Some tumor types, including rare forms of EPT and NET of the duodenum and small intestine, exhibited mutations more frequently than other types. Furthermore, somatic mutations were not restricted to foregut tumors but were also detectable in a midgut tumor (15.2% *versus* 16.6%). Our data indicate that somatic *MEN1* gene mutations contribute to a subset of sporadic EPT and NET, including midgut tumors. Because the frequency of mutations varies significantly among the investigated tumor subgroups and allelic deletions are 2 to 3 times more frequently observed,factors other than *MEN1* gene inactivation, including other tumor-suppressor genes on 11q13, may also be involved in the tumorigenesis of these neoplasms.

http://www.ncbi.nlm.nih.gov/pubmed/9361035

Identification of MEN1 gene mutations in sporadic carcinoid tumors of the lung.

Citation
Human & Molecular Genetics, 1997, 6(13): 2285-2290.

Authors
Debelenko, L.V., Brambilla, E., Agarwal, S.K., Swalwell, J.I., Kester, M.B., Lubensky, I.A., Zhuang, Z., Guru, S.C., Manickam, P., Olufemi, S.E., Chandrasekharappa, S.C., Crabtreee, J.S., Kim, Y.S., Hep;ner, C., Burns, A.L., Spiegel, A.M., Marx, S,J., Liotta, L.A., Collins, F.S., Travis, W.D., & Emmert-Buck, M.R..

Abstract
Lung carcinoids occur sporadically and rarely in association with multiple endocrine neoplasia type 1 (MEN1). There are no well defined genetic abnormalities known to occur in these tumors. We studied 11 sporadic lung carcinoids for loss of heterozygosity (LOH) at the locus of the MEN1 gene on chromosome 11q13, and for mutations of the MEN1 gene using dideoxy fingerprinting. Additionally, a lung carcinoid from a MEN1 patient was studied. In four of 11 (36%) sporadic tumors, both copies of the MEN1 gene were inactivated. All four tumors showed the presence of a MEN1 gene mutation and loss of the other allele. Observed mutations included a 1 bp insertion, a 1 bp deletion, a 13 bp deletion and a single nucleotide substitution affecting a donor splice site. Each mutation predicts truncation or potentially complete loss of menin. The remaining seven tumors showed neither the presence of a MEN1 gene mutation nor 11q13 LOH. The tumor from the MEN1 patient showed LOH at chromosome 11q13 and a complex germline MEN1 gene mutation. The data implicate the MEN1 gene in the pathogenesis of sporadic lung carcinoids, representing the first defined genetic alteration in these tumors.

http://www.ncbi.nlm.nih.gov/pubmed/1968779

Somatostatin-producing duodenal carcinoids in patients with von Recklinghausen's neurofibromatosis. A predilection for black patients.

Citation
Cancer, 1990, 65(7): 1591-1595.

Authors
Burke, A.P., Sobin, L.H., Shekitka, K.M., Federspiel, B.H., & Helwig, E.B.

Abstract
Eight patients with von Recklinghausen's disease (VRD) and duodenal carcinoids are presented. Seven patients were black, and one white. Six of the eight were women. The presenting symptom was either jaundice or abdominal pain. All tumors were located in the second portion of the duodenum, and three were multiple. Associated tumors other than neurofibromas included multiple leiomyomas, meningioma, neurofibrosarcoma, and prostatic sarcoma. Seven tumors had psammoma bodies, and in three they were numerous. Somatostatin-positive cells were demonstrated in all cases. Two tumors had spread to regional lymph nodes at the time of surgery. There appears to be a predilection for black patients among those with VRD and duodenal carcinoids.

MOLECULAR GENETIC ALTERATIONS

OVERVIEW

http://www.ncbi.nlm.nih.gov.ezproxy1.library.arizona.edu/pubmed/19115524

Genetics and molecular pathology of neuroendocrine gastrointestinal and pancreatic tumors (gastroenteropancreatic neuroendocrine tumors).

Citation
Current Opinion in Endocrinology, Diabetes and Obesity, 2009, 16(1): 72-78.

Authors

Oberg, K.

Abstract
PURPOSE OF REVIEW: Gastrointestinal and pancreatic neuroendocrine tumors (GEP-NETs) originate from cells of the diffuse endocrine system. Most GEP-NETs are sporadic, however, some of them, especially pancreatic endocrine tumors, may occur as part of familial syndromes. The genetic and molecular pathology of neuroendocrine tumor development is incomplete and remains largely unknown. However, the WHO classification introduced in clinical practice will give more insight into genetic and molecular changes related to tumor subtypes. RECENT FINDINGS: In sporadic endocrine pancreatic tumors, losses of chromosome 1 and 11q as well as gain on 9q appear to be early invents in development of pancreatic tumors because they are already present in small tumors. Multiple genetic defects may accumulate with time and result in pancreatic neuroendocrine tumor progression and malignancy. Gastrointestinal endocrine tumors (carcinoids) show predominantly genetic alterations concentrated on chromosome 18. There are losses of the entire chromosome as well as smaller deletions. The most frequently reported mutated gene in gastrointestinal neuroendocrine tumors is b-catenin. Overexpression of cyclin D1 and cMyc has also been reported. Recently, a set of genes NAP1L1, MAGE-2D and MTA1 has been correlated with malignant behavior of small intestinal carcinoids. SUMMARY: Molecular profiling of GEP-NETs demonstrates that pancreatic endocrine tumors and gastrointestinal neuroendocrine tumors (carcinoids) display different genetic changes and should, therefore, be considered to be different tumor entities; thereby, also differently managed clinically. Although the number of genetic changes is higher in malignant tumors, we are still far away from defining a malignant profile in GEP-NETs.

STUDIES

http://www.ncbi.nlm.nih.gov/pubmed/20037573

MicroRNA expression in ileal carcinoid tumors: downregulation of microRNA-133a with tumor progression.

Citation
Modern Pathology, 2010, 23(3): 367-375.

Authors
Reubel, K., Leontovich, A.A., Stilling, G.A., Zhang, S., Righi, A., Jin., L., & Lloyd, R.V.

Abstract
MicroRNAs (miRNAs) are involved in cell proliferation, differentiation, and apoptosis and can function as tumor suppressor genes or oncogenes. The role of miRNAs in neuroendocrine

tumors such as ileal carcinoids is largely unknown. We examined the differential expression of 95 miRNAs by RT-PCR using the QuantiMir System in eight matching primary and metastatic carcinoid tumors from the ileum. All miRNAs chosen for the QuantiMir System array were based on their potential functions related to cancer biology, cell development, and apoptosis. The expression of miRNAs for the samples was normalized to miRNA-197, and the matching primary and metastatic tumors were compared. There was downregulation of miRNA-133a, -145, -146, -222, and -10b in all samples between the primary and matching metastatic tumors and upregulation of miRNA-183, -488, and -19a+b in six of eight metastatic carcinoids compared to the primary tumors. miRNA-133a was further analyzed by TaqMan real-time RT-PCR and northern hybridization using six additional matching primary and metastatic samples, which supported the PCR array findings. There were significant differences in miRNA-133a expression with downregulation in the metastasis compared to the primary in the eight original cases ($P<0.009$) and in the six additional cases used for validation ($P<0.014$). Laser capture microdissection and real-time RT-PCR analysis using normal ileum found miRNA-133a expression in normal enterochromaffin cells. In situ hybridization in normal ileum showed that some of the mucosal endocrine cells expressed miRNA-133a. Both primary and metastatic ileal carcinoid tumors expressed miRNA-133a by in situ hybridization. These results provide information about novel marker miRNAs that may be used as biomarkers and/or therapeutic targets in intestinal carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/19816005

Vascular endothelial growth factors, angiogenesis, and survival in human ileal enterochromaffin cell carcinoids.

Citation
Neuroendocrinology, 2009, 90(4): 402-415.

Authors
Besig, S., Voland, P., Baur, D.M., Perren, A., & Prinz, C.

Abstract

BACKGROUND AND AIMS: Well-differentiated neuro-endocrine ileal carcinoids are composed of serotonin-producing enterochromaffin (EC) cells. Life expectancy is determined by metastatic spread to the liver because medical treatment options are still very limited. Selective inhibition of angiogenesis or lymphangiogenesis might prevent tumour growth and metastatic spread. We examined the role of the vascular endothelial growth factors (VEGFs) A, B, C, D, and their receptors (VEGFRs) 1, 2, 3 in angiogenesis and lymphangiogenesis of ileal EC cell carcinoids with and without liver metastases. METHODS: The expression of various VEGFs and VEGFRs was determined by quantitative real-time RT-PCR in healthy mucosa, primary tumour, lymph node metastases and liver metastases of 25 patients with ileal EC cell carcinoids. Microvessel density (MVD) was determined by CD-31 staining in primary tumours and lymphatic vessel density (LVD) by LYVE-1 staining. VEGF expression levels, MVD, LVD, and patients' survival time were correlated using logistic regression and Kaplan-Meier survival analysis. RESULTS: VEGF-A was highly expressed with no difference between normal mucosa and tumours. VEGF-B and -D as well as VEGFR-1 and -2 expression levels were significantly increased in the tumours when compared to normal mucosa. Patients with liver metastasis, however, had a significantly lower expression of the factors A, B, and C and the receptors 2 and 3. MVD in primary tumours positively correlated with the expression of VEGF ligands and their receptors, except for VEGF-D. LVD did not correlate with any VEGF ligand or receptor. Interestingly, low expression levels of VEGF-B were associated with poor

survival. CONCLUSION: Patients with more aggressive metastatic spreading had relatively decreased expression levels of VEGF ligands and receptors. Thus, anti-angiogenic therapy may not be a suitable target in metastatic ileal EC cell carcinoids.

http://www.ncbi.nlm.nih.gov/pubmed/19234439

Glucose transporter-1 in pulmonary neuroendocrine carcinomas: expression and survival analysis.

Citation
Modern Pathology, 2009, 22(5): 633-638.

Abstract
Glucose transporter-1 (GLUT-1) mediates the transport of glucose across the cellular membrane. Its elevated levels and/or activation have been shown to be associated with malignancy. The aim of this study was to investigate GLUT-1 expression in pulmonary neuroendocrine carcinomas. Tissue microarray-based samples of 178 neuroendocrine carcinomas, including 48 typical carcinoids, 31 atypical carcinoids, 27 large cell neuroendocrine carcinomas and 72 small cell carcinomas from different patients, were studied immunohistochemically for GLUT-1 expression. Forty-seven percent (75/161) of pulmonary neuroendocrine carcinomas were immunoreactive with GLUT-1. GLUT-1 was observed in 7% (3/46) of typical carcinoid, 21% (6/29) of atypical carcinoid, 74% (17/23) of large cell neuroendocrine carcinoma and 78% (49/63) of small cell carcinoma. GLUT-1 expression correlated with increasing patient age (P=0.01) and with neuroendocrine differentiation/tumor type (P<0.001), but not with gender, tumor size or stage. GLUT-1 expression was seen in a characteristic membranous pattern of staining along the luminal borders or adjacent to necrotic areas. GLUT-1 expression was associated with an increased risk of death for neuroendocrine carcinomas as a group (risk ratio=2.519; 95% confidence interval=1.519-4.178; P<0.001) and carcinoids (risk ratio=4.262; 95% confidence interval=1.472-12.343; P=0.01). In conclusion, GLUT-1 is expressed in approximately half of the pulmonary neuroendocrine carcinomas and shows a strong correlation with neuroendocrine differentiation/grade, but not with other clinicopathologic variables. Further studies appear plausible to elucidate the prognostic significance of GLUT-1 expression in pulmonary carcinoids**.**

http://cme.medscape.com/medline/abstract/18383209

High-resolution analysis of genetic alterations in small bowel carcinoid tumors reveals areas of recurrent amplification and loss.

Citation
Genes, Chromosomes, and Cancer, 2008, 47(7): 591-603.

Authors
Kulke, M.H., Freed, E., Chiang, D.Y., Philips, J., Zahrieh, D., Glickman, J. N., & Shivdasani, R.A.

Abstract
Carcinoid tumors of the small intestine are characterized by an indolent clinical course, secretion of neuropeptides, and resistance to standard cytotoxic chemotherapy. To evaluate the molecular events underlying carcinoid tumorigenesis, we used high-resolution arrays of

single nucleotide polymorphisms to study chromosomal gains and losses in 24 primary and metastatic small bowel carcinoid tumors derived from 18 patients. Regions of gain or loss comprising whole chromosomes or large chromosomal regions constituted the most common class of anomalies. Loss of all or most of chromosome 18 was the commonest finding, evident in 11 of the 18 cases. Heterozygosity was also lost on chromosome arms 9p and 16q. The amplitude of observed gains was modest in comparison to those reported in some other tumor types. One focal region of recurrent gain on 14q mapped to the locus of the gene encoding the antiapoptotic protein DAD1, and immunohistochemical staining confirmed DAD1 protein expression in tumor samples. This detailed study of an uncommon neoplasm provides a basis to investigate putative oncogenes and tumor suppressor genes in intestinal carcinoid tumors.

http://www.caringforcarcinoid.org/research/documents/Hoxc6.pdf

Hoxc6 Is Overexpressed in Gastrointestinal Carcinoids and Interacts With JunD to Regulate Tumor Growth.

Citation

Gastroenterology, 2008, 135: 907–916.

Authors

Fujiki, K., Duerr, E., Kikuchi, H., Ng, A., Xavier, R.J., Mizukami, Y., Imamura, T., Kulke, M.H., & Chung, D.C.

ABSTRACT

Background & Aims*:* The molecular alterations that underlie carcinoid tumor pathogenesis remain poorly defined. The homeobox gene *HOXC6* was highly upregulated in human gastrointestinal carcinoid tumors, and we sought to define its pathogenic role. *Methods:* The functional and physical properties of Hoxc6 were investigated by establishing carcinoid cells that stably overexpressed Hoxc6 or were deficient in Hoxc6. Cellular proliferation assays, luciferase reporter assays, Western blotting, immunoprecipitation, DNA affinity precipitation, and DNA microarray studies were performed. Results*:* Expression of Hoxc6 in cultured human BON1 carcinoid cells enhanced their proliferation, and knock-down of Hoxc6 inhibited their growth. Hoxc6 activated the oncogenic activator protein-1 signaling pathway through a physical interaction with JunD. Mutations in the homeodomain of Hoxc6 blocked this interaction and inhibited proliferation of carcinoid cells. Of note, Hoxc6 induced the expression of genes that characteristically are up-regulated in carcinoid tumors, including neurotensin and connective tissue growth factor. Conclusions*:* A novel molecular pathway has been identified that links Hoxc6 with oncogenic signaling through the activator protein-1 pathway in carcinoid tumorigenesis.

http://www.ncbi.nlm.nih.gov/pubmed/18719002

Gastrin increases mcl-1 expression in type I gastric carcinoid tumors and a gastric epithelial cell line that expresses the CCK-2 receptor.

Citation

American Journal of Physiology. Gastrointestinal & Liver Physiology, 2008, 295(4): G798-G805.

Authors

Pritchard, D.M., Berry, D., Przemeck, S.M., Campbell, F., Edwards, S. W., & Varro, A.

Abstract

Elevated serum concentrations of the hormone gastrin are associated with the development of gastric carcinoid tumors, but the mechanisms of tumor development are not fully understood. We hypothesized that the antiapoptotic effects of gastrin may be implicated and have

therefore investigated the role of antiapoptotic members of the bcl-2 family of proteins. AGS-G(R) human gastric carcinoma cells stably transfected with the CCK-2 receptor were used to assess changes in the expression of bcl-2 family members following gastrin treatment and the function of mcl-1 during apoptosis was investigated by use of small-interfering RNA (siRNA). Treatment of AGS-G(R) cells with 10 nM gastrin for 6 h caused maximally increased mcl-1 protein abundance. Gastrin-induced mcl-1 expression was inhibited by the transcription inhibitor actinomycin D and by the protein synthesis inhibitor cycloheximide. Downstream signaling of mcl-1 expression occurred via the CCK-2 receptor, protein kinase C, and MAP kinase pathways, but not via PI 3-kinase. Transfection with mcl-1 siRNA significantly suppressed mcl-1 protein expression and abolished the antiapoptotic effects of gastrin on serum starvation-induced apoptosis. Mcl-1 protein expression was also specifically increased in the type I enterochromaffin-like cell carcinoid tumors of 10 patients with autoimmune atrophic gastritis and hypergastrinemia. Gastrin therefore signals via the CCK-2 receptor, protein kinase C, and MAP kinase to induce expression of antiapoptotic mcl-1 in AGS-G(R) cells, and mcl-1 expression is also increased in human hypergastrinemia-associated type I gastric carcinoid tumors. Gastrin-induced mcl-1 expression may therefore be an important mechanism contributing toward type I gastric carcinoid development.

http://www.ncbi.nlm.nih.gov/pubmed/17483816

Hypomethylation of LINE-1 and Alu in well-differentiated neuroendocrine tumors (pancreatic endocrine tumors and carcinoid tumors).

Citation

Modern Pathology, 2007, 20(7): 802-810.

Authors

Cho, I.S., Estecio, M.R., Nagano, Y., Kim Do, H., White, J.A., Yao, J.C., & Rashid, A.

Abstract

Neuroendocrine tumors including carcinoid tumors and pancreatic endocrine tumors are uncommon, and the genetic alterations in these indolent tumors are not well characterized. We studied global hypomethylation by analyzing long interspersed nucleotide elements (LINE)-1 and Alu methylation using pyrosequencing in 35 neuroendocrine tumors and corresponding normal tissue. The tumor samples were less methylated than normal tissue at LINE-1 (P=0.04) and Alu (P=0.001). The mean relative tumor hypomethylation (difference in methylation between normal tissue and in tumor) was 11.5+/-10.0 for LINE-1 and 5.8+/-6.4 for Alu, and were correlated with each other (correlation coefficient 0.6, P=0.001). Relative tumor hypomethylation of LINE-1 was higher in ileal carcinoid tumors than in non-ileal carcinoid tumors and pancreatic endocrine tumors (P=0.047), and tumors with lymph node metastasis (P=0.02), chromosome 18 loss (P=0.001) and RAS-association domain family 1, isoform A gene methylation (P=0.02). Alu methylation in tumors was inversely correlated with methylation of O(6)-methyl-guanine methyltransferase gene (P=0.02). Our study shows that hypomethylation is more common in carcinoid tumors than in pancreatic endocrine tumors and is associated with clinicopathologic features, and genetic and epigenetic alterations in these tumors, including lymph node metastasis.

http://www.ncbi.nlm.nih.gov/pubmed/17950274

IL-6-174 C/G polymorphism in the gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Citation

Experimental and Molecular Pathology, 2007, 83(3): 474-479.

Authors

Berković, M.C., Jokić, M., Marout, J., Radosević, S., Zjacić-Rotkvić, V., & Kapitanović, S.

Abstract
IL-6 is a pleiotropic cytokine with still controversial role in tumorigenesis of different cancer types. Its promoter SNP-174 C/G is associated with increased IL-6 transcription and in some tumor types with elevated IL-6 serum levels. The role of IL-6 polymorphisms and IL-6 serum values and their correlation in the gastroenteropancreatic neuroendocrine tumors is lacking. We investigated for the first time frequencies of IL-6-174 genotypes in 80 GEP-NET patients and 162 age- and sex-matched healthy controls, serum values of IL-6 in GEP-NET patients and their correlation with IL-6-174 genotypes. To analyze IL6-174 C/G polymorphism PCR-NlaIII RFLP method was used, and serum levels were measured on Immulite analyzer by enzymatic solid-phase chemiluminescent immunometric method. Serum IL-6 values were elevated (>5.9 pg/ml) in 36.8% GEP-NET patients. Differences in genotypes distribution between patients and healthy controls as well as between patients with gastrointestinal and pancreatic neuroendocrine tumors (PETs) and functioning and nonfunctioning PETs were tested by chi(2) test and Fisher's Exact test. Analysis of variance (ANOVA with proc GLM in SAS/Stat) was performed for the group comparison. Level of significance was alpha=0.05. Patients with nonfunctioning PETs had only high expression IL-6-174 CG and GG genotypes and according to genotypes differed significantly (p=0.0289) from functioning PETs. High serum IL-6 values in all GEP-NET patients correlated significantly with GG IL-6-174 genotype (p=0.0139). Nonfunctioning PET patients had significantly (p=0.000777) higher IL-6 serum values in comparison to patients with functioning PETs and gastrointestinal NETs. Serum IL-6 values correlated significantly with IL-6-174 genotypes in nonfunctioning PETs and gastrointestinal NETs (p<0.05), but not in functioning PETs.

http://www.ncbi.nlm.nih.gov/pubmed/17342373

HER2 expression in gastrointestinal carcinoid tumors: high in intestinal but not in gastric tumors.

Citation
Surgery Today, 2007, 37(3): 270-271.

Authors

Yamaguchi, M., Hirose, K., & Hirai, N.

Abstract
We investigated HER2 expression immunohistochemically in 12 patients with a gastrointestinal (GI) carcinoid tumor. The tumors were located in the stomach in three patients, the duodenum in four, the vermiform appendix in one, and the rectum in four. HER2 was highly expressed in the nine intestinal, but not in the three gastric carcinoid tumors. These findings suggest that HER2 might be highly expressed in intestinal, but not in gastric, carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/16465412

Microsatellite instability and loss of heterozygosity at the MEN1 locus in lung carcinoid tumors: a novel approach using real-time PCR with melting curve analysis in histopathologic material.

Citation
Oncology Reports, 2006, 15(3): 557-564.

Authors
Vageli, D., Daniil, Z., Dahabreh, J., Karagianni, E., Liloglou, T., Koukoulis, G., & Gourgoulainis, K.

Abstract
The possible causes and genetic mechanisms of pulmonary carcinoid tumor development are unclear. In this study, we examined genetic alterations at the MEN1 locus in archival material from 15 pulmonary carcinoids. We employed, for the first time in this setting, real-time PCR with melting curve analysis in order to identify loss of heterozygosity (LOH) or microsatellite instability (MI) in two polymorphic markers (PYGM, D11S449) at the MEN1 locus and one additional marker (D11S906) of a putative oncosuppressive region distal to the MEN1 gene. Sequencing data were available in a selected subset of tumors in order to verify the reliability of real-time PCR analysis. We observed LOH at PYGM in 38% of the cases and MI in 13.3% of the cases. Our data indicate that real-time PCR with melting curve analysis is a reliable technique for LOH and MI detection and indicate that genetic errors at the MEN1 locus but also distal to it may be involved in the development of sporadic pulmonary carcinoid tumors.

http://cme.medscape.com/medline/abstract/16424981

The role of genetic markers--NAP1L1, MAGE-D2, and MTA1--in defining small-intestinal carcinoid neoplasia.

Citation
Annals of Surgical Oncology, 2006, 13(2): 253-262.

Authors
Kidd, M., Modlin, I. M., Mane, S.M., Camp, R. L., Eick, G., & Latich, I.

Abstract
BACKGROUND: Standard clinical and immunohistochemical methods cannot reliably determine whether a small intestinal carcinoid (SIC) is indolent or aggressive. We hypothesized that carcinoid malignancy could be defined by using quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) and immunohistochemical approaches that evaluate potential marker genes. METHODS: Candidate marker gene expression (nucleosome assembly protein 1-like 1 [NAP1L1], melanoma antigen D2 [MAGE-D2], and metastasis-associated protein 1 [MTA1]) identified by Affymetrix transcriptional profiling was examined by QRT-PCR in SIC, liver, and lymph node (LN) metastases, colorectal carcinomas, and healthy tissues. Immunohistochemical expression levels of MTA1 were analyzed quantitatively by a novel automated quantitative analysis in a tissue microarray of 102 gastrointestinal carcinoids and in a breast/prostate carcinoma array. RESULTS: Affymetrix transcriptional profiling identified three potentially useful malignancy-marker genes (out of 1709 significantly altered genes). By QRT-PCR, NAP1L1 was significantly ($P < .03$) overexpressed in SIC compared with colorectal carcinomas and healthy tissue. Increased levels ($P < .05$) were identified in both liver and LN metastases. Levels in colorectal carcinomas were the same as in healthy mucosa. MAGE-D2 and MTA1 were increased ($P < .05$) in primary tumors and metastases and overexpressed in carcinomas. Automated quantitative analysis demonstrated the highest levels of MTA1 immunostaining in malignant primary SICs and in metastases to the liver and LN. These were significantly increased ($P < .02$) compared with nonmetastatic primary tumors. MTA1 was overexpressed in breast and prostate carcinomas ($P < .05$). CONCLUSIONS: SICs overexpress the neoplasia-related genes NAP1L1 (mitotic regulation), MAGE-D2 (adhesion), and MTA1 (estrogen antagonism). The

ability to determine the malignant potential of these tumors and their propensity to metastasize provides a biological rationale for the management of carcinoids and may have prognostic utility.

http://www.ncbi.nlm.nih.gov/pubmed/17009161

Nuclear translocation of beta-catenin protein but absence of beta-catenin and APC mutation in gastrointestinal carcinoid tumor.

Citation
Annals of Surgical Oncology, 2006, 13(12): 1604-1609.

Authors
Su, M.C., Wang, C.C., Chen, C.C., Hu, R.H., Wang, T.H., Kao, H.L., Yeng, Y.M., & Yuan, R.H.

Abstract
BACKGROUND: Carcinoid tumors are a group of heterogeneous tumors with neuroendocrine differentiation and are mainly located in the gastrointestinal tract. A high frequency of cytoplasmic accumulation and/or nuclear translocation of beta-catenin with frequent mutations of exon 3 of beta-catenin gene in gastrointestinal carcinoid tumor has been previously described, but the role of Wnt/beta-catenin/APC pathway in the genesis of carcinoid tumor remains largely unknown. METHODS: To further characterize the role of Wnt/beta-catenin/APC pathway, we investigated 91 gastrointestinal carcinoid tumors and, for comparison, 26 extragastrointestinal carcinoid tumors by immunohistochemical detection of beta-catenin protein and direct sequencing of exon 3 of the beta-catenin gene and exon 15 of the APC gene. RESULTS: Cytoplasmic accumulation and/or nuclear translocation of beta-catenin were found in 27 gastrointestinal carcinoid tumors (29.7%) but not in any extragastrointestinal carcinoid tumors. Interestingly, neither beta-catenin nor APC gene mutation was detected in all of the cases with nuclear expression of beta-catenin. CONCLUSIONS: Our results indicate that the role beta-catenin plays in the genesis of gastrointestinal and extragastrointestinal carcinoid tumors is different. Nuclear expression of beta-catenin does not occur in extragastrointestinal carcinoid tumors, and mutation of exon 3 of beta-catenin gene and exon 15 of APC gene does not contribute to the activation of Wnt/beta-catenin/APC pathway in gastrointestinal carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/16258509

Epigenetic alterations in neuroendocrine tumors: methylation of RAS-association domain family 1, isoform A and p16 genes are associated with metastasis.

Citation
Modern Pathology, 2005, 18(12): 1632-1640.

Authors
Liu, L., Broaddus, R.R., Yao, J.C., Xie, S., White, J.A., Wu, T.T., Hamilton, S.R., & Rashid, A.

Abstract
Well-differentiated neuroendocrine tumors including pancreatic endocrine tumors and carcinoid tumors are uncommon neoplasms that have site-specific differences in clinicopathological features, clinical course and genetic alterations. The epigenetic alterations in these tumors are not well characterized. We therefore compared methylation of the RAS-association domain family 1, isoform A (RASSF1A), p14, p16 and O6-methyl-guanine methyltransferase genes in neuroendocrine tumors from 47 patients including 16 pancreatic,

15 nonileal and 16 ileal neuroendocrine tumors. Methylation of the RASSF1A gene was present in 57% of tumors, p14 in 49%, p16 in 26% and O6-methyl-guanine methyltransferase in 13% of tumors. Ileal neuroendocrine tumors lacked methylation of O6-methyl-guanine methyltransferase gene (P = 0.04). RASSF1A methylation was associated with histopathologic type of tumors (P = 0.03) and lymph node metastasis (P = 0.004), and p16 methylation with older patient age (P = 0.002) and liver metastasis (P = 0.04). Two or more genes were methylated in 53% of tumors, one gene was methylated in 30% of tumors, and all four genes were unmethylated in 17% of tumors. Methylation of one or more gene was associated with older age of patients (P = 0.01), and methylation of two or more genes was associated with liver metastasis (P = 0.044). Our study shows that in neuroendocrine tumors epigenetic alterations vary by tumor subsite and clinicopathologic features, including age of onset, histopathologic type and metastasis status.

http://cme.medscape.com/medline/abstract/15920555

Comparison of genetic alterations in neuroendocrine tumors: frequent loss of chromosome 18 in ileal carcinoid tumors.

Citation
Modern Pathology, 2005, 18(8): 1079-1087.

Authors
Wang, G.G., Yao, J.C., Worah, S., White, J. A., Luna, R., Wu, T., Hamilton, S. R., & Rashid, A.

Abstract
Carcinoid tumors and pancreatic endocrine tumors are uncommon neuroendocrine neoplasms, and their genetic alterations are not well characterized. These tumors have site-specific differences in neuroendocrine characteristics, clinical course and genetic alterations. We compared clinicopathological features and loss of heterozygosity of chromosomes 11q, 16q and 18, and BRAF gene mutations in 47 patients with neuroendocrine tumors including 16 with pancreatic endocrine tumors, 15 with nonileal carcinoid tumors and 16 with ileal carcinoid tumors. Patients with carcinoid tumors had more frequent history of alcohol consumption compared to patients with pancreatic endocrine tumors (P=0.02), and patients with ileal carcinoid tumors more frequently had liver metastasis compared to patients with nonileal carcinoid tumors and pancreatic endocrine tumors (P=0.02). Allelic loss of chromosome 11q was present in 21% of tumors, chromosome 16q in 13%, and chromosome 18 in 30%. These alterations differed with the anatomical subsite of tumor: allelic loss of chromosome 18 was present in 69% of ileal carcinoid tumors, 13% of nonileal carcinoid tumors and 6% of pancreatic endocrine tumors (P=0.001). In contrast to pancreatic endocrine tumors and nonileal carcinoid tumors, all 11 ileal tumors with loss of chromosome 18 had complete loss of both chromosomal arms. No BRAF mutations were identified. Complete allelic loss of chromosome 18 was associated with smaller tumor size (P=0.02). Our study indicates that genetic alterations vary by tumor subsite and clinicopathologic features, and ileal carcinoid tumors have distinctive clinicopathologic and genetic profiles.

http://www.ncbi.nlm.nih.gov/pubmed/15578070

Malignancy-associated X chromosome allelic losses in foregut endocrine neoplasms: further evidence from lung tumors.

Citation

Modern Pathology, 2005, 18(6): 795-805.

Authors
D'Adda, T., Bottarelli, L., Azzoni, C., Pizzi, S., Bongiovanni, M., Papotti, M., Pelosi, G., Maisonneuvre, P., Antonetti, T., Rindi, G., & Bordi, C.

Abstract
Association of X chromosome allelic losses with tumor malignancy has been identified in foregut but not in midgut endocrine neoplasms. The aim of this study was to investigate the association of deletions on X chromosome with malignancy in lung neuroendocrine tumors, another family of foregut neoplasms comprising four categories with increased malignancy: typical and atypical carcinoids, large cell neuroendocrine and small cell lung carcinomas. To evaluate loss of heterozygosity, DNA extracted from nine typical carcinoids, 17 atypical carcinoids, six large cell neuroendocrine carcinomas and five small cell lung carcinomas was PCR-amplified for 18 microsatellite markers spanning the whole X chromosome. All tissue samples were formalin-fixed and paraffin-embedded. X chromosome losses were absent in typical carcinoids, whereas they were found in nine out of 17 atypical carcinoids and in five out of six large cell neuroendocrine carcinomas (involving 28 and 70% of informative loci, respectively). On the contrary, deletions on X chromosome were an extremely rare event in small cell lung carcinomas. In atypical carcinoids, the presence of losses was associated with larger tumor size, higher pT status and advanced stage. No death occurred in atypical carcinoid patients without deletions on X chromosome, whereas all atypical carcinoid patients who had died from disease showed allelic losses. In conclusion, X chromosome allelic losses, absent in benign 'typical' carcinoids, progressively increased in frequency from intermediate-grade 'atypical' carcinoids to high-grade large cell neuroendocrine carcinomas. These results extend the association of deletions on X chromosome with malignancy, already demonstrated in other foregut endocrine neoplasms, to lung neuroendocrine tumors. The absence of X chromosome allelic losses in small cell lung carcinomas underlines a striking difference from large cell neuroendocrine carcinomas, possibly linked to different pathogenetic mechanisms of these two highly aggressive neuroendocrine lung tumors.

http://www.ncbi.nlm.nih.gov/pubmed/12875635

Genetic alteration in carcinoid tumors of the lung.

Citation
Annals of Thoracic & Cardiovascular Surgery, 2003, 9(3): 149-154.

Authors Sugio, K., Osaki, T., Oyama, T., Takenoyama, M., Hanagiri, T., Morita, M., Yamazaki, K., Nagashima, A., Maehara, Y., & Yasumoto, K.

Abstract
Surgically resected specimens of 13 carcinoid tumors of the lung including nine typical carcinoids and four atypical carcinoids, and eight salivary gland type carcinomas (six mucoepidermoid carcinomas and two adenoid cystic carcinomas) were analyzed regarding p53 expression, loss of heterozygosity (LOH) in chromosome 3p, 9p, and K-ras mutation. The overexpression of p53 was identified in four atypical carcinoid tumors, one mucoepidermoid carcinoma, and one adenoid cystic carcinoma, however, none of typical carcinoids showed p53 immunoreactivity. LOH in 3p14 was demonstrated in three of seven informative cases in all tumors. LOH in 9p was demonstrated in two of five informative cases in all tumors. Two of three cases with LOH at 3p14 had a poor prognosis, one of which also had LOH at 9p. No

mutation of the K-ras gene was observed in any of these tumors. These data thus indicate that p53 overexpression might distinguish atypical carcinoid tumors from typical tumors and might therefore be useful as an adjunct modality in the differential diagnosis of pulmonary carcinoid tumors. The presence of LOH at 3p14 or 9p may thus help to identify lung cancer patients with a poor prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/11247899

Analysis of sporadic neuroendocrine tumours of the enteropancreatic system by comparative genomic hybridisation.

Citation
Gut, 2001, 48(4): 536-541.

Authors
Tönnies, H., Toliat, M.R., Ramel, C., Pape, U.F., Neitzel, H., Berger, W., & Wiedenmann, B.

Abstract
BACKGROUND: Chromosomal instability is observed in a wide spectrum of human cancer syndromes. However, to date, little is known of the characteristic genetic changes in sporadic neuroendocrine tumours of the gastroenteropancreatic system. AIMS AND METHOD: We have studied copy number aberrations (CNAs) in 26 sporadic neuroendocrine tumours of the enteropancreatic system (12 foregut and 14 midgut tumours) by comparative genomic hybridisation (CGH), allowing simultaneous evaluation of the entire tumour genome. RESULTS: Nearly all tumours (25/26; that is, 96%) showed chromosomal imbalances, including full chromosomal aneuploidies, losses and gains of chromosome arms, interstitial deletions, and amplifications. Whereas gains of chromosomes 4, 5, and 19 were found in both foregut and midgut tumours, gains of chromosomes 20q (58%), 19 (50%), as well as 17p (50%), and partial losses of chromosomes 1p (42%), 2q (42%), 3p, 4q, and 6q (25% each) were frequently observed only in foregut tumours. In contrast, midgut tumours displayed less CNAs. Gains were detected for chromosomes 17q and 19p (57%). Most frequent losses affected chromosomes 18 (43%) and 9p (21%). CONCLUSIONS: The results of our CGH analyses revealed new distinct candidate regions in the human genome associated with sporadic neuroendocrine tumours. Some of the genetic alterations were shared by foregut and midgut tumours while others discriminated between the two groups. Thus our results allude to the involvement of identical as well as discriminative genetic loci in tumorigenesis and progression of neuroendocrine neoplasms of the foregut and midgut. Based on these findings potential new candidate genes will be discussed.

http://www.ncbi.nlm.nih.gov/pubmed/11337378

Comparative genomic hybridization identifies loss of 18q22-qter as an early and specific event in tumorigenesis of midgut carcinoids.

Citation
American Journal of Pathology, 2001, 158(5): 1803-1808.

Authors
Kytölä, S., Höög, A., Nord, B., Cedermark, B., Frisk, T,, Larsson, C., & Kjellman, M.

Abstract
Carcinoid tumors are rare neuroendocrine tumors occurring in the lung or in the digestive

tract where they are further subclassified as foregut, midgut, or hindgut carcinoids. To gain a better understanding of the genetic basis of the different types of carcinoid tumors, we have characterized numerical imbalances in a series of midgut carcinoids, and compared the results to previous findings in carcinoids from the lung. Numerical imbalances were revealed in 16 of the 18 tumors, and the most commonly detected aberrations were losses of 18q22-qter (67%), 11q22-q23 (33%), and 16q21-qter (22%), and gain of 4p14-qter (22%). The total number of alterations found in the metastases was significantly higher than in the primary tumors, indicating the accumulation of acquired genetic changes in the tumor progression. Losses of 18q and 11q were present both in primary tumors and metastases, whereas loss of 16q and gain of 4 were only detected in metastases. Furthermore, the pattern of comparative genomic hybridization alterations varied depending on the total number of detected alterations. Taken together, the findings would suggest a progression of numerical imbalances, in which loss of 18q and 11q represent early events, and loss of 16q and gain of 4p are late events in the tumor progression of midgut carcinoids. When compared to previously published comparative genomic hybridization abnormalities in lung carcinoids, loss of 11q was found to occur in both tumor types, whereas loss of 18q and 16q and gain of 4 were not revealed in lung carcinoids. The results indicate that inactivation of a putative tumor suppressor gene in 18q22-qter represents a frequent and early event that is specific for the development of midgut carcinoids.

http://cme.medscape.com/medline/abstract/11073802

Genomic alterations in well-differentiated gastrointestinal and bronchial neuroendocrine tumors (carcinoids): marked differences indicating diversity in molecular pathogenesis.

Citation
American Journal of Pathology, 2000, 157(5): 1431-1438.

Authors
Zhao, J., de Krijger., R. R., Meier, D., Speel, E. J., Saremaslani, P., Muletta-Feurer, S., Matter, C., Roth, J., Heitz, P.U., & Komminoth, P.

Abstract
Neuroendocrine tumors (carcinoids) are a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system. Genetic changes underlying their tumorigenesis are primarily unknown. We used comparative genomic hybridization to screen 32 well-differentiated neuroendocrine tumors (21 gastrointestinal and 11 bronchial) and three associated metastases for genomic alterations. There were striking differences of genomic imbalances between the two subgroups of neuroendocrine tumors. Losses of chromosome 18q and 18p were shown in eight (38%) and seven (33%), respectively, out of 21 gastrointestinal tumors and in none of the 11 bronchial tumors. Conversely, deletions of 11q occurred in four of 11 (36%) bronchial tumors but only in one gastrointestinal tumor. These comparative genomic hybridization findings were confirmed by interphase cytogenetics. Our data indicate that neuroendocrine tumors of the two subgroups develop via different molecular pathways. Inactivation of one or several tumor suppressor genes on chromosome 18 may be important for the biological behavior of gastrointestinal tumors, whereas gene inactivation on 11q seems to be associated with tumor development of the bronchi.

http://www.ncbi.nlm.nih.gov/pubmed/10969809

Insulin-like growth factor-I is an autocrine regulator of chromogranin A

secretion and growth in human neuroendocrine tumor cells.

Citation
Cancer Research, 2000, 60(16): 4573-4581

Authors
Von Wichert, G., Jehle, P. M., Hoeflich, A., Koschnick, S., Dralle, H., Wolf, E., Wiedenmann, B., Boehm, B.O., Adler, G., & Seufferlin T.

Abstract
Carcinoid tumors are predominantly found in the gastrointestinal tract and are characterized by hypersecretion of various substances, including bioamines and neuropeptides, leading to functional tumor disease. Here, we demonstrate that human BON carcinoid tumor cells express functionally active insulin-like growth factor-I (IGF-I) receptors and secrete IGF-I, suggesting an autocrine action of this growth factor. The IGF-I receptor was functionally active. IGF-I stimulated phosphatidylinositol 3-kinase (PI3-kinase), p70 S6 kinase (p70s6k), and extracellular signal-regulated kinase 2 activity in BON cells. Furthermore, immunoneutralization of endogenously released IGF-I markedly reduced the high basal activity of p70s6k and extracellular signal-regulated kinase 2 in serum-starved BON cells. Exogenously added IGF-I induced a marked increase in chromogranin A secretion, a marker protein for neuroendocrine secretion, by a process that was largely dependent on PI3-kinase activity. In addition, immunoneutralization of endogenously released IGF-I markedly reduced basal chromogranin A release by BON cells. Thus, the autocrine IGF-I loop regulates basal neuroendocrine secretion in BON cells. Next, we investigated the role of IGF-I as a growth promoting agent for BON cells. Our data demonstrate that IGF-I stimulates anchorage-dependent and anchorage-independent growth of BON cells by a pathway that involves PI3-kinase, mammalian target of rapamycin/p70s6k, and mitogen-activated protein kinase kinase 1 activity. Interestingly, mitogen-activated protein kinase kinase 1 activity was less important for anchorage-independent growth of BON cells. Endogenously released IGF-I was found to be largely responsible for autonomous growth of BON cells in serum-free medium and for the constitutive expression of cyclin D1 in these cells. In conclusion, IGF-I is a major autocrine regulator of neuroendocrine secretion and growth of human BON neuroendocrine tumor cells. Because our data also demonstrate that a significant proportion of neuroendocrine tumors express the IGF-I receptor and its ligand, interference with this pathway could be useful in the treatment of hypersecretion syndromes and growth of human neuroendocrine tumors.

CLASSIFICATION

HISTOLGY

http://www.ncbi.nlm.nih.gov/pubmed/16183524

Epidemiology, tumour biology and histopathological classification of neuroendocrine tumours of the gastrointestinal tract.

Citation
Best Practice & Research in Clinical Gastroenterology, 2005, 19(4): 507-517.

Authors
Klöppel, G., & Anlauf, M.

Abstract

The diffuse neuroendocrine cell gives rise to a heterogeneous population of tumours which differ in their morphological and functional features. The term 'carcinoid', although well established in medical terminology, is therefore no longer adequate to cover the entire spectrum of neuroendocrine neoplasms. Here we use the term neuroendocrine tumours (NET), which was suggested in the WHO classification of 2000, and review the most important NET entities that are currently recognised in the gastrointestinal tract, highlighting their distinguishing features.

http://annonc.oxfordjournals.org/content/16/8/1374.full

Is the new WHO classification of neuroendocrine tumours useful for selecting an appropriate treatment?

Citation
Annals of Oncology, 2005, 16(8): 1374-1380.

Authors
Bajetta, E., Catena, L., Procopio, G., Bichisao, E., Ferrari, L., Della Torre, S., De Dosso, S., Iacobelli, S., Buzzoni, R., Mariani, L., & Rosai, J.

Abstract
Background: Neuroendocrine tumours (NETs) are a rare and heterogeneous group of neoplasms. The most recent WHO classification provides clinical tools and indications to make the diagnosis and to suggest the correct treatment in different subgroups of patients. The aim of this trial was to apply the new classification criteria in clinical practice and, accordingly, to choose the most appropriate treatment.

Patients and methods: Thirty-one evaluable patients, not previously treated, classified as advanced well differentiated NETs according to the new classification, were given long-acting release octreotide 30 mg every 28 days until evidence of disease progression. The treatment activity was evaluated according to objective, biochemical and symptomatic responses. Safety and tolerability were also assessed.

Results: Two partial objective tumour responses were obtained (6%), stabilization occurred in 16 patients (52%) and 95% of patients had a disease stabilisation lasting ≥6 months. However, eight patients showed rapid disease progression within 6 months of therapy and six patients after 6 months. Biochemical responses, evaluated by changes in serum chromogranin A levels were reported in 20/24 patients (83%). Symptomatic responses were observed in 6/14 patients (43%): a complete syndrome remission in one patient, partial syndrome remission in five patients, no change in four patients and progressive disease in four patients. The median overall survival was not reached, and the median time to disease progression was 18 months (range 1–49 months). The treatment was well tolerated, no severe adverse events were observed and no patient withdrew from the study because of adverse events. Conclusions: The WHO classification enables identification of low-grade NET patients who may be suitable for hormonal treatment. Octreotide LAR was seen to be effective in controlling the disease and was well tolerated. However, eight patients failed to respond to the treatment, despite histological evidence of a well differentiated tumour according to the new classification. This suggests that further histological examination should be carried out, especially in patients with visceral metastases and a short disease-free interval.

http://cme.medscape.com/medline/abstract/15153416

The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification.

Citation
Annals of the New York Academy of Science, 2004, 1014: 13-27.

Authors
Klöppel, G., Perren, A., & Heitz. P.U.

Abstract
Although well established in medical terminology, the term carcinoid is no longer adequate to cover the entire morphological and biological spectrum of neoplasms of the disseminated neuroendocrine cell system. Therefore, instead of carcinoid, the WHO classification published in 2000 uses the general terms neuroendocrine tumor and neuroendocrine carcinoma. In this review a classification of gastroenteropancreatic neuroendocrine tumors based on the WHO criteria is described. We also classify and comment on the most important tumor entities. On the basis of localization and of various morphological and biological criteria, we distinguish between benign neuroendocrine tumors, tumors with uncertain malignant potential, and tumors showing low-grade and high-grade malignancy.

http://www.ncbi.nlm.nih.gov/pubmed/12454818
Classification of low-grade neuroendocrine tumors of midgut and unknown origin.
Citation
Human Pathology, 2002, 33(11):1126-1132.

Authors
Van Eeden, S., Quaedvlieg, P.F., Taal, B.G., Offerhaus, G.J., Lamers, G.B., & Van Velthuysen, M.L.

Abstract
Metastasized neuroendocrine tumors of the gastrointestinal tract and of unknown origin show a highly variable clinical course. Within this group, low-grade and high-grade malignant tumors can be recognized based on the revised classification of neuroendocrine tumors of the lung, pancreas, and gut published by Capella et al in 1995. The present study investigated whether fine-tuning the prediction of prognosis was possible by dividing the group of low-grade malignant tumors of the midgut and of unknown origin into typical and atypical carcinoids by grading them according to the World Health Organization (WHO) classification criteria for neuroendocrine tumors of the lung. Moreover, the prognostic value of immunohistochemical stainings and clinical parameters was evaluated. The study group comprised patients diagnosed between 1983 and 1999 with liver metastases of a neuroendocrine tumor of the midgut n = 40) or of unknown origin (n = 16). As a control for the consistency of grading, 10 patients with metastasized neuroendocrine tumors of the lung also were evaluated. Immunohistochemical stainings for chromogranin A, synaptophysin, Leu 7/CD57, neural cell adhesion molecule/CD56, cytokeratin 8, bcl-2, p53, ki67, and HER2/neu were performed. The clinical parameters age, gender, urinary 5-HIAA level, and presence or absence of the carcinoid syndrome were evaluated. Tumors of the midgut and of unknown origin were evaluated together, because they were clinically similar. In this group of 56 patients, both the Capella and the WHO classification systems recognized the high-grade malignant tumors with a bad prognosis. When the low-grade malignant tumors (Capella) were divided into typical and atypical carcinoids (WHO), no difference in survival was observed, but when the dichotomy into typical and atypical was based on mitotic count alone, the difference became borderline significant (P =.072). Of the immunohistochemical stainings used, synaptophysin, cytokeratin 8, and ki67 had limited prognostic value. Age above 60 was

the only clinical parameter of unfavorable prognostic significance. We conclude that high-grade malignant neuroendocrine tumors of the midgut and of unknown origin are recognized by both the Capella classification and the WHO classification of neuroendocrine tumors of the lung. Further subdividing low-grade malignant tumors at this location appears to be of less value than in the lung, but assessing the mitotic activity of these tumors might be of prognostic value

http://www.ncbi.nlm.nih.gov/pubmed/7697211

Revised classification of neuroendocrine tumours of the lung, pancreas and gut.

Citation
Virchows Archiv, 1995, 425(6): 547-560.

Authors
Capella, C., Heitz, P.U., Höfler, H., Solcia, E., & Klöppel, G.

Abstract
In this article new classifications of the neuroendocrine tumours of the lung, pancreas and gut are proposed. These classifications use a common frame work and attempt to consider the morphological, functional as well as biological features of the tumours.

EMBRYOLOGICAL ORIGINS

http://www.ncbi.nlm.nih.gov/pubmed/140

The classification of carcinoid tumours.
Citation
Lancet, 1963, 1: 238–239.
Authors
Williams, E.D., & Sandler, M.

Abstract
Carcinoid tumours arising from the bronchus, stomach, and pancreas form a distinct group and these can be conveniently separated from small intestinal carcinoids on an embryological basis: bronchus stomach, and pancreas are all foregut derivatives. The small intestine from the mid-duodenum, together with the caecum and colon as far as the mid transverse colon from the midgut. The hindgut, comprising descending colon and rectum gives rise to a group of carcinoid tumours which are often trabecular in pattern an infrequently argentaffin.

SITE SPECIFIC

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/10998653
Gastrointestinal carcinoids: characterization by site of origin and hormone production.
Citation
Annals of Surgery, 2000, 232(4): 549-556.

Authors
Onaitis, M.W., Kirshbom, P.M., Hayward, T.Z., Quayle, F.J., Feldman, J.M., Seigler, H.F., & Tyler, D.S.

Abstract
OBJECTIVE: To describe a large series of patients with carcinoid tumors in terms of presenting symptoms, hormonal data, stage at diagnosis, pathologic features, and survival. SUMMARY BACKGROUND DATA: Published series have described significant prognostic features of carcinoid tumors as site of origin, age, sex, stage at diagnosis, presence of high hormone levels, and increased T stage. Of these, stage at diagnosis and T stage seem to emerge most often as independent predictors of survival in multivariate analyses. Of carcinoid tumors, those arising from a midgut location have higher levels of serotonin and serotonin breakdown products, as well as more frequent metastatic disease at presentation, than those arising from either foregut or hindgut locations. METHODS: A prospective database of carcinoid patients seen at Duke University Medical Center was kept from 1970 to the present. Retrospective medical record review was performed on this database to record presenting symptoms, hormonal data, pathologic features, and survival. Statistical methods included analysis of variance, Kaplan-Meier analysis, and Mantel-Cox proportional hazard survival analysis, with P <.05 considered significant for all tests. RESULTS: Carcinoids arising in different locations had different presentations: rectal carcinoids presented significantly more often with gastrointestinal bleeding, and midgut carcinoids presented significantly more often with flushing, diarrhea, and the carcinoid syndrome. Patients with midgut tumors had significantly higher levels of serotonin and serotonin breakdown products, corresponding to higher metastatic tumor burdens. Although age, stage, region of origin, and urinary level of 5-hydroxyindoleacetic acid predicted survival by univariate analysis, only the latter three were independent predictors of survival by multivariate analysis. Of the patients with metastatic disease at diagnosis, those with midgut tumors had better survival than those with foregut or hindgut tumors. CONCLUSIONS: Although region of origin is certainly an important factor in determination of prognosis, stage of disease at presentation is more predictive of survival. Pancreatic and midgut carcinoids are metastatic at diagnosis more often than those arising in other locations, leading to a worse overall prognosis. Among patients with distant metastases, patients with midgut primary tumors have improved survival despite increased hormone production compared with patients with tumors arising in other primary sites.

SITE ORIGIN
http://www.ncbi.nlm.nih.gov/pubmed/20485130
Thymic neuroendocrine tumors: a SEER database analysis of 160 patients.
Citation
Annals of Surgery, 2010, 251(6): 1117-1121

Authors
Gaur, P., Leary, C., & Yao, J.C.

Abstract
INTRODUCTION: Thymic neuroendocrine tumors (NETs) are uncommon but malignant tumors of the thymus gland that are usually associated with systemic symptoms due to hypersecretion of biogenic amines from metastatic lesions. Due to the limited number of studies in the literature, very little is known about progress or trends made in the treatment and survival of patients with thymic NET. METHODS: We reviewed 160 patients diagnosed with thymic NET in the SEER database to evaluate patient demographics and their clinical

course. Specifically, we evaluated the role of surgery and adjuvant radiation in the SEER cohort. We also performed univariable and multivariate Cox proportional hazard modeling of standard prognostic factors. RESULTS: According to our results, thymic NETs afflict males and whites primarily. As expected, advanced stage correlates with poorer long-term survival (P = 0.009) and those patients who undergo surgery do better than their counterpart (P = 0.005). We did not observe any survival benefit for radiation delivered as a part of primary therapy. Univariable and multivariate analyses demonstrated that tumor stage (P = 0.009), grade (P = 0.002), surgical resection (P = 0.005), and tumor size (P = 0.02) correlated with overall survival. CONCLUSIONS: Our study demonstrates that surgery continues to be the mainstay of treatment, and that there is a need to define a staging system for thymic NETs that can perhaps allow clinicians to formulate better therapeutic strategies for such patients.

http://www.ncbi.nlm.nih.gov/pubmed/10884805

Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases.

Citation
American Journal of Clinical Pathology, 2000, 114(1): 100-110.

Authors
Moran, C.A., & Suster, S.

Abstract
We studied 80 cases of primary thymic neuroendocrine carcinomas. Most patients had symptoms; approximately one third were asymptomatic. All cases were treated by surgical excision. The tumors were divided according to histopathologic features into low- (n = 29), intermediate- (n = 36), and high-grade (n = 15) types. The tumors displayed a variegated histologic appearance and unusual cytologic features. Some cases showed transition from low to high grade within the same tumor mass. Mitotic activity ranged from fewer than 3 to more than 10 mitotic figures per 10 high-power fields, and most tumors displayed marked cellular atypia and areas of necrosis. In 73 patients, the tumor was confined to the anterior mediastinum. Positive immunohistochemical reaction was observed using antibodies for CAM 5.2 low-molecular-weight cytokeratins, broad-spectrum keratin, chromogranin, synaptophysin, and Leu-7. The clinical follow-up obtained in 50 patients correlated well with tumor differentiation. Therefore, the behavior of these tumors seems to correlate with histologic grade, which seems directly proportional to degree of differentiation. We propose replacing the term thymic carcinoid with thymic neuroendocrine carcinoma, which better reflects the aggressive biologic behavior of these tumors in the mediastinal location.

http://www3.interscience.wiley.com/journal/122468252/abstract

Pulmonary neuroendocrine/carcinoid tumors

Citation
Cancer, 2009, 115(19): 4434-4441.

Authors
Bertino, E.M., Confer, P.D., Colonna, J.E., Ross, P., & Otterson, G.A.

Abstract
Neuroendocrine tumors are a unique malignant neoplasm that can arise from the respiratory

tree. Although well-differentiated bronchial neuroendocrine tumors (also called carcinoid tumors) are reported to account for approximately 25% of all neuroendocrine tumors, they represent only 1% to 2% of all lung cancers. The epidemiology, clinical behavior, and treatment of neuroendocrine carcinoid tumors differ significantly from other lung malignancies. In this article the recent data regarding these tumors were reviewed with attention to the treatment modalities used. Although conventional cytotoxic therapy has not been reported to demonstrate much promise in this entity over the past 4 decades, newer molecular targeted agents including those that targeted angiogenesis and the mammalian target of rapamycin (mTOR) pathway have shown encouraging results in early phase trials for advanced carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/12839856

Update in pulmonary carcinoid tumors: a review article.

Citation
Annals of Surgical Oncology, 2003, 10(6): 697-704.

Authors
Hage, R., de la Riviére, A.B., Seldenrijk, C.A., & van den Bosch, J.M.

Abstract
Pulmonary carcinoid tumors are neuroendocrine malignant tumors that make up 1% to 2% of all lung tumors. According to histopathologic criteria, carcinoids can be divided into typical (TC) and atypical (AC) carcinoids. Carcinoids can be placed in a spectrum of neuroendocrine tumors, ranging from low-grade malignant TC to intermediate AC to high-grade large-cell neuroendocrine carcinoma and small-cell lung carcinoma. Familial pulmonary carcinoids are rare. The most common symptoms are hemoptysis, cough, recurrent pulmonary infection, fever, chest discomfort and chest pain, unilateral wheezing, and shortness of breath. Paraneoplastic syndromes are rare and include carcinoid syndrome, Cushing's syndrome, and ectopic growth hormone-releasing hormone secretion. The diagnosis is usually established by flexible bronchoscopy and biopsy, although occasionally this can result in severe hemorrhage. Immunoscintigraphy by somatostatin analogs can also be useful in diagnosis. The treatment of choice is surgical resection, and prognosis is relatively good in TC, although it is worse in AC. The role of radiotherapy and chemotherapy as part of multimodality treatment or palliation is still debated.

http://www3.interscience.wiley.com/journal/112688450/abstract?CRETRY=1&SRETRY=0

Gastric carcinoids. An immunohistochemical and clinicopathologic study of 104 patients

Citation
Cancer, 2006, 73(8): 2053-2058.

Authors
Thomas, R. M.., Baybick, J.H., Al M. Elsayed, Al. M., & Sobin, L.H.

Abstract
Background. Gastric carcinoids are uncommon, and are unlike carcinoids at other gastrointestinal sites, clinically and pathologically. Methods. The authors studied specimens from 104 patients with gastric carcinoid, with study emphasis being placed on pathologic

features, immunohistochemistry, clinical associations, and prognostic factors. Results. The average age of the 47 male patients and 57 female patients was 61 years. Twenty-seven patients had chronic atrophic gastritis, 12 had pernicious anemia, and 6 had hypergastrinemia; no patient had carcinoid syndrome. Most of the tumors were confined to the mucosa and submucosa. Lymph node metastases were present in only one patient. The tumors were argyrophilic in 84% and argentaffin in 14%. Chromogranin tested positive in all patients; serotonin was detected in one-third; other hormones were much less common. Gastrin-positive tumors were antral. Of the 62 patients with follow-up, 44 were alive without disease, 4 were alive with disease, and 14 were dead (4 died of carcinoid-related disease). None of the deceased had pernicious anemia or hypergastrinemia. The tumors in patients with a fatal outcome were 2 cm or larger. Conclusion. Gastric carcinoids generally are indolent tumors, particularly when associated with pernicious anemia or hypergastrinemia or when smaller than 2 cm. Chromogranin is the most sensitive marker.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1357706/

Gastric Carcinoids: Biologic Behavior and Prognosis After Differentiated Treatment in Relation to Type.

Citation
Annals of Surgery, 2005, 242(1): 64–73.
Authors
Borch, K., Ahrén, B., Ahlman, H., Falkmer, S., Granérus, G., & Grimelius, L.

Abstract
OBJECTIVE: To analyze tumor biology and the outcome of differentiated treatment in relation to tumor subtype in patients with gastric carcinoid. BACKGROUND: Gastric carcinoids may be subdivided into ECL cell carcinoids (type 1 associated with atrophic gastritis, type 2 associated with gastrinoma, type 3 without predisposing conditions) and miscellaneous types (type 4). The biologic behavior and prognosis vary considerably in relation to type. METHODS: A total of 65 patients from 24 hospitals (51 type 1, 1 type 2, 4 type 3, and 9 type 4) were included. Management recommendations were issued for newly diagnosed cases, that is, endoscopic or surgical treatment of type 1 and 2 carcinoids (including antrectomy to abolish hypergastrinemia) and radical resection for type 3 and 4 carcinoids. RESULTS: Infiltration beyond the submucosa occurred in 9 of 51 type 1, 4 of 4 type 3, and 7 of 9 type 4 carcinoids. Metastases occurred in 4 of 51 type 1 (3 regional lymph nodes, 1 liver), the single type 2 (regional lymph nodes), 3 of 4 type 3 (all liver), and 7 of 9 type 4 carcinoids (all liver). Of the patients with type 1 carcinoid, 3 had no specific treatment, 40 were treated with endoscopic or surgical excision (in 10 cases combined with antrectomy), 7 underwent total gastrectomy, and 1 underwent proximal gastric resection. Radical tumor removal was not possible in 2 of 4 patients with type 3 and 7 of 9 patients with type 4 carcinoid. Five- and 10-year crude survival rates were 96.1% and 73.9% for type 1 (not different from the general population), but only 33.3% and 22.2% for type 4 carcinoids. CONCLUSION: Subtyping of gastric carcinoids is helpful in the prediction of malignant potential and long-term survival and is a guide to management. Long-term survival did not differ from that of the general population regarding type 1 carcinoids but was poor regarding type 4 carcinoids.

http://www.ncbi.nlm.nih.gov/pubmed/20380002

Pathologic research update of colorectal neuroendocrine tumors.

Citation
World Journal of Gastroenterology, 2010, 16(14):1713-1719.

Authors Ni, S.J., Sheng, W.Q., & Du, X.

Abstract
Colorectal neuroendocrine tumors (NETs) originate from neuroendocrine cells in the intestinal tract, and represent a small area within oncology, but one which has provided increasing new data during the past years. Although the World Health Organization has determined clinical and histological features to predict prognosis for such tumors, they may not be valid on an individual basis. We aim to give an overview of the recent findings with regard to pathology, molecular genetics and diagnosis of NETs.

http://www.ncbi.nlm.nih.gov/pubmed/17133089
Large bowel carcinoid tumors.
Citation
Current Opinion in Gastroenterology, 2007, 23(1): 74-78.
Authors
Northrop, J.A., & Lee, J.H.

Abstract
PURPOSE OF REVIEW: Gastrointestinal carcinoids comprise 90% of all carcinoid tumors and all carcinoids have malignant potential. This review focuses on the morphology, prognosis, detection and treatment for appendiceal, colonic and rectal carcinoids. RECENT FINDINGS: Computed tomography exists as an initial examination for the primary carcinoid tumor as well as for metastases. There have, however, been recent developments of newer and more accurate modalities. Octreotide scanning has a sensitivity of primary tumor detection of 90%; additionally, I- or I-meta-iodobenzylguanidine scanning and tracer-specific positron emission tomographic scans have demonstrated encouraging results. Further advancements in treatment with tumor-targeted therapy and biochemical evaluation of carcinoids have shown promise. SUMMARY: The recent progress with scintigraphic and radiologic modalities has provided better means for diagnosis of primary and metastatic carcinoid tumors. These newly discovered diagnostic modalities have been more encouraging than the recent treatment approaches that have been studied with regard to metastatic carcinoids. While surgery remains the mainstay of treatment of nonmetastatic carcinoid, there have been studies for various medical treatments of metastatic disease. Unfortunately, there have been disappointing results with regard to improvement of tumor response and patient survival, but a foundation has been established for future trials employing alternative agents and exploration of combination therapies.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2780103/?tool=pubmed
Carcinoid and Neuroendocrine Tumors of the Colon and Rectum.

Citation
Clinics in Colon & Rectal Surgery, 2006, 19(2): 45–48.

Authors
Chung, T.P., & Hunt, S.R.

Abstract
Carcinoid and neuroendocrine tumors of the colon and rectum arise from the amine precursor uptake and decarboxylation (APUD) cells of the intestine. Carcinoid tumors are most commonly found in the gastrointestinal tract and are located in decreasing order of frequency in appendix, ileum, rectum, stomach, and colon. The vast majority of lesions are asymptomatic and are found incidentally during endoscopy. The management of these lesions depends upon the size of the lesion, involvement of the muscularis, location, and presence of metastatic disease. Small lesions (1 cm) can often be treated locally, either endoscopically or transanally. However, larger lesions (> 2 cm) require a formal oncologic resection. Adjuvant therapy is indicated only for metastatic disease, and admirable advances have been made in the realm of chemotherapy for reduction of disease and palliation of the symptoms of carcinoid syndrome. In this article, we discuss the nature of these interesting and uncommon tumors, clinical presentation, treatment options, and prognosis.

http://www.archivesofpathology.org/doi/full/10.1043/1543-2165-134.6.871

Endocrine Tumors of the Appendix: A Pathologic Review.

Citation
Archives of Pathology & Laboratory Medicine, 2010, 13496): 871-875**.**

Authors
Deschamps, L. & Couvelard, A.

Abstract
Context: Although rare, appendiceal endocrine tumors are the most common neoplasms of the appendix. Pathologic analysis is important for guiding the management of patients. Objective: To provide recent data that focus on the pathology of endocrine tumors of the appendix including classifications and guidelines for patient management. Data Sources.: A review of the recent literature including TNM classifications and patient management guidelines. Conclusions*:* Appendiceal endocrine tumors are separated into 2 main groups: classic endocrine tumors and goblet cell carcinoids. They can be classified according to World Health Organization and TNM classifications. Evaluation of their prognoses and risks of malignancy, according to these classifications, depends on several parameters including tumor size, proliferation rate, and infiltration of appendiceal wall and mesoappendix. Most patients with classic endocrine tumors of the appendix have a favorable prognosis. Indications for postappendectomy, complementary surgery, which are still controversial, especially for tumors between 1 and 2 cm, are presented and discussed. In contrast, in patients presenting with a goblet cell carcinoid, a right hemicolectomy after the initial appendectomy is considered the standard surgical intervention.

http://www.ncbi.nlm.nih.gov/pubmed/16253897

Neuroendocrine tumours (carcinoids) of the appendix.

Citation
Best Practice and Research in Clinical Gastroenterology, 2005, 19(5): 729-738.

Authors
Skinner, B. & Rothmund, M.

Abstract
Neuroendocrine tumours (NETs) of the appendix (formerly 'carcinoids') are rare and are

usually detected incidentally after appendectomy. Histopathologically they derive from a subepithelial cell population, which is different from NETs in other sites. They are preferentially located at the tip of the appendix. Tumours <1 cm hardly ever metastasize and are treated by appendectomy. Tumours >2 cm require right hemicolectomy because of a significant risk of metastatic spread. Treatment for lesions 1-2 cm is controversial and needs further characterization of the tumour (i.e. mesoappendiceal invasion, vascular invasion, mitotic activity, proliferation markers) and careful patient risk evaluation. Goblet-cell carcinoids have features resembling both carcinoid and adenocarcinoma and should be treated by hemicolectomy. Overall prognosis of small appendiceal NET is excellent in all ages.

http://www.ncbi.nlm.nih.gov/pubmed/16104045

Carcinoids of the pancreas: an analysis of 156 cases.

Citation
Cancer, 2005, 104(6): 1180-1187.

Authors
Soga, J.

Abstract
BACKGROUND: The aim of the current study was to clarify the actual clinicopathologic status of extremely rare pancreatic carcinoids. To date, statistical evaluation of such carcinoids has been hampered because an insufficient number of cases has prevented any reliable statistical analyses. METHODS: The Niigata Registry for Gut-Pancreatic Endocrinomas contains a total number of 156 cases of pancreatic carcinoids among 165 endocrinocarcinomas registered worldwide. This figure of 156 cases comprises 144 typical and 12 atypical carcinoids, which were compared statistically with carcinoids in other representative sites, according to various clinicopathologic criteria. RESULTS: Pancreatic carcinoids made up 1.4% of the total number of registered cases (n = 11,343) and were characteristic in the following five ways. 1) They exhibited a high metastatic rate (66.7%), somewhat lower than that for the ileocecum (76.1%), identical to that for the ileum (66.9%), and far higher than that for the total average of 35.7%. 2) They displayed the largest average tumor size (68.6 mm), followed by that for the ovary (68.2 mm), and ileocecum (46.5 mm) against a total average of 30.2 mm. 3) They revealed a relatively high incidence of the carcinoid syndrome (23.3%), almost equal to that for the ileocecum (24.1%), and exceeded by that for the small intestine (35.8%), when compared with that for the total average of 11.0%. 4) They showed a high rate of immunohistochemical detection for serotonin (92.9%), lower than that for the testicle (100.0%), but higher than the total average of 54.9%. 5) Five-year survival rate was extremely low (28.9% +/- 16.7%) compared with those for the appendix (89.7% +/- 2.0%) and the small intestine (82.1% +/- 3.3%). It was noteworthy that silver impregnations in the pancreatic carcinoid series indicated a result identical to that for the total average: Grimelius argyrophilia, 84.8% versus 85.4%; argyrophil cell type, 59.1% versus 58.5%; and argentaffin cell type, 22.7% versus 22.3%. CONCLUSION: It may be said that in the treatment of patients with pancreatic carcinoids, appropriate procedures should be carried out with these distinguishing characteristics always kept in mind.

http://www.ncbi.nlm.nih.gov/pubmed/9629513

Carcinoid tumors of the pancreas. Status report based on two cases and review of the world's literature.

Citation
International Journal of Pancreatology, 1998, 23(2): 153-164.

Authors

Mao, C., el Attar, A., Domenico, D.R., Kim K., & Howard, J.M.

Abstract
CONCLUSION: The diagnosis of a pancreatic carcinoid should be based on the measurement of serotonin in serum or its demonstration in the tumor and/or by the measurement of its derivative (5-HIAA) in urine. Carcinoid of the pancreas is a rare but definite entity; usually having metastasized by the time of diagnosis. The term "serotonin-producing tumor of the pancreas" has been suggested as an alternative designation for "pancreatic carcinoid." BACKGROUND: The literature on carcinoid tumors of the pancreas is confusing because much of it preceded the development of the more specific immunological, chemical and staining techniques currently available. METHODS: 43 case reports were collected from the world's literature, based on a demonstrable pancreatic neuroendocrine tumor plus a positive finding of at least one of the following without another dominant hormone being demonstrated: elevation of 5-Hydroxytryptamine (5-HT) (serotonin) in the serum or detected in tumor tissue, and/or elevation of 5-Hydroxyindole acetic acid (5-HIAA) in the urine. In addition to these two hormone-specific assays, information was collected on the silver-staining properties of the tumor; properties which have traditionally been associated with carcinoid tumors. Positive silver staining in tumor cells (argyrophilic and/or argentaffin reaction) is strongly indicative of the carcinoid tumor but the findings are less specific than the hormone assays and immunohistologic stains. RESULTS: In this review of 43 cases, including two current ones, the pancreatic carcinoid tumor has the following important features: 1. It is a rare tumor that is usually diagnosed late when the tumor is large and has metastasized. Thirty-eight (88.4%) have been malignant. They are, therefore, associated with a high incidence of the "carcinoid syndrome." 2. To date, prognosis in therapy is poor, based on delayed diagnosis, a resultant low incidence of resectability, and an uncertain duration of survival after resection. 3. Pancreatic carcinoid tumors remain difficult to differentiate from other endocrine tumors. The measurement of urinary 5-HIAA excretion or the demonstration of elevated serotonin level in the tumor or in serum is essential to its distinction. Silver staining of the tumor, although of historic importance, has been superceded by the hormone-specific studies. 4. To distinguish it from other endocrine tumors of the pancreas, the terms "pancreatic serotoninoma" or "serotonin-producing tumor of the pancreas" have been suggested as possible alternatives. Its growth characteristics may be related more to its cell of origin than to its extent of hormone secretion. Not all of the tumors result in recognizable hyperserotoninemia.

http://www.ncbi.nlm.nih.gov/pubmed/11144518

Carcinoids of the ovary: an analysis of 329 reported cases.

Citation
Journal of Experimental & Clinical Cancer Research, 2000, 19(3): 271-280.

Authors
Soga, J., Osaka, M., & Yakuwa, Y.

Abstract
This evaluation was undertaken to supply precise and reliable detailed information to

investigators actively working in carcinoid and related gynecological research fields. A statistical evaluation was performed on 329 cases of ovarian carcinoid registered in the Niigata Registry where world-wide information of gut-pancreatic endocrinomas has been maintained by a computer-analyzing system. Cases without individual identification or those recorded in groups were excluded. The evaluation was carried out mainly by a comparison between two groups of cases with cystic teratoma/dermoid (Group A) and those without such lesions (Group B). The former group consisted of 189 cases (57.4%) and the latter of 140 (42.6%). Statistically significant differences between these two groups were recognized in tumor size (44.7 mm vs 89.8 mm), rate of metastases (5.8% vs 22.1%), rate of hepatic involvement (2.1% vs 15.0%), incidence of associated carcinoid syndrome (13.8% vs 22.9%) and 5-year survival rate (93.7% vs 84.0%). Insular type and trabecular type carcinoids were recorded at an almost equal rate of one fourth ranging between 22% and 26% in either group. Another significant difference in the incidence of carcinoid syndrome was evident between the series of insular type and trabecular type carcinoids (38.9% vs 7.8%). The present evaluation on ovarian carcinoids disclosed definite, statistically significant differences in various clinical and pathophysiologic aspects between Group A and Group B, as well as between insular type and trabecular type histologic structures.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WG6-45MH060-6D

Primary Ovarian Carcinoid Tumors

Citation
Gynecologic Oncology, 1996, 61(2): 259-265.

Authors
Davis, P., Hartmann, L.K., Keeney, G.L. & Shapiro, H.

Abstract
Primary ovarian carcinoid tumors were reviewed from Mayo Clinic and Colorado Tumor Registry data. A total of 17 patients with this diagnosis were identified. Histologic analysis of these carcinoid tumors revealed 9 (53%) were insular, 5 (29%) were trabecular, and 4 (26%) were strumal carcinoid with or without a mature dermoid component. There were 11 patients with stage I and 6 patients with stage III or IV disease at diagnosis. Carcinoid syndrome was found in 29% of patients. Pressure or pain with defecation was noted in 41% of cases. Recurrence of tumor occurred in 1 of 11 patients with suspected stage I disease 13 years after initial diagnosis. Overall survival was excellent in the 11 patients whose disease was confined to one ovary (100% 5-year survival), but only 1 of 6 patients survived (33% 5-year survival) if advanced stage at diagnosis. Systemic chemotherapy for advanced disease achieved a complete response in 1 patient and stable disease in another. Although rare, primary ovarian carcinoid tumors treated with surgery alone and found to be confined to the ovary can be expected to have an excellent overall outcome.

http://www.ncbi.nlm.nih.gov/pubmed/15599742

An analysis of rare carcinoid tumors: clarifying these clinical conundrums.

Citation
World Journal of Surgery, 2005, 29(1):92-101.

Authors
Modlin, I.M., Shapiro, M.D., & Kidd, M.

Abstract
Carcinoid tumors are distinct neuroendocrine neoplasms with characteristic histological, clinical, and biological properties. Though commonly associated with the gastrointestinal tract and bronchopulmonary system, a substantial number of these tumors originate in less common anatomical sites and can range from indolent, unrecognized entities to highly active, metastatic secretory tumors. Their presentation within unfamiliar locations often results in clinical confusion, and they persist as unrecognized lesions, subjecting patients to delayed, inappropriate, or ineffective treatment. The authors reviewed 13,715 carcinoid tumors identified by three consecutive registries of the National Cancer Institute (NCI) from 1950 to 1999, focusing on the anatomic sites accounting for less than one percent of all carcinoids. In addition, data from the world's literature published on carcinoid tumors within these particular anatomic locations were then analyzed with respect to incidence, clinical presentation, symptoms, diagnostic evaluation, microscopic and immunohistochemical findings, treatment strategies, and prognosis. The primary organs in which carcinoids are most commonly mistaken for some of the more conspicuous endemic tumors include the esophagus, pancreas, liver, biliary tract, gallbladder, and Meckel's diverticulum, as well as within the pelvic and otolaryngeal organs and the breast. In general, the highest proportion of "rare" carcinoids was identified in the gastrointestinal (GI) tract, with the ovary as the single most affected extra-GI site. Tumors with the worst prognosis were those that involved the pancreas (37.5%: 5-year survival) and those in the cervix (12-33%: 3-year survival). While gastrointestinal carcinoids have become a more recognized entity and thus more amenable to identification, similar lesions are often not considered in other sites and have often either been overlooked or misdiagnosed. Widespread reports of their occurrence in rare locations warrants attention. The diminution of the likelihood of inadvertently neglecting these often benign, indolent neoplasms that are well known to metastasize if unaddressed would represent an important advance. Familiarity with such unusual sites of origin will facilitate appropriate recognition and characterization of such tumors, allowing for timely intervention.

http://www.ncbi.nlm.nih.gov/pubmed/9854584

Carcinoids of unknown origin: comparative analysis with foregut, midgut, and hindgut carcinoids.

Citation
Surgery, 1998, 124(6): 1063-1070.

Authors
Kirshbom, P.M., Kherani, A.R., Onaitis, M.W., Feldman, J.M. & Tyler, D.S.

Abstract
BACKGROUND: Carcinoids are rare neuroendocrine tumors typically arising in the gastrointestinal tract. A significant percentage of these tumors present as metastatic disease of unknown primary site. The aim of this study was to better define the functional and clinical characteristics of carcinoids of unknown primary (CUP) site. METHODS: This study examines the hormonal activity, clinical characteristics, and survival of 434 patients with carcinoids originating in the foregut, midgut, hindgut, or unknown location. The 143 patients with CUP were compared with the other groups with regard to presenting characteristics, diagnostic tests and therapeutic modalities used, hormonal activity, and survival. RESULTS: The hormone levels (urinary 5-hydroxyindoleacetic acid and serotonin, serum and platelet serotonin) of CUP were not significantly different from midgut carcinoids with metastatic disease. Although survival with CUP was shorter than with carcinoids with identified primaries (10-year survivals of 22% vs 62%, 50%, and 48% for foregut, midgut, and hindgut, respectively), the survival curve for CUP was quite similar to that of patients with midgut

carcinoids with distant disease (10-year survival of 22% vs 28%). CONCLUSIONS: CUP are similar to midgut carcinoids presenting with metastatic disease with regard to hormone production and survival. Like other carcinoids, CUP can be an indolent disease process with gradual progression over decades.

CLINICAL PRESENTATION

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/15180952
The diagnosis and medical management of advanced neuroendocrine tumors
Citation
Endocrine Reviews, 2004, 25: 458-511.
Authors
Kaltsas, G.A., Besser, G.M., & Grossman, A. B.

Excerpt
Foregut carcinoids (including respiratory tract, thymus, stomach, duodenum, and pancreas) have a low content of serotonin (5-HT) and often secrete the serotonin precursor 5-HTP, histamine, and a multitude of polypeptide hormones causing characteristic clinical syndromes.. Foregut carcinoids are associated with an atypical Carcinoid Syndrome and have the potential to metastasize to bone. Midgut carcinoids ((including small intestine, appendix, right colon) have a high 5-HT content, rarely secrete 5-HTP or peptide hormones, but do release 5-HT and other vasoactive compounds such as kinins, prostaglandins, and substance P; they are more likely to cause the classic Carcinoid Syndrome with the development of hepatic metastases and rarely metastasize to bone. Hindgut (including transverse colon, sigmoid, and rectum) carcinoid tumors rarely contain 5-HT, secrete 5-HTP, and/or cause the Carcinoid Syndrome; however, they can contain numerous GI hormones and very infrequently metastasize to bone.

http://annonc.oxfordjournals.org/content/12/suppl_2/S95.abstract
Epidemiology, clinical features and diagnosis of gastroenteropancreatic endocrine tumours.
Citation
Annals of Oncology, 2001, 12(Suppl 2): S95-S99.

Authors
Tomassetti, P., Migliori, M., Lalli, S., Campana, D., Tomassetti, V., Corinaldesi, R.

Abstract
Gastroenteropancreatic (GEP) neoplasms originate from any of the various cell types belonging to the neuroendocrine system. A general characteristic of GEP endocrine tumours is that the vast majority produce and secrete a multitude of peptide hormones and amines. Many patients with malignant metastasising tumours present clinical symptoms related to hormone hyperproduction. These include the so-called carcinoid syndrome, characterised by flushing, diarrhoea, wheezing and right heart disease, which is predominantly associated with the serotonin-and tachykinins-producing carcinoids of the midgut. Several types of syndrome associated with GEP endocrine tumors are caused by overproduction of a specific hormone.

For instance, the well-known Zollinger-Ellison syndrome is gastrin-mediated. The so-called 'insulinoma syndrome' depends on excessive production of insulin and proinsulin, resulting in hypoglycemia. The 'glucagonoma syndrome' is characterised by necrolytic migratory erythema, diabetes and diarrhoea. The Verner-Morrison syndrome, which is brought about by high circulating levels of vasointestinal peptide (VIP), produces severe secretory diarrhoea. Finally the 'somatostatinoma syndrome' involves gallbladder dysfunction and gall stones, diarrhoea with or without steatorrhea, and impaired glucose tolerance. The biochemical diagnosis of endocrine digestive tumors is based on general and specific markers. The best general markers are chromogranin A (CgA) and pancreatic polypeptide (PP). Specific markers for endocrine tumors include insulin, gastrin, glucagon , vaso intestinal polypeptide (VIP), somatostatin and the primary cathabolic product of serotonin, 5-hydroxyndoleacetic acid (5-HIAA). Localisation procedures commonly applied, in the diagnosis of endocrine tumours include ultrasound (US), computed tomography (Cl and somatostatin receptor scintigraphy (SRS).

CARCINOID SYNDROME

http://emedicine.medscape.com/article/282515-overview
Malignant carcinoid syndrome.
Citation
Emedicine (Oncology), November 19, 2009.
Authors
Santacroce, L., Diomede, L., & Balducci, L.

Abstract
Malignant carcinoid syndrome is the constellation of symptoms typically exhibited by patients with metastases from carcinoid tumors. Carcinoid tumors usually secrete excessive amounts of the hormone serotonin. Carcinoid tumors arise from neuroendocrine cells, which are widespread in the human body, especially in the organs derived from the primitive intestine. Diarrhea is common, as is flushing of the face and neck. Wheezing, facial telangiectasis with cyanosis and edema, pallor, flushing, macular erythema, and periorbital edema, accompanied by hepatomegaly, pellagralike skin lesions, steatorrhea, and chronic diarrhea, all suggest the diagnosis.

http://www.ncbi.nlm.nih.gov/pubmed/19336516

Development and characterization of a novel in vivo model of carcinoid syndrome.

Citation
Clinical Cancer Research, 2009, 15(8): 2747-2755.

Authors
Jackson, L.N., Chen, L.A., Larson, S.D., Silva, S.R., Rychachou, P.G., Boor, P.J., Li, J., Defreitas, G., Stafford, W.L., Townsend, C.M. Jr., & Evers, B.M.

Abstract
PURPOSE: Carcinoid syndrome, characterized by flushing, diarrhea, and valvular heart disease, can occur following carcinoid tumor metastasis to the liver and systemic release of bioactive hormones into the systemic circulation. Treatment of this devastating disease is hampered by the lack of an in vivo model that recapitulates the clinical syndrome.

EXPERIMENTAL DESIGN: Here, we have injected BON cells, a novel human carcinoid cell line established in our laboratory, into the spleens of athymic nude mice to establish liver metastases. RESULTS: The majority of mice injected intrasplenically with BON cells developed significant increases in plasma serotonin and urine 5-hydroxyindoleacetic acid, and several mice exhibited mesenteric fibrosis, diarrhea, and fibrotic cardiac valvular disease reminiscent of carcinoid syndrome by both echocardiographic and histopathologic evaluation. Mice pretreated with octreotide, a long-acting somatostatin analogue, or bevacizumab, a vascular endothelial growth factor inhibitor, developed fewer liver metastases and manifestations of carcinoid syndrome, including valvular heart disease. CONCLUSION: We have provided an important in vivo model to further delineate novel treatment modalities for carcinoid syndrome that will also be useful to elucidate the factors contributing to the sequelae of carcinoid disease (e.g., mesenteric fibrosis and valvular heart disease).

http://www.medscape.com/medline/abstract/18068329

Carcinoid syndrome.

Citation

European Journal of Surgical Oncology, 2008, 34(3): 289-296.

Authors

Bendlow, J., Apps, E., Jones, L.E., & Poston, G.J.

Abstract

As clinical awareness increases, carcinoid is becoming increasingly identified, often at an earlier stage in the course of the disease. However, many patients remain undiagnosed until well into the late stages of the illness, at the time when their carcinoid syndrome becomes apparent. This review examines contemporary methods of detecting and assessing advanced carcinoid disease, and then continues to discuss strategies (both potentially curative and palliative) to control symptoms, and both prolong and improve quality of life for these patients.

http://www.ncbi.nlm.nih.gov/pubmed/15477713

Complications of midgut carcinoid tumors and carcinoid syndrome.

Citation

Neuroendocrinology, 2004, 80(Suppl 1): 28-32.

Authors

van der Horst-Schrivers, A.N., Wymenga, A.N., Links, T.P., Willemse, P.H., Kema, I.P, & de Vries, E.G.

Abstract

The carcinoid syndrome, associated with carcinoid tumors of the midgut, consists of symptoms such as diarrhea, flushing, wheezing and cardiovascular symptoms. This review focuses on these symptoms and discusses therapeutic options. The symptoms are caused by the secretion of biogenic amines, polypeptides and other factors of which serotonin is the most prominent. However, diarrhea is also due to factors such as malabsorption. Besides antitumor therapy, more specific interventions such as serotonin receptor blockers can be useful. The carcinoid heart disease involves the tricuspid and pulmonary valve. In the pathogenesis, serotonin plays a central role. The therapeutic approach is mostly symptomatic. Other cardiovascular complications include bowel ischemia and hypertension. Pellagra and psychiatric symptoms are due to a depletion of tryptophan, which is consumed by the carcinoid tumor for serotonin synthesis. Finally, follow-up and clinical practice of patients with carcinoid tumors are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/10464698

Carcinoid syndrome: a statistical evaluation of 748 reported cases.

Citation
Journal of Experimental and Clinical Cancer Research, 1999, 18(2): 133-141.

Authors
Soga, J., Yakuwa, Y., & Osaka, M.

Abstract
No statistical evaluation of patients with carcinoid syndrome in a reliable number of cases has been available in the past 35 years. To update our knowledge about the syndrome, we have evaluated from various clinicopathologic viewpoints a large series of patients with the syndrome reported up to date. The data of 748 patients with the syndrome were collected from 8876 carcinoid patients reported in the literature and analyzed by the Gut-Pancreatic Endocrinoma Analyzing System (the Niigata Registry). The results are summarized as follows. 1) The patients with the syndrome had a tendency to be older than those without it. 2) The incidence of the syndrome was 8.4% of 8876 carcinoid patients. 3) Serotonin activities were extremely high in patients with the syndrome as compared to those without it (91.7% versus 26.6%). 4) The rate of metastases was higher in patients with the syndrome than in those without it (84.8% versus 29.2%), and higher in the liver than in lymph nodes among patients with the syndrome (73.4% versus 37.4%). 5) Flushing and carcinoid heart as most specific clinical manifestations of the syndrome were recorded at 78.3% and 17.4%, respectively. 6) The 5-year survival rate after resection of primary lesions was 76.0% of 304 patients with the syndrome, lower in patients with digestive carcinoids than in those with extradigestive lesions (67.2% versus 88.7%). It is expected that the results obtained in the present evaluation on patients with carcinoid syndrome will provide investigators active in this specialized field with useful and extensive information for their future activities.

CARCINOID HEART DISEASE

http://www.ncbi.nlm.nih.gov/pubmed/19402369
Carcinoid heart disease--a hidden complication of neuroendocrine tumours.
Citation
Acta Gastro-enterologica Belgica, 2009, 72(1): 34-38.

Authors
Dero, I., De Pauw, M., Borbath, I., Delaunoit, T., Demetter, P., Demolin, G., Hendlisz, A., Pattyn, P., Pauwels, S., Roeyen, G., Vancutsem, E., Van Hootegem, P., Van Laetheim, J.L., Verslype, C., & Peeters, M.

Abstract
Carcinoid heart disease (CHD) develops in serotonin-producing neuroendocrine tumours (NET) due to fibrotic endocardial plaques with associated valve dysfunction leading most often to right-sided heart failure. The classical carcinoid syndrome usually occurs when serotonin-producing NET metastasize to the liver. Up to 50% of those patients will exhibit carcinoid heart disease. The pathophysiological process is not yet completely understood: serotonin is considered to be a major initiator of the fibrotic process, but other tumour secreted factors may contribute to the pathogenesis. Histopathology reveals intact valvular cusps with superimposed fibrotic plaques, leading to thickening and retraction of the valves, causing valvular dysfunction. A high index of clinical suspicion to diagnose CHD is needed

since symptoms can be rather non-specific. Transthoracic echocardiography is the gold standard for diagnosis and should probably be performed at the time of diagnosing serotonin-producing NET and then repeated annually. On the other hand, when diagnosing right-heart failure, the presence of CHD and underlying serotonin-producing NET should be taken into account. Therapeutic options include pharmacotherapy for heart failure, control of the systemic carcinoid disease and in selected individuals cardiac valve replacement. The elucidation of the pathologic process is necessary to develop targeted antifibrotic therapeutic agents since CHD seems to be irreversible and associated with poor prognosis.

http://www.onlinejase.com/article/S0894-7317%2809%2900440-4/abstract

Role of Serotoninergic Pathways in Drug-Induced Valvular Heart Disease and Diagnostic Features by Echocardiography.

Citation

Journal of the American Society of Echocardiography, 2009, 22(80): 883-889.

Authors

Sakima, A., Smith, A. D., Waggoner, L,& Davila-Roman, V.G.

ABSTRACT:

Serotonin plays a significant role in the development of carcinoid heart disease, which primarily leads to fibrosis and contraction of right-sided heart valves. Recently, strong evidence has emerged that the use of specific drug classes, such as ergot alkaloids (for migraine headaches), 5-hydroxytryptamine (5-HT or serotonin) uptake regulators or inhibitors (for weight reduction), and ergot-derived dopamine agonists (for Parkinson's disease), can result in left-sided heart valve damage that resembles carcinoid heart disease. Recent studies have suggested that both right-sided and left-sided drug-induced heart valve disease involves increased serotoninergic activity and in particular activation of the 5-HT receptors, including the 5-HT2B receptor subtype, which mediate many of the central and peripheral functions of serotonin. G-proteins that inhibit adenylate cyclase activity mediate the activity of the 5-HT2B receptor subunit, which is widely expressed in a variety of tissues, including liver, lung, heart, and coronary and pulmonary arteries; it has also been reported in embryonic mouse heart, particularly on mouse heart valve leaflets. In this review, the authors discuss the salient features of serotoninergic manifestations of both carcinoid heart disease and drug-induced cardiac valvulopathy, with an emphasis on echocardiographic diagnosis.

http://www.ncbi.nlm.nih.gov/pubmed/18571250

Carcinoid heart disease.

Citation

International Journal of Cardiology, 2008, 129(3): 318-324.

Authors

Gustafsson, B.I., Hauso, O., Drozdov, I., Kidd, M., & Modlin, I.M.

Abstract

The carcinoid syndrome is usually evident when enterochromaffin (EC) cell-derived neuroendocrine tumors (carcinoids) metastasize to the liver. In addition to carcinoid symptomatology, about 40% of patients exhibit carcinoid heart disease (CHD) with fibrotic endocardial plaques and associated heart valve dysfunction. The mechanism behind CHD development is not fully understood, but serotonin (5-HT) is considered to be a major initiator of the fibrotic process. Most patients present with right-sided heart valve dysfunction since pulmonary and tricuspid valves lesions are the most common (>95%) cardiac pathology.

Left-sided valvular involvement, and angina associated with coronary vasospasm occur in ~10% of subjects with CHD. Pathognomonic echocardiograpic features include immobility of valve leaflets and thickening and retraction of the cusps most commonly resulting in tricuspid valve regurgitation and pulmonary stenosis. Therapeutic options include cardioactive pharmacotherapy for heart failure and, in selected individuals, cardiac valve replacement. Previously valve replacement was reserved for advanced disease due to a perioperative mortality of >20% however in the last decade, technical advances as well as an earlier diagnosis have decreased surgical mortality to <10% and valve replacements are undertaken more frequently. A recent analysis of 200 cases demonstrated an increase in median survival from 1.5 years to 4.4 years in the last two decades. Although the improved prognosis might also reflect the increased use of surgical cytoreduction, hepatic metastatic ablative therapies and somatostatin analogs a robust correlation between diminution of circulating tumor products and an increased long-term survival in CHD has not been rigorously demonstrated.

http://www.ncbi.nlm.nih.gov/pubmed/12637610

Factors associated with progression of carcinoid heart disease.

Citation

New England Journal of Medicine, 2003, 348(11): 1005-1015.

Authors

Møller, J.E., Connolly, H.M., Rubin, J., Seward, J.B., Modesto, K., & Pellikka, P.A.

Abstract

BACKGROUND: By releasing vasoactive substances into the circulation, carcinoid tumors can cause right-sided valvular heart disease. Factors associated with the progression of carcinoid heart disease are poorly understood. We conducted a retrospective study to identify such factors. METHODS: Our sample included 71 patients with the carcinoid syndrome who underwent serial echocardiographic studies performed more than one year apart and 32 patients referred directly for surgical intervention after an initial echocardiographic evaluation. A score for carcinoid heart disease was determined on the basis of an assessment of valvular anatomy and function and the function of the right ventricle. An increase of more than 25 percent in the score between studies was considered suggestive of disease progression. Tumor progression was assessed on the basis of abdominal computed tomographic scans and changes in the level of urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin. RESULTS: Of the patients with serial echocardiographic studies, 25 (35 percent) had an increase of more than 25 percent in the cardiac score. As compared with patients whose score changed by 25 percent or less, these patients had higher urinary peak 5-HIAA levels (median, 265 mg per 24 hours [interquartile range, 209 to 593] vs. 189 mg per 24 hours [interquartile range, 75 to 286]; P=0.004) and were more likely to have biochemical progression (10 of 25 patients vs. 9 of 46, P=0.05) and to have received chemotherapy (13 of 25 vs. 10 of 46, P=0.009). Logistic-regression analysis showed that a higher peak urinary 5-HIAA level and previous chemotherapy were predictors of an increase in the cardiac score that exceeded 25 percent (odds ratio for each increase in 5-HIAA of 25 mg per 24 hours, 1.08 [95 percent confidence interval, 1.03 to 1.13]; P=0.009); odds ratio associated with chemotherapy, 3.65 [95 percent confidence interval, 1.74 to 7.48]; P=0.001). CONCLUSIONS: Serotonin is related to the progression of carcinoid heart disease, and the risk of progressive heart disease is higher in patients who receive chemotherapy than in those who do not.

http://www.ncbi.nlm.nih.gov/pubmed/12408507

Carcinoid heart disease: an update.

Citation
Scandinavian Journal of Gastroenterology. Supplement., 2002, (236): 66-71.

Authors
Quaedvlieg, P.F., Lamers, C.B., & Taal, B.G.

Abstract
BACKGROUND: Carcinoid tumours are a poorly defined collection of lesions, histopathologically indistinguishable from gastroentero-pancreatic neuroendocrine tumours. In this report, we discuss epidemiology and survival, clinical presentation, carcinoid valvular heart disease (CVHD), histopathological considerations and treatment options. METHODS: Review and update of the literature. RESULTS: The term carcinoid suggests a disease entity, but with increasing knowledge it becomes progressively confusing. To avoid further confusion, it is advisable to define these tumours using differentiation, stage, primary site, known tumour products and an associated clinical syndrome. Incidence varies between 0.8 and 1.9/100,000 population. About 20% present with metastases, with a 5-year survival varying between 15% and 35%. Metastatic disease frequently accompanies the carcinoid syndrome (flushing, diarrhoea, wheezing and CVHD). CVHD incidence is about 50%, and seems unrelated to disease duration and tumour mass. An aetiological relation of CVHD with urinary 5-HIAA remains to be confirmed. Resection is the only curative option. Surgery can also offer prolonged palliation and is needed to restore bowel transit in obstructive/ischaemic bowel problems. Adequate palliation of hormone-related symptoms can also be achieved by somatostatin analogues, meta-iodo-benzyl-guanidine preparations and interferon-alpha formulations, all with a 70% response rate. Embolization of liver metastases has led to objective responses in about 50% of patients, but is accompanied by significant side effects. CONCLUSIONS: Most patients are cured by surgery. Symptom relief is the main target in metastatic disease and can be achieved by a range of equally potent biologically active medications, debulking surgery and hepatic embolization.

FIBROSIS

http://www.ncbi.nlm.nih.gov/pubmed/20123681

Intra-abdominal fibrosis in a recent cohort of patients with neuroendocrine ('carcinoid') tumours of the small bowel.

Citation
Quarterly Journal of Medicine, 2010, 103(3): 177-185.

Authors
Druce, M.R., Bharwani, N., Akker, S.A., Drake, W.M., Rockall, A., & Grossman, A.B.

Abstract
BACKGROUND: Fibrosis is a hallmark of neuroendocrine tumours (NETs) arising in the jejunum and ileum and may manifest in the mesentery and elsewhere. It is clinically important and once-established, there are few effective therapies. AIM: To examine the frequency, radiological manifestations and clinical significance of intra-abdominal fibrosis in a patient cohort using modern cross-sectional imaging. Current prevalence is compared to historical series and correlation with cardiac fibrosis evaluated. DESIGN: Cross-sectional,

retrospective survey of a cohort of patients with mid-gut NETs from a single centre. METHODS: Review of clinical features, biochemistry and imaging of patients with sporadic mid-gut NET and available imaging between 2002 and 2008. RESULTS: Thirty-one patients were included: 26 (83.9%) had liver metastases and 11 (35.4%) had small-bowel wall thickening; 17 patients (55%) had mesenteric involvement, with a mass, which contained coarse calcification in seven patients and fine calcification in a further two. There was soft-tissue stranding in 13 patients (plus in a further patient with no mass) and 'indrawing' of tissues in 11 patients. Two patients had a 'misty' mesentery and two had early retroperitoneal fibrosis. Mesenteric involvement was unrelated to gender and urinary 5HIAA excretion. CONCLUSION: Intra-abdominal fibrosis can be detected radiologically in around half of patients with mid-gut NET using contemporary cross-sectional imaging. Although not statistically significant, small-bowel obstruction was seen more frequently in the group with fibrosis. There was no relationship with cardiac fibrosis. Prospective studies are needed to evaluate predictors of fibrosis onset and clinical course and determine optimal methods of prevention and treatment.

http://cme.medscape.com/viewarticle/590694

Fibrosis and Carcinoid Syndrome -- From Causation to Future Therapy.

Citation
Nature Reviews. Endocrinology, 2009, 5(5): 276-283.

Authors
Druce, M., Rockall, A., & Grossman, A. B.

Abstract
Carcinoid tumors are part of a heterogeneous group of gastrointestinal and pancreatic endocrine tumors that are characterized by their capacity to produce and secrete hormones, 5-hydroxytryptamine, tachykinins and other mediators. These substances are thought to be responsible for the collection of symptoms, which include diarrhea, flushing and wheezing, that is known as carcinoid syndrome. Fibrosis that occurs either local to or distant from the primary tumor is one of the hallmarks of carcinoid tumors that originate from the midgut. The fibrotic process can occur in the mesentery as a desmoplastic response and may lead to obstruction of the small bowel, but it can also occur in the lungs, skin or retroperitoneum. Importantly, up to one-third of patients develop cardiac valvulopathy. One or more products that are secreted by the tumor and enter into the circulation are likely to have a role in this process. This review discusses the incidence and prevalence of fibrosis in carcinoid syndrome and explores evidence to date for causative agents, in particular the roles of 5-hydroxytryptamine and elements of the downstream signaling pathway. Improved understanding of the etiology of carcinoid-tumor-related fibrosis may lead to better treatments for this condition than those we currently have.

http://www.ncbi.nlm.nih.gov/pubmed/17966781

Retroperitoneal and mesenteric fibrosis. An uncommon "carcinoid syndrome"

Citation
Chirugia Italia, 2007, 59(4): 565-574.

Authors

Spivach, A., Sartori, A., Martinolli, S., Contardo, T., & Zanconati, F.

Abstract
Retroperitoneal fibrosis is an uncommon disease in which dense fibrous tissue proliferates in the retroperitoneum. It frequently consists in an abdominal mass involving alimentary structures, ureters with obstruction, and vascular elements with stenosis. This pathological event may be associated with a history of ergotamine usage or a wide range of conditions including malignancy, injuries and infections. In the case described here, the cause was a midgut carcinoid tumour, releasing high concentrations of serotonin and other metabolites directly into the peritoneal fluid. Because carcinoid tumours of the bowel can remain silent for many years it is possible that similar cases of retroperitoneal fibrosis may be identified only many years after onset. For that reason, a long history of bowel obstruction must be considered a kind of unusual but no less important carcinoid syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/16086212

Abdominal angina in patients with a midgut carcinoid, a sign of severe pathology.

Citation
World Journal of Surgery, 2005, 29(9):1139-1142.

Authors
de Vries, H., Wijffels, R.T., Willemse, P.H., Verscheren, R.C., Kema, I.P., Karrenblad, A., Prins, T.R., & de Vries, E.G.

Abstract
In 36 consecutive patients with a foregut carcinoid with extensive local tumor growth and liver metastases with a carcinoid syndrome, six patients had complaints of postprandial abdominal pain and attacks of subileus based on segmental intestinal ischemia. A diagnosis of abdominal angina was supported by a positive response to nitroglycerin in two and ischemia of the ileum demonstrated by angiography in two other patients. Complaints were reduced in all patients after surgery. Histopathology of the resected small bowel specimens showed elastic vascular sclerosis in three patients and ischemic changes in three other patients, confirming the clinical diagnosis. Resection of ischemic bowel can provide relief in patients with segmental intestinal ischemia caused by carcinoid-induced vascular sclerosis.

http://www.ncbi.nlm.nih.gov/pubmed/15571597

Carcinoid tumors and fibrosis: an association with no explanation

Citation
American Journal of Gastroenterology, 2004, 99(12): 2466-2478.

Authors
Modlin, I. M., Shapiro, M. D., & Kidd, M.

Abstract
Carcinoid tumors are slow-growing neuroendocrine neoplasms most commonly associated with the gut and broncho-pulmonary system. In many instances, they are identified at surgery for unexplained bowel obstruction or during exploration of the small bowel in search of a primary tumor once distant metastases have been detected. Carcinoid tumors of the small bowel often present with pronounced fibrosis in the peri-tumoral tissues, distant in the heart

or lungs, and locally in the peritoneal cavity. Despite medical and therapeutic advances that have alleviated symptoms and prolonged life, a substantial subset of patients develops mesenteric and small bowel carcinoid fibrosis and/or carcinoid heart disease. Fibrosis, and increasingly cardiac heart disease, are important components of intestinal carcinoid disease and are of considerable clinical concern, as both of these conditions reflect a connective tissue disorder whose etiology, biology, and therapy are unknown. In the past, individuals with carcinoid disease died of metastasis and uncontrollable symptomatology. Currently, there exists no clinical method to determine the development of fibrosis and little is understood about the biological basis of fibrosis. The elucidation of the biology and management of fibrosis is thus an issue of paramount clinical and scientific importance in determining appropriate diagnostic and therapeutic strategy. Therefore, the unraveling of the molecular events indicative of fibrosis in these cells and the identification of appropriate therapeutic targets is of considerable patient-care relevance. We have surveyed the world literature over the past 40 yr to evaluate both the incidence of carcinoid processes and track the evolving understanding of this process. In addition, we have provided more current mechanistic information in regard to the biological basis of fibrosis associated with small bowel carcinoid tumors.

http://qjmed.oxfordjournals.org/cgi/content/abstract/86/1/49

Pleural involvement in the carcinoid syndrome.

Citation
Quarterly Journal of Medicine, 1993; 86(1) : 49-53.

Authors
Moss, S.F., Lehner,P.J., Gilbey, S.G., Kennedy, A., Hughes, J.M.B., Bloom, S.R., & Hodgson, H.G.F.

Abstract
Tissue fibrosis is a recognized complication of the carcinoid syndrome but pleural changes have not been described. Prompted by the finding of severe pleural thickening in two patients with the metastatic carcinoid syndrome but no thoracic metastases or previous pleural disease we reviewed the chest radiographs and CT scans in 50 patients with the carcinoid syndrome investigated from 1981 to 1990. Pleural abnormality was noted in 14 of the 50 patients (28%), five of whom had other possible causes for pleural disease. However, nine (18%) patients had 'idiopathic' pleural thickening. Pleural disease had developed within 2 years of the diagnosis in all cases, and seven of the nine patients had fibrosis elsewhere (heart valves, skin or mesentery). There were no features to suggest a more rapid disease progression in the patients with pleural disease. We suggest that the pleural abnormality is a complication of metastatic carcinoid disease.

COGNITIVE IMPAIRMENT

http://www.ncbi.nlm.nih.gov/pubmed/20127244

Impairment of cognitive function reported by patients suffering from carcinoid syndrome.

Citation

World Journal of Surgery, 2010, 34(6): 1356-1360.

Authors
Chambers, A.J., Longman, R.S., Pasieka, J.L., Dixon, E., Rorstad, O., Rach-Longman, K., & Jones, J.

Abstract
BACKGROUND: Carcinoid syndrome (CS) is characterized by symptoms of diarrhea, flushing, bronchospasm, and valvular heart disease. It has been our impression that patients with CS also exhibit features of cognitive impairment. The purpose of this pilot study was to evaluate if symptoms of cognitive impairment were reported by patients with CS. METHODS: Patients with proven CS completed a 38-question multiple-ability self-report questionnaire (MASQ) to assess symptoms in five cognitive domains: language skills, attention/concentration (A/C), visual-perceptual function, visual memory, and verbal memory. Patients subsequently underwent neurocognitive assessment using a battery of six standardized tests. Results of the MASQ and the cognitive test were compared to published results for healthy individuals. RESULTS: Twenty-one patients with CS were studied. MASQ symptom scores were higher than published norms in all five cognitive domains. Patients reported greatest difficulty with verbal memory (mean +/- SD = 2.74 +/- 0.5), followed by A/C (2.41 +/- 0.65), language (2.31 +/- 0.55), visual memory (2.30 +/- 0.65), and visual-perceptual function (2.17 +/- 0.59). In contrast, neurocognitive tests for verbal memory immediate recall, visual memory, language, and executive function were within the normal range. CS patients, however, scored lower than expected in tests of verbal memory delayed recall and visual-perceptual function. CONCLUSIONS: Patients with CS report high levels of symptoms of impairment in all cognitive domains; however, on formal neurocognitive testing, patients scored lower than expected only in tests of verbal memory delayed recall and visual-perceptual function. These findings appear to confirm our clinical impression that cognitive impairment may be an additional feature of CS. Further studies are needed to confirm and elucidate the cause of this cognitive impairment.

http://www.ncbi.nlm.nih.gov/pubmed/19428501

Effects of acute tryptophan depletion on memory, attention and executive functions: a systematic review.

Citation
Neuroscience & Biobehavioral Review, 2009, 33(6): 926-952.

Authors
Mendelsohn, D., Riedel, W.J., & Sambeth, A.,

Abstract
The serotonergic system is implicated in the regulation of mood and cognition. Acute tryptophan depletion (ATD) is an experimental procedure for lowering central serotonin levels. Here, the effects of ATD on psychomotor processing, declarative memory, working memory, executive functions and attention are discussed. The most robust finding is that ATD impairs the consolidation of episodic memory for verbal information. Semantic memory appears to be unaffected by ATD although a limited variety of tasks examined effects in this domain. Similarly, evidence suggests ATD does not influence verbal, spatial and affective working memory. Most studies investigating effects on executive functions have produced non-specific or negative findings. In terms of attention, ATD either does not affect or may improve focused attention and ATD likely does not impact sustained and divided attention or

attentional set-shifting. Although ATD is known to affect mood in certain vulnerable populations, the effects of ATD on cognition in non-vulnerable participants are independent of mood changes. Suggestions for future directions and implications for psychiatric illnesses are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/17428340

Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study.

Citation
Health Quality of Life Outcomes, 2007, 5: 18.

Authors
Fröjd, C., Larsson, G., Lampic, C., & von Essen, L. A.

Abstract
BACKGROUND: The aim was to investigate HRQoL and psychosocial function among patients with carcinoid tumours, longitudinally and prospectively, and to compare HRQoL among patients with carcinoid tumours to that of the Swedish general population. The aim was also to investigate the prevalence of distress during the first year after diagnosis. METHODS: At four assessments during the first year after diagnosis, HRQoL was measured by the EORTC QLQ-C30 3.0, anxiety and depression by the HADS, and prevalence, and worst aspects of distress by an interview guide. ANOVA was performed in order to study changes over time with regard to HRQoL, anxiety and depression. Comparisons regarding HRQoL between patients and the Swedish population were made by the use of one-sample t-tests and changes over time regarding the prevalence of distress was investigated by means of Cochran's Q. RESULTS: High levels of physical-, emotional-, cognitive-, and social function and somewhat lower levels of role function and global quality of life were reported at all assessments. Role- and emotional function increased over time. Patients reported lower role function and global quality of life and more problems with fatigue and diarrhoea than the Swedish general population, at all assessments. Fatigue, limitations to work and pursue daily activities, and worry that the illness will get worse were among the most prevalent aspects at all assessments. At all assessments the majority reported worrying about the family's situation, the ability to care for the family, and worrying before the check-up. CONCLUSION: It is concluded that HRQoL and psychosocial function among patients with carcinoid tumours remains stable during the first year, that the patients report a lower HRQoL than the Swedish general population, and that a majority of the patients report a number of aspects of emotional distress. In the clinical care, it should be considered that the majority of patients report not only fatigue and diarrhea but also worries about their prognosis, their families, tests, and examinations. Efforts to reduce these worries should be made.

http://www.ncbi.nlm.nih.gov/pubmed/15184706

Patients with carcinoid syndrome exhibit symptoms of aggressive impulse dysregulation.

Citation
Psychosomatic Medicine, 2004, 66(3): 422-425.

Authors

Russo, S., Boon, J.C., Kema., I.P., Willemse, P.H., den Boer, J.A., Korf, J., & de Vries. E.G.

Abstract
OBJECTIVE: Carcinoid tumors can produce excessive amounts of biogenic amines, notably serotonin. We assessed psychiatric symptoms in carcinoid patients and peripheral metabolism of tryptophan, the precursor of serotonin. METHODS: Twenty consecutive patients with carcinoid syndrome underwent a structured psychiatric interview applying DSM-IV (Diagnostical Statistical Manual) criteria. Tumor activity was measured by determination of 24-hour urine excretion of 5-hydroxyindoleacetic acid (5-HIAA) and platelet serotonin levels. Plasma tryptophan levels were measured and compared with sex- and age-matched references. RESULTS: Fifteen patients (75%) fulfilled diagnostic DSM-IV criteria for a disorder of impulse control. Tryptophan plasma levels were lower in patients compared with controls (p =.031) and were correlated negatively with urinary 5-HIAA excretion (p =.001). CONCLUSIONS: Impulse control disorders are prevalent in patients with carcinoid syndrome. The serotonin production by the tumor possibly decreases the tryptophan pool in the cerebrospinal fluid, which is the essential substrate for the production of brain serotonin as a pivotal neurotransmitter.

http://www.ncbi.nlm.nih.gov/pubmed/12695876

Neuropsychological investigation into the carcinoid syndrome.

Citation
Psychopharmocology (Berlin) 2003, 168(3): 324-328.

Authors
Russo, S., Nielsen, M.M., Boon, J.C., Kema, I.P., Willemse, P.H., de Vries, E.G., Korf,, J., & den Boer, J.A.

Abstract
RATIONALE: In patients suffering from metastatic carcinoid tumors, chronic disturbances of serotonergic metabolism are frequently present. Serotonin is supposed to influence a range of cognitive functions. OBJECTIVES: The present study evaluated the cognitive performance of carcinoid patients. METHODS: In 14 patients with proven carcinoid syndrome, neuropsychological functioning was studied. Visual search, sustained attention, set shifting ability and spatial working memory were assessed using tests from the CANTAB neuropsychological battery. This was compared with the performance of matched healthy controls. RESULTS: Plasma tryptophan levels were lower than controls. Patients showed an enhanced ability to learn new stimulus-response associations. Sustained visual attention, however, was impaired. CONCLUSION: Cognitive patterns were different from those found in depressive patients and partly mimicked those found in tryptophan depletion experiments. Further investigation has to point out the role of serotonergic changes in the accomplishment of affective states.

PELLAGRA

http://www.ncbi.nlm.nih.gov/pubmed/16181385
Biochemical assessment of niacin deficiency among carcinoid cancer patients.
Citation
American Journal of Gastroenterology, 2005, 100(10): 2307-2314.

Authors
Shah, G.M., Shah, R.G., Veillette, H., Kirkland, J.B., Pasieka, J.L., & Warner, R.R.

Abstract
OBJECTIVE: Carcinoid cancer patients often have elevated levels of serotonin or its precursor 5-hydroxytryptophan. Normally, serotonin synthesis accounts for a small fraction of tryptophan catabolism, which should be directed along a pathway that allows partial conversion to niacin; hence, increased diversion of tryptophan toward serotonin could cause variable degrees of niacin deficiency in carcinoid patients. Therefore, the prevalence of niacin deficiency among carcinoid patients was investigated by clinical assessment of pellagra and biochemical assessment of whole blood niacin number, a ratio derived from two biologically active forms of niacin (NAD/NADP x 100). METHODS: Clinical and biochemical niacin status were assessed in a cohort of newly diagnosed carcinoid patients with carcinoid syndrome (CCS, n = 36), carcinoid patients without carcinoid syndrome (CWCS, n = 32) and noncarcinoid controls (n = 24) recruited at two primary care clinics. Other aspects of serotonin metabolism were measured by analyses of plasma serotonin and tryptophan and urinary excretion of 5-hydroxyindoleacetic acid. RESULTS: Biochemical niacin deficiency (niacin number < 130) was significantly more common in CCS patients (10 out of 36) compared to controls ($p < 0.05$, Fisher's exact test), while CWCS patients displayed an incidence that was not significantly elevated (4 out of 32). Only one CCS patient, who was also identified biochemically as niacin deficient, was clinically diagnosed with pellagra. CONCLUSION: Biochemical niacin deficiency is more prevalent among newly diagnosed CCS patients than in controls. Manifestation of pellagra is a less sensitive indicator, and dependence on this endpoint could lead to a lack of appropriate nutritional support for this group of patients.

http://www.ncbi.nlm.nih.gov/pubmed/14693013

Pellagra: dermatitis, dementia, and diarrhea.

Citation
International Journal of Dermatology, 2004, 43(1):1-5.

Authors
Hegyi, J., Schwartz, R.A., & Hegyi, V.

Abstract

Pellagra defines systemic disease as resulting from a marked cellular deficiency of niacin. It is characterized by 4 "D's": diarrhea, dermatitis, dementia, and death. Diagnosis of pellagra is difficult in the absence of the skin lesions, and is often facilitated by the presence of characteristic ones. The dermatitis begins as an erythema. Acute pellagra resembles sunburn in its first stages, but tanning occurs more slowly than typically in sunburn. Exacerbation follows re-exposure to sunlight. In this work we review the findings of this once mysterious disorder, one that still challenges clinicians world-wide.

CUTANEOUS MANIFESTATIONS OF CARCINOID SYNDROME

http://www.ncbi.nlm.nih.gov/pubmed/16605288
Cutaneous manifestations of internal malignancy: diagnosis and management.
Citation

American Journal of Dermatology, 2006, 7(2): 71-84.
Authors
Kleyn, C.E., Lai-Cheong, J.E., & Bell, H.K.

Abstract
An association between systemic malignancy and cutaneous manifestations has long been recognized. The cutaneous features that can occur are numerous and heterogeneous, and many different etiologic mechanisms are represented - from direct tumor invasion of skin or distant metastases to a wide variety of inflammatory dermatoses that may occur as paraneoplastic phenomena. In addition, there are a number of inherited syndromes that carry an increased risk of cutaneous as well as internal malignancies. While some of these inherited syndromes and paraneoplastic phenomena are exceedingly rare, all clinicians will be aware of the common cutaneous manifestations of advanced malignant disease such as generalized xerosis and pruritus. This review classifies these wide-ranging cutaneous manifestations of internal malignancy into five basic groups and provides practical advice regarding diagnosis and screening of patients who initially present with a cutaneous complaint. Also included is up-to-date information on two rapidly expanding and exciting areas of research that are likely to have far-reaching clinical implications: (i) clarification of underlying humoral mechanisms, for example, in the malignant carcinoid syndrome; and (ii) identification of an increasing number of specific genetic defects that confer a susceptibility to malignancy. Increased clinician awareness regarding the associations between these lesions and internal malignancy or inherited syndromes will facilitate screening and early diagnosis.

http://www.ncbi.nlm.nih.gov/pubmed/15656803
Cutaneous manifestations of the malignant carcinoid syndrome.
Citation
British Journal of Dermatology, 2005, 152(1): 71-75.
Authors
Bell, H.K., Poston, G.J., Vora, J., & Wilson, N.J.

Abstract
BACKGROUND: The incidence of carcinoid tumours is approximately 1.5 per 100 000 of the population. The malignant carcinoid syndrome, which is caused by circulating neuroendocrine mediators produced by the tumour, occurs in less than 10% of patients. Cutaneous involvement, although recognized in this rare syndrome, has rarely been reported. OBJECTIVES: To examine a series of patients with the malignant carcinoid syndrome, to establish the prevalence and types of cutaneous involvement and to assess whether these could be used as indicators of disease activity, progression and prognosis. METHODS: Patients with the malignant carcinoid syndrome who attended a multidisciplinary clinic for neuroendocrine tumours over a 23-month period between February 2001 and December 2002 were invited to participate in the study. This involved completion of a standard history proforma and a detailed cutaneous examination with findings recorded by clinical photography. RESULTS: Twenty-five patients were enrolled. All but one had experienced flushing, three had rosacea, five had clinical features of pellagra and two had scleroderma. Flushing was generally an early manifestation of the syndrome, whereas both the pellagra and scleroderma tended to occur in more advanced disease. CONCLUSIONS: This descriptive case series indicates that cutaneous features are not uncommon in the syndrome. They are readily diagnosed on clinical examination, and may be useful indicators of disease activity and prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/10748948

Differential diagnosis of the patient with unexplained flushing/anaphylaxis.

Citation
Allergy & Asthma Proceedings, 2000, 21(1): 21-24.

Authors
Metcalfe, D.D.

Abstract
In unusual cases of flushing and anaphylaxis, and after the elimination of the more obvious causes of anaphylaxis or those that may be evaluated by readily available techniques, it is possible to confront a limited and difficult differential diagnosis, which includes idiopathic flushing, anaphylaxis, and neoplastic syndromes associated with mastocytosis and carcinoid tumor. Interestingly, there are rather few features that distinguish one of these possibilities from another. However, the presence of allergic signs and symptoms tend to favor the diagnosis of recurrent idiopathic anaphylaxis; and right-sided valvular heart disease, the presence of excessive 5-HIAA in the urine, and a response to somatostatin favor the diagnosis of carcinoid syndrome. The distinguishing features of mastocytosis include the presence of characteristic skin lesions and diagnostic histopathologic findings on bone marrow biopsy. Counts of absolute mast cell numbers in the skin are less helpful. Following such guidelines, it is often possible to focus on the most likely diagnosis, be it idiopathic anaphylaxis, benign cutaneous flushing, mastocytosis, or carcinoid tumor.

http://pmj.bmj.com/content/71/835/299.abstract

Cutaneous scleroderma in association with carcinoid syndrome.
Citation
Postgraduate Medical Journal, 1995, 71: 299-300
Authors
Durward, G., Blackford, S., Roberts, S, & Jones, M.K.
Abstract
A case of scleroderma in a woman with carcinoid syndrome is described and the similarities between our case and those in the literature are reviewed. The carcinoid tumours were all of midgut origin and liver metastases were present. All subsequently developed fibrotic heart disease and none had clinical features or autoantibodies suggestive of systemic sclerosis. The association between carcinoid syndrome and particular features of scleroderma is likely to be more than fortuitous.

http://www.ncbi.nlm.nih.gov/pubmed/8313648

Scleroderma and the carcinoid syndrome.

Citation
Clinical Experiments in Dermatology, 1994, 19(1): 83-85.

Authors
Ratnavel, R.C., Burrows, N.P., & Pye, R.J.

Abstract

The follow up of a case of the carcinoid syndrome complicated by scleroderma is reported, in which progress of the disease may have been halted by treatment with a combination of cyproheptadine, parachlorophenylalanine and prednisolone. Impairment of tryptophan and 5-hydroxytryptamine (serotonin) metabolism appears central to the development of skin fibrosis in the carcinoid syndrome and may be indicative of important mechanisms in the pathogenesis of idiopathic scleroderma.

http://www.ncbi.nlm.nih.gov/pubmed/2461688

Distinguishing features of idiopathic flushing and carcinoid syndrome.

Citation
Archives of Internal Medicine, 1988, 148(12): 2614-2618.

Authors
Aldrich, L.B., Moatari, A.R., & Vinik, A.I.

Abstract
We compared the clinical and biochemical profiles of 11 patients with idiopathic flushing (IF) with those of eight patients with carcinoid syndrome (CS). Patients with IF were more often women, had a longer duration of symptoms, and were younger. Palpitations, syncope, and hypotension occurred only in patients with IF, while wheezing and abdominal pain occurred only with CS; diarrhea occurred in both types of patients. Elevated blood serotonin levels were present primarily in CS. Increased levels of urine 5-hydroxyindoleacetic acid was specific for CS but unsufficiently sensitive to detect all cases. Abnormalities of gut and vasoactive peptides failed to distinguish the two conditions. Flushing in carcinoid patients responds uniformly to octreotide (Sandostatin), but only one third of the patients with IF are relieved of the symptom. Patients with IF have features that distinguish them from individuals with flushing from other causes, such as CS, postmenopausal state, chlorpropamide-alcohol flush, panic attacks, medullary thyroid carcinoma, and autonomic epilepsy. Familiarity with the clinical and biochemical features of IF should facilitate evaluation and identification of these patients.

Cushing's Syndrome

http://www.ncbi.nlm.nih.gov/pubmed/16824644

Cushing's syndrome secondary to bronchopulmonary carcinoid tumor: report of two cases and literature review.

Citation
Lung Cancer, 2006, 53(3): 381-386.

Authors
de Matos, L.L., Trufelli, D.C., das Neves-Pereira, J.C., Danel, C., & Riquet, M.

Abstract
Bronchopulmonary carcinoid tumors have been associated with a variety of endocrine disorders including Cushing's syndrome (CS), which is caused by ectopic adrenocorticotrophic hormone (ACTH) secretion. We report two cases of CS secondary to bronchopulmonary carcinoid tumors. The first patient, a 29-year-old woman, presented hypokalemia, high serum ACTH level and high free-urinary cortisol, raising suspicion of an ectopic ACTH syndrome.

Chest computed tomography and Octreoscan showed a peripheral nodule in the left-superior lobe of the lung. After lobectomy, a typical bronchopulmonary carcinoid was diagnosed. The second patient, a 16-year-old boy, presented "moon face" and progressive asthenia, high serum ACTH level and high free-urinary cortisol, raising the same hypothesis. Chest computed tomography and Octreoscan showed a peripheral nodule in the middle lobe. After lobectomy, an atypical bronchopulmonary carcinoid was diagnosed. Both cases had IA stage (T1N0M0), positively immunostaining for chromogranin and ACTH. Neither of these patients had hypophysary microadenomas, adrenal adenomas or recurrence of CS after surgical treatment, demonstrating that CS was caused solely by the presence of the bronchopulmonary carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/15038649

Cushing's syndrome induced by bronchopulmonary carcinoid tumours: a review of 98 cases and our experience of two cases.

Citation
Chirugia Italia, 2004, 56(1): 63-70.

Authors
Scanagatta, P., Montresor, E., Pergher, S., Mainente, M., Bonadiman, C., Benato, C., Feil, B., Destefanis, M.L., Pea, M., Spinoso, A., Scilanga, L., & Francia, G.

Abstract
Bronchopulmonary carcinoids are one of the most common cause of ectopic secretion of corticotropin (ACTH) and account for approximately 1% of all the patients in whom Cushing's syndrome develops. We reviewed 98 cases described in the World Literature and we report on two new cases. A 60-year old woman affected by Cushing's syndrome underwent to surgical wedge resection of a peripheral pulmonary nodule and a 30-year old woman with similar clinical features underwent to middle lobectomy for a small hilar neoplasm. Histopathologic examination of the tumours defined them as typical bronchopulmonary carcinoids. The patients are asymptomatic and with no sign of recurrence 72 and 30 months after surgery. According to our review we found no clear evidence that bronchial carcinoids associated with Cushing's syndrome should be considered a more aggressive variant or subtype of the typical carcinoid. If Cushing's syndrome does not disappear after surgery, the presence of residual disease (often a nodal involvement) should be investigated. A long-term relapse of the syndrome requires a careful search for local or distant neoplastic recurrence.

SECOND PRIMARY MALIGNANCIES

http://www.ncbi.nlm.nih.gov/pubmed/16567020

Secondary cancers after a lung carcinoid primary: a population-based analysis.

Citation
Lung Cancer, 2006, 52(3): 273-279.

Authors
Cote, M.L., Wenzlaff, A.S., Philip, P.A., & Schwartz, A.G.

Abstract

Carcinoid tumors of the lung were first described in 1937, yet little is known about their etiology. The aim of the present investigation was to determine if there was excess risk of secondary cancers in a population-based sample after a lung carcinoid tumor diagnosis which may provide insight to the etiology. Subjects were 1882 cases diagnosed with carcinoid tumors of the lung between 1988 and 2000 whose information was obtained from the Surveillance, Epidemiology and End Results (SEER) Program database. Standardized incidence ratios were calculated by dividing the observed number of second primary cancers by the expected number of cancers. Excess risk of breast cancer was seen following diagnosis of a carcinoid tumor (SIR=1.80 95% CI 1.22-2.55). When stratified by time after diagnosis, excess risk of breast cancers in women was seen in the first 5 years after carcinoid diagnosis (SIR=1.68 95% CI 1.08-2.50) but fewer than expected breast cancers were diagnosed greater than 5 years after carcinoid diagnosis (SIR=0.29 95% CI 0.09-0.68). Prostate cancers also occurred 2.8 times more often than expected (95% CI 1.66-4.43), with risk being elevated only in the first 5 years post-carcinoid diagnosis. Development of lung carcinoids may be the result of genetic predisposition or environmental exposures, particularly those that are hormonally related. The role of genetics and sex hormones in lung carcinoid development, as well as the identification of other risk factors, should be explored.

http://www.ncbi.nlm.nih.gov/pubmed/15154621

Neuroendocrine tumors and second primary malignancy--a relationship with clinical impact?

Citation
Anticancer Research, 2004, 24(2C):1049-1051.

Authors
Prommegger, R., Ensinger, C., Steiner, P., Sauper, T., Profanter, C., & Margreiter, R.

Abstract
BACKGROUND: Neuroendocrine tumors (NET) are frequently associated with synchronous or metachronous secondary primary malignancies (SPM). The aim of this study was to report on 14 patients with NET and SPM from a series of 96 patients with NET. PATIENTS AND METHODS: Fourteen patients with NET and synchronous or metachronous SPM were reviewed for primary site and characteristics of NET and associated SPMs as well as the outcome of these combined malignancies. RESULTS: From 1987 to 2002, 14 (14.6%) out of 96 patients with NET were identified with SPM. The median age of the patients at diagnosis of NET was 69 years (range: 56-86 yrs). There were nine female and five male patients. The localization of NET was: four in appendix, three ileum, two duodenum, one stomach, one jejunum, one pancreatic tail, one rectum and one lung. Five patients had synchronous SPM (two colon cancers with one double colon cancer, one gastric cancer, one bladder cancer, one ovarian cancer) and nine metachronous SPM (two basal cell carcinomas, one colon cancer, two breast cancer, one gastric MALT-lymphoma, one ductal pancreatic adenocarcinoma, one bladder cancer, one hepatocellular carcinoma), three months to five years after diagnosis of NET. Five patients died of metastatic tumor (three SPM: 1, 7, 10 yrs; two NET: 1, 9 yrs), two patients died of other causes (1, 7 yrs), three patients are alive with metastatic tumor (two NET: 5, 6 yrs; one SPM: 10 yrs) while four patients are tumor-free (6 ms, 2, 9, 10 yrs). CONCLUSION: NET is associated to a high degree with gastrointestinal and genitourinary SPM. In 5/14 (36%) patients SPM was diagnosed synchronously, while in 8/14 (57%) patients SPM was diagnosed metachronously. In 8/14 patients (57%) primary symptoms were caused by SPM. As a consequence, every NET should be regarded as an index tumor and risk-adapted

follow-up with thorough investigation, mainly of the GI and genitourinary tracts, is to be recommended.

http://www.springerlink.com/content/902vred51gk5reqe/

Risk of Second Cancers in Patients with Colorectal Carcinoids.

Citation

Diseases of the Colon and Rectum, 2002, 45(1): 91-97.

Authors

Tichansky, D.S., Cagir, B.,Borrazzo, E., Topham, A., Palazzo, J., Eric J. Weaver, E.J., Lange, A., & Fry, R.

Abstract

INTRODUCTION: It is often stated that patients with colorectal carcinoid tumors have an increased risk of developing other malignancies. However, this risk has not been conclusively documented. A comprehensive evaluation is needed to more thoroughly assess the risk of second cancers in patients with colorectal carcinoids. METHODS: A search of the National Cancer Institute Surveillance, Epidemiology, and End Result database from 1973 to 1996 revealed 2,086 patients with colorectal carcinoids. This subset of patients was examined for occurrence of second cancers. The observed incidence of cancer for each site was compared with the expected incidence based on the gender-adjusted and age-adjusted cancer rates in the remaining Surveillance, Epidemiology, and End Result file. A Poisson distribution probability was used to determine the significance of these comparisons. RESULTS: Patients with colorectal carcinoids had an increased rate of cancer in the colon and rectum ($P < 0.001$), small bowel ($P < 0.001$), esophagus/stomach ($P = 0.02$), lung/bronchus ($P < 0.001$), urinary tract ($P = 0.005$), and prostate ($P < 0.001$), when compared with a control population. Most of the gastrointestinal tract cancers were synchronous cancers, whereas lesions outside the gastrointestinal tract were most commonly metachronous tumors. CONCLUSIONS: A significantly increased risk of synchronous colorectal, small-bowel, gastric, and esophageal cancers and metachronous lung, prostate, and urinary tract neoplasms is clearly demonstrated. After the diagnosis of colorectal carcinoid tumors, patients should undergo appropriate screening and surveillance for cancer at these sites.

http://www.ncbi.nlm.nih.gov/pubmed/11135275

Gastrointestinal carcinoid tumors and second primary malignancies.

Citation

Journal of Surgical Oncology, 2000, 75(4): 310-316.

Authors

Habal, N., Sims, C., & Bilchik, A.J.

Abstract

The development of second primary malignancies (SPM) in patients with gastrointestinal carcinoid tumors is a well-described phenomenon, with reported rates as high as 55%. There is a predilection for gastrointestinal and genitourinary adenocarcinomas, but a variety of other malignancies have been reported as well. The etiology of this malignant predisposition may be rooted in the tumorigenic properties of the various neuroendocrine peptides elaborated and secreted by neuroendocrine cells. Peptides such as secretin, gastrin, bombesin, cholecystokinin (CCK), and vasoactive intestinal peptide (VIP) are believed to promote the growth of tumor cells. As many as 30 peptides and amines identified in neuroendocrine cells may have similar properties. This review of the literature on carcinoid-associated second

primary malignancies is accompanied by a case report of metastatic carcinoid identified during surgical exploration for a perforating colon adenocarcinoma.

http://www.ncbi.nlm.nih.gov/pubmed/7719546

The incidence, management, and outcome of patients with gastrointestinal carcinoids and second primary malignancies.

Citation
Journal of the American College of Surgeons, 1995, 180(4): 427-432.

Authors
Gerstle, J.T., Kauffman, G.L. Jr., & Koltun, W.A.

Abstract
BACKGROUND: A higher than expected incidence of second primary malignancies in patients with gastrointestinal carcinoids has been reported. How patients with such concurrent neoplasms should be managed and whether or not the discovery of an incidental carcinoid at the time of operation for another malignancy affects patient management or outcome, has never been previously addressed. STUDY DESIGN: We retrospectively reviewed our 20-year experience with gastrointestinal carcinoid tumors with the purpose of determining the appropriate management and eventual outcome of patients with these multiple malignancies. RESULTS: Sixty-nine patients with carcinoids of the gastrointestinal tract were discovered, of whom 29 (42 percent) had second synchronous tumors and three (4 percent) had metachronous tumors. The gastrointestinal tract accounted for 42.9 percent of the tumors, and carcinoma of the colon and rectum was found in seven (21.9 percent) of 32 patients. None of the 29 patients with a second synchronous tumor presented with symptoms referable to their carcinoid, each of which was incidentally discovered: nine at autopsy and 20 at laparotomy for the treatment of other tumors. All of the 20 surgical patients had the gastrointestinal carcinoids resected for cure, although three had histopathologic criteria for invasion. None of the 29 patients died as a result of, had recurrence of, or had their postoperative therapy altered by the carcinoid diagnosis. CONCLUSIONS: Gastrointestinal carcinoid is associated with a high incidence of second primary malignancy, 46 percent in this study. The most common site for the second primary malignancy in these patients is the gastrointestinal tract, suggesting a site specific predisposition to malignant degeneration. Most gastrointestinal carcinoids are incidentally discovered at laparotomy or autopsy. The discovery of an asymptomatic gastrointestinal carcinoid during the operative treatment of another malignancy will usually only require resection without additional treatment and will have little affect on the prognosis of the individual.

DIAGNOSTIC PROCEDURES

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/16917396

Gastrointestinal carcinoids: the evolution of diagnostic strategies.

Citation
Journal of Clinical Gastroenterology. 2006 Aug;40(7):572-82.

Authors
Modlin, I.M., Latich, I., Zikusoka, M., Kidd, M., Eick., G., & Chan, A.K.

Abstract
Carcinoid tumors are rare, often insidious neoplasms arising from neuroendocrine cells. The majority arise in the gastrointestinal system, and are often incidentally found during investigation, although some may present as an emergency bleed or perforation. The prosaic symptoms of flushing, diarrhea, and sweating are often overlooked; thus, the diagnosis is usually much delayed and the tumor is advanced at presentation. This diagnostic delay renders effective management difficult and adversely affects outcome. This overview provides a current assessment of the evolution of the diagnostic techniques available to establish an accurate biochemical (5-hydroxyindole-3-acetic acid and chromogranin A) and topographic diagnosis (octreoscan, radio-labeled metaidobenzylguanidine, computerized tomography, magnetic resonance imaging, positron emission tomography, enteroclysis, endoscopic ultrasound, enteroscopy, capsule endoscopy, and angiography) of carcinoid tumors. The utility and shortcomings of the respective modalities available are evaluated. Although considerable advances have been made in establishing the diagnosis of carcinoid tumors and in defining the topography of metastatic disease, the major limitation is the inability to establish an early and timely diagnosis before the advent of metastatic disease.

IMAGING

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/16762613
Imaging of neuroendocrine tumors.

Citation
Seminars in Nuclear Medicine, 2006, 36(3): 228-247.

Authors
Rufini, V., Calcagni, M.L., & Baum, R.P.

Abstract
Neuroendocrine tumors (NETs) are rare neoplasms, which are characterized by the presence of neuroamine uptake mechanisms and/or peptide receptors at the cell membrane and these features constitute the basis of the clinical use of specific radiolabeled ligands, both for imaging and therapy. Radiolabeled metaiodobenzylguanidine (MIBG) was the first radiopharmaceutical used to specifically depict and localize catecholamine-secreting tumors (pheochromocytomas, paragangliomas, and neuroblastomas) and is still regarded as a first-choice imaging technique for diagnosis and follow-up; in patients with malignant disease, MIBG scintigraphy is an essential step to select patients for (131)I-MIBG therapy. Scintigraphy with (111)In- or (99m)Tc-labeled somatostatin analogs has become the main imaging technique for NETs, particularly those expressing a high density of somatostatin receptors, such as gastroenteropancreatic tumors; this procedure is used routinely for localizing the primary tumor, evaluating disease extension, monitoring the effect of treatment and for selecting patients for radioreceptor therapy. Since the recent development of hybrid machines, it has been possible to obtain images that simultaneously hold both anatomic (computed tomography [CT]) and functional (single-photon emission computed tomography [SPECT] or positron emission tomography [PET]) information, with great impact on diagnostic accuracy. Significant improvements have been made during the past few years with

the development of highly specific radiopharmaceuticals for PET studies that reflect the different metabolic pathways of NETs, such as glucose metabolism ((18)F-fluorodeoxyglucose), the uptake of hormone precursors ((11)C-5-hydroxytryptophan, (11)C- or (18)F-dihydroxyphenylalanine, (18)F-fluorodopamine), the expression of receptors ((68)Ga-labeled somatostatin analogs), as well as the synthesis, storage, and release of hormones ((11)C-hydroxyephedrine and others). Among these radiopharmaceuticals, (68)Ga-labeled somatostatin analogs are increasingly used in specialized centers in Europe for PET and PET/CT imaging and show very promising results with high diagnostic sensitivity. New somatostatin analogs with different receptor affinity as well as other peptides are currently under investigation and will further improve our diagnostic and therapeutic capabilities in the future.

STUDIES

http://www.ncbi.nlm.nih.gov/pubmed/20395333

Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET.

Citation
Journal of Nuclear Medicine, 2010, 51(5): 704-712.

Authors
Binderup, T., Knigge, U., Loft., A., Mortenson, J., Pfeifer, A., Federspiel, B., Hansen, C.P., Højgaard, L., & Kjaer, A.

Abstract
Functional techniques are playing a pivotal role in the imaging of cancer today. Our aim was to compare, on a head-to-head basis, 3 functional imaging techniques in patients with histologically verified neuroendocrine tumors: somatostatin receptor scintigraphy (SRS) with (111)In-diethylenetriaminepentaacetic acid-octreotide, scintigraphy with (123)I-metaiodobenzylguanidine (MIBG), and (18)F-FDG PET. METHODS: Ninety-six prospectively enrolled patients with neuroendocrine tumors underwent SRS, (123)I-MIBG scintigraphy, and (18)F-FDG PET on average within 40 d. The functional images were fused with low-dose CT scans for anatomic localization, and the imaging results were compared with the proliferation index as determined by Ki67. RESULTS: The overall sensitivity of SRS, (123)I-MIBG scintigraphy, and (18)F-FDG PET was 89%, 52%, and 58%, respectively. Of the 11 SRS-negative patients, 7 were (18)F-FDG PET-positive, of which 3 were also (123)I-MIBG scintigraphy-positive, giving a combined overall sensitivity of 96%. SRS also exceeded (123)I-MIBG scintigraphy and (18)F-FDG PET based on the number of lesions detected (393, 185, and 225, respectively) and tumor subtypes. (123)I-MIBG scintigraphy was superior to (18)F-FDG PET for ileal neuroendocrine tumors, and (18)F-FDG PET was superior to (123)I-MIBG scintigraphy for pancreaticoduodenal neuroendocrine tumors. The sensitivity of (18)F-FDG PET (92%) exceeded that of both SRS (69%) and (123)I-MIBG scintigraphy (46%) for tumors with a proliferation index above 15%. CONCLUSION: The overall sensitivity of (123)I-MIBG scintigraphy and (18)F-FDG PET was low compared with SRS. However, for tumors with a high proliferation rate, (18)F-FDG PET had the highest sensitivity. The results indicate that, although SRS should still be the routine method, (18)F-FDG PET provides complementary diagnostic information and is of value for neuroendocrine tumor patients with negative SRS findings or a high proliferation index.

http://www.ncbi.nlm.nih.gov/pubmed/19962915

Incremental value of 111-in pentetreotide SPECT/CT fusion imaging of neuroendocrine tumors.

Citation
Academic Radiology, 2010, 17(3): 291-297.

Authors
Wong, K.K., Cahill, J.M., Frey, K.A., & Avram, A.M.

Abstract
RATIONALE AND OBJECTIVES: Hybrid single photon-emission computed tomographic (SPECT) and computed tomographic (CT) imaging for the investigation of neuroendocrine tumors allows the fusion of functional and anatomic information in a rapid and efficient method. The aim of this study was to assess the incremental diagnostic value of (111)In pentetreotide SPECT/CT imaging compared with traditional planar and SPECT imaging with respect to lesion localization and characterization and reader confidence. MATERIALS AND METHODS: Forty-nine patients (23 male, 26 female; mean age, 56.9 years; range, 14-88 years) who underwent (111)In pentetreotide planar, SPECT, and SPECT/CT imaging were eligible for this retrospective study, including patients with suspected or confirmed carcinoid tumors (n = 24), endocrine pancreatic tumors (n = 18), medullary thyroid cancer (n = 3), paragangliomas (n = 2), and multiple endocrine neoplasia type I (n = 2). Planar and SPECT images were reviewed by two blinded readers, followed by interpretation using additional SPECT/CT images in a subsequent session. A third reader provided consensus in cases with disagreements. RESULTS: In 55 of 89 lesions (61.8%), (111)In pentetreotide SPECT/CT imaging improved lesion localization compared to planar and SPECT imaging; in 25 of 89 lesions (28.1%), SPECT/CT imaging changed lesion classification. In 20 of 49 patients (40.8%) for reader 1 and 14 of 49 patients (28.6%) for reader 2, (111)In pentetreotide SPECT/CT imaging provided incremental diagnostic value, which was considered likely to affect patient management in twelve of 20 and seven of 14 patients, respectively. Increased reader confidence was found in 32 of 49 patients (65.3%) for both readers with uniformly high confidence after SPECT/CT interpretation. CONCLUSIONS: Hybrid (111)In pentetreotide SPECT/CT imaging provides incremental diagnostic value and greater reader confidence over planar and SPECT imaging. This is achieved though superior lesion localization, the identification of physiologic activity, and additional anatomic information derived from the nondiagnostic CT portion of the study.

http://www.ncbi.nlm.nih.gov/pubmed/20395323

68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors.

Citation
Journal of Nuclear Medicine, 2010, 51(5), 669-673.

Authors
Ambrosini, V., Campana, D., Bodei, L. Nanni, C., Castellucci, P., Allegri, V., Montini, G.C., Tomassetti, P., Paganelli, G., & Fanti, S.

Abstract
Several authors reported the superiority of (68)Ga-DOTANOC PET/CT to conventional imaging (CI) for the assessment of neuroendocrine tumors (NET). However, the detection of a higher number of lesions is not necessarily followed by a modification of disease stage or therapeutic approach. The aim of this study was to assess the impact of (68)Ga-DOTANOC

PET/CT on the clinical management of NET patients. METHODS: The study included 90 patients with pathologic confirmation of NET, CT performed within a month of (68)Ga-DOTANOC PET/CT, and a follow-up period of at least 1 y. PET/CT results were compared with CI results. As a standard of reference to finally evaluate PET results, clinical and imaging follow-up data were used. To assess the clinical impact of PET findings, all referring physicians were contacted after PET and asked about how patients were managed. Stage or therapy modifications were independently recorded, and the overall impact was evaluated patient by patient if PET results either affected therapy or caused a change in disease stage. RESULTS: Considering PET/CT and CI concordant cases (47/90 [52.2%]), PET findings affected the therapeutic management in 17 of 47 (36.2%) patients. Although PET did not result in modification of disease stage, (68)Ga-DOTANOC detected a higher lesion number in most patients. PET/CT and CI findings were discordant in 42 of 90 (46.7%) patients: PET resulted in a modification of stage in 12 patients (28.6%) and affected the treatment plan in 32 patients (76.2%). PET and CT were both equivocal in 1 patient (1/90). Considering all cases, (68)Ga-DOTANOC PET/CT affected either stage or therapy in 50 of 90 (55.5%) patients. The most frequent impact on management (27 patients) was the initiation or continuance of peptide receptor radionuclide therapy, followed by the initiation or continuance of somatostatin analog medical treatment (7 patients) and referral to surgery (6 patients). PET prevented unnecessary surgery in 6 patients and excluded from treatment with somatostatin analogs 2 patients with NET lesions that did not express somatostatin receptors. Less frequent impacts on management included the initiation of radiotherapy (1 patient), further diagnostic investigation (1 patient), and liver transplantation (1 patient). CONCLUSION: (68)Ga-DOTANOC PET/CT either affected stage or caused a therapy modification in more than half the patients, thus confirming the clinical role of PET in the management of NET.

http://www.ncbi.nlm.nih.gov/pubmed/19920029

Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI.

Citation
Circulation. Cardiovascular Imaging, 2010, 3(1): 103-111.

Authors
Bhattacharyya, S., Toumpanakis, C., Burke, M., Taylor, A.M., Caplin, M.E., & Davar, J.

Abstract

BACKGROUND: Carcinoid heart disease is a rare form of valvular heart disease. We sought describe the spectrum of carcinoid heart disease identified by echocardiography and cardiac MRI. METHOD AND RESULTS: Two hundred fifty-two patients with carcinoid syndrome underwent a range of investigations including 2D transthoracic echocardiography, 3D transthoracic echocardiography and transesophageal echocardiography, and cardiac MRI. Fifty-two patients had evidence of carcinoid heart disease. Involvement of the tricuspid, pulmonary, mitral, and aortic valves were found in 47 (90%), 36 (69%), 15 (29%), and 14 (27%), respectively. Myocardial metastases were found in 2 (3.8%) patients. Several patterns of disease were identified depending on the extent and severity to which each leaflet and its associated subvalvular apparatus was affected. Thirteen of 15 (87%) patients with left-sided carcinoid involvement had a patent foramen ovale. Three patients with severe degree of shunting had severe valvular regurgitation. Patients with mild/moderate degree of shunting had mild or moderate valvular regurgitation. Three-dimensional transthoracic echocardiography/transesophageal echocardiography provided detailed anatomic information particularly for the tricuspid and pulmonary valves. Cardiac MRI allowed

complementary assessment of valvular heart disease and delineation of myocardial metastases. Gallium-68 octreotide positron emission tomography identified neuroendocrine metastases. CONCLUSIONS: Carcinoid heart disease is a heterogeneous disease with a wide spectrum of echocardiographic findings. A multimodality approach is needed in patients with this complex pathology.

http://www.ncbi.nlm.nih.gov/pubmed/20173138

Value of CT enteroclysis in suspected small-bowel carcinoid tumors.

Citation

American Journal of Roentgenology, 2010, 194(3): 629-633.

Authors

Kamaoui, I., De-Luca, V., Ficarelli, S., Mennesson, N., Lombard-Bohas, C., & Pilleul, F.

Abstract

OBJECTIVE: The purpose of this study was to evaluate the value of CT enteroclysis in depicting small-bowel carcinoid tumors in symptomatic patients with surgical, histologic, or clinical follow-up findings as a reference standard. SUBJECTS AND METHODS: At our institution, 44 patients with symptoms of suspected gastrointestinal carcinoid tumors underwent CT enteroclysis. Clinical symptoms were as follows: carcinoid syndrome (n = 3), abdominal pain with diarrhea (n = 24), hypervascular liver metastases (n = 7), subileus condition (n = 1), hypervascular peritoneal lesion (n = 3), abnormal ileal stenosis on optical colonoscopy (n = 3), and follow-up extraintestinal carcinoid lesion (n = 3). Positive CT enteroclysis findings were compared with pathology results after surgical procedures (n = 19). Negative examinations were compared with surgery results (n = 3) or clinical follow-up (n = 22). RESULTS: CT enteroclysis findings were positive in 19 patients and negative in 25 patients. The sizes of the carcinoid tumors identified were 5-30 mm in axial diameter. These tumors were depicted as focal nodular lesions located in the small-bowel wall or as intraluminal polypoid masses with marked enhancement. Twenty-two patients underwent only clinical follow-up, with a mean clinical follow-up time of 20 months. The overall sensitivity and specificity of CT enteroclysis in identifying patients with small-bowel carcinoid tumors were 100% and 96.2%, respectively. The negative predictive value of CT enteroclysis was 100% and the positive predictive value, 94.7%. Pathologic findings confirmed small-bowel carcinoid tumors in 18 patients. CONCLUSION: CT enteroclysis should be considered an excellent tool for the diagnosis of the carcinoid tumor before any surgical procedures.

http://www.ncbi.nlm.nih.gov/pubmed/20152249

Comparison of prognostic value of tissue Doppler imaging in carcinoid heart disease versus the value in patients with the carcinoid syndrome but without carcinoid heart disease.

Citation

American Journal of Cardiology, 2010, 105(4):527-531.

Authors

Mansencal, N., McKenna, W., Mitry, E., Beauchet, A., Pellerin, D., Rougier, P., & Dubourg, O.

Abstract

The aim of this study was to evaluate the prognostic value of tissue Doppler imaging (TDI) in carcinoid heart disease (CHD). We prospectively enrolled 56 consecutive patients with proved digestive endocrine tumor and carcinoid syndrome. All patients underwent serial conventional, contrast, and TDI echocardiographic studies. The end point was all-cause mortality. Mean follow-up was 34 +/- 21 months. At the end of follow-up, 30 patients (54%)

presented right CHD and 13 patients (23%) left CHD. A progression of CHD was documented in 23 patients (41%). Twenty-two patients (39%) died during follow-up. According to mortality receiver operating characteristic curves, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity (E/e' ratio) associated with an optimal sensitivity of 80% and specificity of 90% was 8. Mortality rate was significantly higher when the E/e' ratio was >or=8 (94% vs 10% when E/e' ratio was <8, p <0.0001). Using univariate analysis, the following factors were associated with death: left-sided CHD (p = 0.07) and E/e' ratio >or=8 (p <0.0001). The only independent marker of death detected by multivariate analysis was an E/e' ratio >or=8 (odds ratio 6.2, 95% confidence interval 1.95 to 19.7, p = 0.002). In conclusion, TDI used during routine transthoracic echocardiography can be helpful to identify high-risk patients with CHD.

http://www.ncbi.nlm.nih.gov/pubmed/19034651

Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography.

Citation
Digestive Diseases & Science, 2009, 54(9): 2040-2046.

Authors
Hoeffel, C., Job, L., Ladam-Marcus, V., Vitry, F., Cadiot, G., & Marcus, C.

Abstract
The purpose of our study was to prospectively compare unenhanced ultrasonography (US) to contrast-enhanced US (CEUS) in the detection of hepatic metastases from carcinoid tumor. Thirty patients with carcinoid tumor prospectively underwent US, CEUS, and magnetic resonance imaging (MRI). Differences in sensitivity at US and CEUS were compared using a combination of the results of MR imaging, fine-needle biopsy, and follow-up imaging. Lesion conspicuity was assessed subjectively for US and CEUS. Seventeen patients had a total of 69 hepatic metastases. The addition of CEUS improved the detection of individual metastases from 47 (Se 68%; 95% CI: 57.0, 79.0) to 68 (Se 99%; 99% CI: 96.7, 100.0). Contrast enhancement improved the subjective conspicuity of metastases in 85% of patients. CEUS showed one more meta

http://www.ncbi.nlm.nih.gov/pubmed/18770038

Detection of neuroendocrine tumors of the small bowel by double balloon enteroscopy.

Citation
Digestive Disease Science, 2009, 54(5): 1050-1058.

Authors
Bellutti, M., Fry, L., Schmitt, J., Seemann, M., Klose, S., Malfertheimer, P., & Mönkemüller, K.

Abstract
BACKGROUND: Neuroendocrine tumors (NET) account for one-third of all small bowel neoplasms. The search for the primary tumor in NET is important, even though it is difficult to localize, as its surgical excision leads to a better prognosis, even in metastasized stages of the disease. The objective of this study was to evaluate the use of double balloon enteroscopy (DBE) for the detection of the primary tumor in patients with NET. METHODS: Twelve

consecutive patients (eight women, four men) with suspected carcinoid syndrome, either metastatic to the liver (n=5), symptoms of a neuroendocrine tumor with elevated tumor markers (n=5), or obscure gastrointestinal bleeding (n=2) underwent DBE for the search of the primary tumor or the source of bleeding. All patients underwent abdominal sonography and a computed tomography (CT) scan, esophagogastroduodenoscopy (EGD), ileocolonoscopy, and octreotide scintigraphy prior to DBE. Capsule endoscopy was performed in four patients. RESULTS: A total of 17 DBE were performed in the 12 patients. The CT scan and sonography of the abdomen as well as EGD and ileocolonoscopy were unable to detect the primary tumor in any patient. A submucosal tumor of the ileum or the jejunum could be detected by DBE was detected in seven patients (58%) (anal route, n=4; oral route, n=3). In four of these patients (33%) this finding could be confirmed by the surgical resection of a NET. In two patients (17%) with a submucosal ileum protrusion suspicious for NET, laparotomy and intraoperative endoscopy did not confirm the tumor. CONCLUSIONS: In this study, the diagnostic yield of DBE for primary tumor search in patients with metastatic or suspected NET was 33%. Although endoscopic small bowel investigation by DBE seems to enrich the diagnostic possibilities for the diagnosis of small bowel-NET, at the present time DBE should only be performed in selected cases, possibly based on a positive previous work-up.

http://www.ncbi.nlm.nih.gov/pubmed/18418596

Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours.

Citation
European Journal of Nuclear Medicine & Molecular Imaging, 2008, 35(8): 1431-1438.

Authors
Ambrosin, V., Tomasetti, P., Castelucci, P., Campana, D., Montini, G., Rubello, D., Nanni, C., Rizello, A., Franchi, R., & Fanti, S.

Abstract
PURPOSE: (18)F-FDG positron emission tomography (PET) value for the assessment of neuro-endocrine tumours (NET) is limited. Preliminary studies indicate that (18)F-DOPA and (68)Ga-DOTA-NOC are more accurate for disease assessment and (68)Ga-DOTA peptides provide additional data on receptor status that are crucial for targeted radionuclide therapy. At present, there are no comparative studies investigating their role in NET. AIM: The aim of this study was to compare (68)Ga-DOTA-NOC and (18)F-DOPA for the evaluation of gastro-entero-pancreatic and lung neuro-endocrine tumours. MATERIALS AND METHODS: Thirteen patients with biopsy-proven NET (gastro-entero-pancreatic or pulmonary) were prospectively enrolled and scheduled for (18)F-DOPA and (68)Ga-DOTA-NOC PET. PET results obtained with both tracers were compared with each other, with other conventional diagnostic procedures (CT, ultrasound) and with follow-up (clinical, imaging). RESULTS: The most common primary tumour site was the pancreas (8/13) followed by the ileum (2/13), the lung (2/13) and the duodenum (1/13). The carcinoma was well differentiated in 10/13 and poorly differentiated in 3/13 cases. (68)Ga-DOTA-NOC PET was positive, showing at least one lesion, in 13/13 cases while (18)F-DOPA PET was positive in 9/13. On a lesions basis, (68)Ga-DOTA-NOC identified more lesions than (18)F-DOPA (71 vs 45), especially at liver, lung and lymph node level. (68)Ga-DOTA-NOC correctly identified the primary site in six of eight non-operated cases (in five cases, the primary was surgically removed before PET), while (18)F-DOPA identified the primary only in two of eight cases. CONCLUSIONS: Although the patients studied are few and heterogeneous, our data show that (68)Ga-DOTA-NOC is accurate for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours in

either the primary or metastatic site and that it offers several advantages over (18)F-DOPA.

http://www.ncbi.nlm.nih.gov/pubmed/18480741

Octreo-SPECT/CT imaging for accurate detection and localization of suspected neuroendocrine tumors.

Citation
Quarterly Journal of Nuclear Medicine & Molecular Imaging, 2008, 52(4): 323-333.

Authors
Perri, M., Erba, P., Voterrani, D., Lazzeri, E., Boni, G., Grosso, M., & Mariani, G.

Abstract
AIM: The aim of the present study was to prospectively evaluate the add value provided by [(111)In]DTPA-octreotide single-photon emission computed tomography/computed tomography (Octreo-SPECT/CT) with respect to [(111)In]DTPA-octreotide SPECT (Octreo-SPECT) in terms of diagnostic accuracy and localization of neuroendocrine tumors (NETs). METHODS: Eighty-one consecutive patients with known or suspected NET underwent [(111)In]DTPA-octreotide scintigraphy using an integrated SPECT/low-energy-CT system (Infinia & Hawkeye; GE Medical Systems, Milwaukee, WI, USA). SPECT and fused SPECT/CT images were interpreted separately and a lesion-by-lesion analysis was performed with regard to classification (probability of NET graded on a 5-point scale) and localization of each abnormal focal tracer uptake. A subgroup analysis, distinguishing between abdominal and thoracic lesions, and a patient-by-patient analysis for likelihood of NET in each patient was also performed. Standard of reference for confirming presence or absence of NET was either histopathology or clinical/imaging follow-up data. The value of SPECT/CT imaging was assessed by ROC analysis and McNemar test. RESULTS: A final diagnosis of NET was achieved in 43 out of 81 patients and a total of 169 areas (138 NET and 31 benign/physiological) with focal tracer uptake were included in the final lesion-by-lesion analysis. SPECT/CT imaging led to a significantly higher proportion of patients (75/81=92.6% vs 64/81=79%) and lesions (163/169=96.4% vs 138/169=81.1%) correctly classified vs SPECT alone. ROC analysis confirmed that Octreo-SPECT/CT performed significantly better than Octreo-SPECT for the detection of NET on both patient- and lesion-based analysis, improving especially evaluation of abnormal tracer uptake in the abdomen. Moreover, Octreo-SPECT/CT accurately localized 160/169 (94.7%) lesions, significantly higher than SPECT alone (77/169= 45.6%). CONCLUSIONS: Octreo-SPECT/CT allows more accurate detection and localization of NETs than simple Octreo-SPECT, with major benefits for lesions located in the abdomen.

http://www.ncbi.nlm.nih.gov/pubmed/17374863

Anatomic and functional imaging of metastatic carcinoid tumors.

Citation
Radiographics, 2007, 27(2): 455-477.

Authors
Scarsbrook, A.F., Ganeshan, A., Staham, J., Thakker, R.V., Weaver, A., Talbot, D., Boardman, P., Bradley, K. M., Gleeson, F.V., & Phillips, R. R.

Abstract
Carcinoid tumors are a fascinating group of neuroendocrine neoplasms that develop either sporadically or as part of an inheritable syndrome. Many tumors arise in the

bronchopulmonary or gastrointestinal tract, but a neuroendocrine tumor can arise in almost any organ. The tumors have varied malignant potential depending on the site of their origin, and the clinical manifestations often are nonspecific. Metastases may be present at the time of diagnosis, which often occurs at a late stage of the disease. Imaging plays a pivotal role in the localization and staging of neuroendocrine tumors and in monitoring the treatment response. Imaging is often challenging, and a combination of anatomic and functional techniques is usually required, depending on the tumor type and location. Techniques include ultrasonography, barium studies, endoscopy, computed tomography, magnetic resonance imaging, somatostatin receptor scintigraphy, iobenguane scintigraphy, and, in select cases, positron emission tomography. Coregistration of structural and functional images is often of incremental value for accurate localization of the primary tumor and any meta-static disease. Radiologists must understand the contribution of each imaging modality in the assessment of different neuroendocrine tumors. In addition, knowledge of the optimal technique for each radiologic and radionuclide imaging examination is essential. Familiarity with the protean imaging appearances of both primary and metastatic disease is essential for accurate staging, treatment monitoring, and surveillance. Finally, an understanding of the wide variety of treatment options for patients with carcinoid tumors is vital for optimal management.

http://www.ncbi.nlm.nih.gov/pubmed/16491425

Comparison of 111In-DOTA-DPhe1-Tyr3-octreotide and 111In-DOTA-lanreotide scintigraphy and dosimetry in patients with neuroendocrine tumours.

Citation
European Journal of Nuclear Medicine & Molecular Imaging, 2006, 33(5): 532-540.

Authors
Rodrigues, M., Traub-Weidinger, T., Li, S., Ibi, B., & Virgolini, I.

Abstract

PURPOSE: Somatostatin receptor scintigraphy with (111)In-DOTA-D: Phe(1)-Tyr(3)-octreotide ((111)In-DOTA-TOC) and (111)In-DOTA-lanreotide ((111)In-DOTA-LAN) has been used for staging of neuroendocrine tumours (NETs). However, the comparative diagnostic value of these radioligands on a lesion basis has not yet been established. The aim of this study was to compare the diagnostic capacity of (111)In-DOTA-TOC and (111)In-DOTA-LAN scintigraphy in patients with NETs, evaluating whether significant differences exist in lesion imaging with these radioligands. Furthermore, dosimetric data were compared. METHODS: Forty-five patients with NETs were investigated with (111)In-DOTA-TOC and (111)In-DOTA-LAN scintigraphy. Scintigraphic results were compared with those of conventional imaging and/or surgery in each patient, and also (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) in 20 patients. RESULTS: (111)In-DOTA-TOC and (111)In-DOTA-LAN scintigraphy were true positive in 42/45 (93%) and 39/45 (87%) patients, and imaged 74/91 (81%) and 73/91 (80%) tumour lesions, respectively. (111)In-DOTA-TOC and (111)In-DOTA-LAN detected liver metastases in 21 and 14 patients, mediastinal metastases in seven and 11 patients, and bone metastases in two and seven patients, respectively. These radioligands revealed lesions not seen by conventional imaging in seven and eight patients, respectively, or by (18)F-FDG-PET in eight and seven patients, respectively. The estimated tumour absorbed doses for (90)Y-DOTA-TOC were higher than those for (90)Y-DOTA-LAN in 14 patients, whereas the opposite was true in 12 patients. CONCLUSION: Both (111)In-DOTA-TOC and (111)In-DOTA-LAN are suitable for imaging tumour lesions in patients with NETs

and can detect lesions that may not be seen by conventional imaging and (18)F-FDG-PET. Compared with (111)In-DOTA-LAN, (111)In-DOTA-TOC has a superior diagnostic capacity for liver metastases, but a lower diagnostic capacity for metastatic lesions in mediastinum and bone.

http://www.ncbi.nlm.nih.gov/pubmed/16813805

Detection of small-bowel neuroendocrine tumors by video capsule endoscopy.

Citation
Gastrointestinal Endoscopy, 2006, 64(1): 66-72.

Authors
Van Tuyl, S.A., van Noorden, J.T., Timmer, R., Stolk, M. F., Kuipers, E.J., & Taal, B.G.

Abstract
OBJECTIVES: Carcinoid tumors are the most common GI neuroendocrine tumors (NET). They often originate in the small intestine. The primary tumor is often difficult to locate, and resection in an early phase is recommended to prevent complications. This study evaluated the value of videocapsule endoscopy (VCE) in the detection of small-intestinal primary carcinoid tumor. DESIGN: Prospective descriptive study. SETTING: Tertiary referral center. PATIENTS: Twenty consecutive patients (13 men, 7 women; 60.5 +/- 9.3 years) with metastatic NET of unknown primary tumor. INTERVENTIONS: All patients underwent CT, enteroclysis, nuclear imaging, and VCE of the small bowel. RESULTS: CTs and enteroclysis did not detect a primary small-intestinal carcinoid tumor. Nuclear imaging demonstrated abnormalities in the abdominal area in 13 patients but was unable to relate this to an intestinal localization in any patient. VCE revealed a small-intestinal tumor in 9 patients. Three other patients showed external compression and erosions. At surgery, 5 patients had a small-intestinal carcinoid tumor, and, in 2 patients, a small-intestinal ischemic segment was present. LIMITATIONS: The number of false-positive VCE findings was not clear, because not all patients underwent surgery. The absence of abnormalities at VCE in patients with abnormalities at nuclear imaging might be related to the presence of carcinoid tumor restricted to the mesenterium or to a false-negative VCE. CONCLUSIONS: VCE had a high diagnostic yield of 45% for identification of primary small-intestinal carcinoid tumors. Although nuclear imaging had a comparable diagnostic yield, it could not differentiate between intestinal and mesenterial localization of the carcinoid.

http://www.ncbi.nlm.nih.gov/pubmed/16721571

99mTc-EDDA/HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience.

Citation
European Journal of Nuclear Medicine & Molecular Imaging, 2006, 33(10): 1123-1133.

Authors
Hubalewska-Dydejczyk, A., Fröss-Baron, K., Mikolajczak, R., Maeke, H.R., Huzno, B, Pach, D., Sowa-Staszczak, A., Jonato, B., Szybiński, P., & Kulig, J.

Abstract
PURPOSE: At all stages of the disease, serious difficulties are encountered in the imaging diagnosis of carcinoids. Somatostatin receptor scintigraphy (SRS) holds great promise for

detecting primary tumours and metastases. 99mTc-EDDA/HYNIC-octreotate should significantly improve the diagnosis of carcinoids in comparison with 111In-Octreoscan owing to the better affinity for SSR2 and the higher count rate. The aim of this study was to assess the diagnostic efficiency of 99mTc-EDDA/HYNIC-octreotate scintigraphy in the detection and staging of carcinoid tumours. METHODS: The study population comprised 75 patients (age 48.5+/-15.5 years): 46 with histological confirmation of carcinoid and 29 with suspected disease. 99mTc-EDDA/HYNIC-octreotate (740 MBq) SRS and CT were performed in all patients. Fifteen patients were examined with 111In-Octreoscan. RESULTS: High-quality 99mTc-EDDA/HYNIC-octreotate images were obtained in all cases, with maximum tumour tracer accumulation 4 h p.i. The mean target/non-target ratios for whole body (WB) and SPECT scans were, respectively, as follows: primary lesions: 4.5 and 10.2; metastases: liver, 3.1 and 12.3; abdominal focal lesions, 2.7 and 5.8; lung, 2.7 and 8.3; mediastinum, 3.4 and 7.6; bones, 6.8 and 19.0. 99mTc-EDDA/HYNIC-octreotate WB scans revealed more metastases than 111In-Octreoscan, with better individual separation. 99mTc-EDDA/HYNIC-octreotate SRS revealed new metastatic lesions in seven patients with confirmed carcinoid, and in four with dissemination the primary focus was found. Five patients qualified for radioguided surgery and 11 were referred to 90Y-DOTA-TATE therapy. The sensitivity of SRS in comparison with CT was higher for primary lesions and liver and abdominal lymph node metastases. In the subgroup of patients with suspected neuroendocrine tumours, two duodenal carcinoids, one thymic carcinoid and one ileal carcinoid were found. CONCLUSION: 99mTc-EDDA/HYNIC-octreotate, with high imaging quality, is an excellent alternative to 111In-Octreoscan for staging of carcinoids, and it seems to be the method of choice for detection of the primary focus in patients with metastases from an unknown primary tumour.

http://www.ncbi.nlm.nih.gov/pubmed/17116005

Use of integrated FDG PET/CT imaging in pulmonary carcinoid tumours.

Citation
Journal of internal Medicine, 2006, 260(6): 545-550.

Authors
Krüger, S., Buck, A.K., Blumstein, N.M., Paul, S., Schelzig, H., Kropf., Schumann, C., Mottaghy, F.M., Hombach, V., & Reske, S.N.

Abstract

BACKGROUND: Integrated positron emission tomography (PET)/computed tomography (CT) scanners have been recently introduced in the diagnostic work-up of suspected pulmonary malignancy and demonstrate encouraging results in the staging of nonsmall-cell lung cancer. OBJECTIVE: To evaluate the usefulness of integrated FDG PET/CT in pulmonary carcinoid tumours. SETTING: University hospital. METHODS: We studied 13 patients (mean age +/- 1 SD, 57 +/- 11 years) with pulmonary carcinoid tumours. All patients demonstrated a single pulmonary lesion. Integrated PET/CT scan and surgical resection were performed in all patients. RESULTS: The pulmonary lesion size ranged from 1.1 to 5.0 cm. Final histological diagnosis confirmed 12 typical and one atypical pulmonary carcinoid. Mean proliferation rate of the typical carcinoids was 1.7 +/- 1.4%. None of the patients had recurrent carcinoid disease or died during follow-up (864 +/- 218 days). Mean standardized uptake value (SUV) of (18)F-fluorodeoxyglucose (FDG) in typical carcinoids was 3.0 +/- 1.5 (range 1.2 - 6.6); SUV in the atypical carcinoid was remarkably high with a value of 8.5. The SUV was lower than 2.5 in 6 of 12 patients (50%). Mediastinal lymph node metastases or extrathoracic metastases were not detected in any patient. CONCLUSIONS: (18)F-fluorodeoxyglucose PET/CT imaging improves accurate localization of metabolic activity and thus the interpretation of pulmonary

lesions on CT. FDG uptake in pulmonary carcinoid tumours is often lower than expected for malignant tumours. Therefore, surgical resection or biopsy of lesions suspected to be carcinoids should be mandatory, even if they show no hypermetabolism on FDG PET images.

http://www.ncbi.nlm.nih.gov/pubmed/15755858

Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography.

Citation
The Journal of Clinical Endocrinology & Metabolism, 90(6): 3392-3400.

Authors
Orlefors, H., Sundin, A., Garske, U., Juhlin, C., Oberg, K., Skogseid, B., Langstrom, B., Bergstrom, M., & Eriksson, B.

Abstract
Neuroendocrine tumors (NETs) can be small and situated almost anywhere throughout the body. Our objective was to investigate whether whole-body (WB) positron emission tomography (PET) with (11)C-5-hydroxytryptophan (5-HTP) can be used as a universal imaging technique for NETs and to compare this technique with established imaging methods. Forty-two consecutive patients with evidence of NET and a detected lesion on any conventional imaging (six bronchial, two foregut, 16 midgut, and two thymic carcinoids; one ectopic Cushing's syndrome; four gastrinomas; one insulinoma; six nonfunctioning endocrine pancreatic tumors; one gastric carcinoid, one paraganglioma; and two endocrine-differentiated pancreatic carcinomas) were studied. The WB-(11)C-5-HTP-PET examinations were compared with WB-computed tomography (CT) and somatostatin receptor scintigraphy (SRS). Tumor lesions were imaged with PET in 95% of the patients. In 58% of the patients, PET could detect more lesions than SRS and CT and equal numbers in 34%, whereas in three cases, SRS or CT showed more lesions. In 84% (16 of 19 patients), PET could visualize the primary tumor compared with 47 and 42% for SRS and CT, respectively. The surgically removed PET-positive primary tumor sizes were 6-30 mm. To conclude, this study indicates that WB-(11)C-5-HTP-PET can be used as a universal imaging method for detection of NETs. This study also shows that WB-(11)C-HTP-PET is sensitive in imaging small NET lesions, such as primary tumors, and can in a majority of cases image significantly more tumor lesions than SRS and CT.

http://www.ncbi.nlm.nih.gov/pubmed/15763700

Nuclear medicine in the detection, staging and treatment of gastrointestinal carcinoid tumours.

Citation
Best Practice & Research in Clinical Endocrinology and Metabolism, 2005, 19(2): 265-276.

Authors
Oberg, K., & Eriksson, B.

Abstract
Carcinoid tumours belong to the family of neuroendocrine tumours with a capacity to take up and concentrate amines and precursors as well as peptides, and can thereby be detected by nuclear medicine techniques. These rare tumours are difficult to diagnose at earlier stages

because of small size and multiplicity. Computed tomography (CT) and magnetic resonance imaging (MRI) are mostly of benefit for detection of larger primary tumours (1-3 cm) and liver and lymph-node metastases. A majority of carcinoid tumours express somatostatin receptors, particularly receptor type 2, and thus somatostatin receptor scintigraphy (SRS) can be used for detection and staging of carcinoid tumours. The detection rate of carcinoid tumours has been reported to be somewhere between 80 and 100% in different studies. The scintigraphy gives a good staging of the disease and detection of unexpected tumour sites, which were not determined by conventional imaging. This method also indicates content of somatostatin receptors, which might indicate efficacy of treatment with octreotide or other somatostatin analogues. Another new non-invasive technique for detection of carcinoid tumours is positron emission tomography (PET). The biological substance for study can be labelled for radioactive imaging with radionuclears, such as (11)C, (15)O and (18)F, with emission of positrons. More than 95% of patients studied displayed high tracer uptake from PET with (11)C-5HTP (5-hydroxytryptophan), which is significantly higher compared to both computer tomography and somatostatin receptor scintigraphy. MIBG has been used for decades to visualize carcinoid tumours, because MIBG is concentrated in the endocrine cells. It was initially developed to detect phaeochromocytomas of the adrenal with reported high sensitivity (87%) and specificity as high as 99%. The method can be used when other methods fail to localize carcinoid tumours and particularly when treatment with (131)I-MIBG is being considered. Tumour-targeted treatment for malignant carcinoid tumour is still investigational, but has become of significant interest with the use of radiolabelled somatostatin analogues. Since a majority of carcinoid tumours present somatostatin receptors and can therefore be visualized in vivo by using radiolabelled somatostatin analogues, it seems logical to try to target these tumours with radioactive substances, not only for visualization but also for treatment. (111)Indium-DTPA-octreotide has been used as the first tumour-targeted treatment, with rather low response rates (in the order of 10-20%) and no significant tumour shrinkage. The second radioactive analogue which has been applied in the clinic is (90)yttrium-DOTA-Tyr3-octreotide, which has given partial and complete remissions in 20-30% of patients. The most significant side-effects have been kidney dysfunction, thrombocytopenia and liver toxicity. The most recent compound is (177)lutetium-DOTA-Tyr3-octreotate, which has been applied by the Rotterdam group and has been reported to give partial remission in about 40% of the patients. In the near future, combined treatment with both (90)yttrium and (177)lutetium coupled to a somatostatin analogue might come into clinical trials. (177)Lutetium may be more effective for smaller tumours whereas (90)yttrium may be more effective for larger tumours.

http://www.ncbi.nlm.nih.gov/pubmed/15669565

Bronchial carcinoid tumors: role of imaging for diagnosis and local staging

Citation
Journal of Radiology, 2004, 85(10 Pt 1): 1711-1719

Authors
Paillas, W., Moro-Sibilot, D., Lantuejoul, S., Brichon, P.Y., Coulomb, M., & Ferretti, G.

Abstract
PURPOSE: To describe the imaging features of bronchial carcinoids and to define the role of CT as a diagnostic and pretherapeutic tool. MATERIALS AND METHODS: We performed a retrospective study including 54 carcinoids. We evaluated and compared the clinical, radiographic, CT, fiberoptic, and pathologic data. RESULTS: At presentation, the mean age

was 48.5 years (14-81) and patients mainly complained of signs related to bronchial obstruction (55.7%). 72% of bronchial carcinoids were located in the proximal airway. CT showed calcifications in 26% of 54 cases and contrast enhancement in 60%. Typical carcinoids differed from atypical carcinoids in their size and lymph node extension. As compared to fiberoptic bronchoscopy, CT identified proximal carcinoids with exo-bronchial extension (7.4%), peripheral tumors (20.4%), and parenchymal complications. The sensitivity and predictive positive-value of CT for lymph node extension was 28% and 20%, respectively. CONCLUSION: CT is a useful technique for diagnosing and localizing bronchial carcinoids. The results of CT in determining lymph node extension is disappointing, and should raise caution in case of localized treatment using fiberoptic bronchoscopy.

http://www.ncbi.nlm.nih.gov/pubmed/12571207

Bone metastases in carcinoid tumors: clinical features, imaging characteristics, and markers of bone metabolism.

Citation
Journal of Nuclear Medicine, 2003, 44(2): 184-191.

Authors
Meijer, W.G., van der Verr, E., Jager, P.L., van der Jagt, E.J., Piers, B.A., Kema, I.P., De Vries, E.G., & Willemse, P.H.

Abstract
The purpose of this study was to describe the clinical presentation of bone metastases in patients with carcinoid tumors and to determine the diagnostic value of imaging techniques and markers of bone metabolism. METHODS: This retrospective study was performed on the entire group of patients with carcinoid tumors treated in our hospital from January 1992 to May 1999. Only patients with metastasized tumors were included. RESULTS: Eleven of 90 patients (12%) (95% confidence interval [CI], 5%-19%) with a metastasized carcinoid tumor had symptomatic bone metastases. All bone metastases occurred in 55 patients with midgut carcinoids (20%; 95% CI, 9%-31%). Plain radiography had a sensitivity of 44% (95% CI, 12%-76%); MRI, 100% (95% CI, 61%-100%); bone scintigraphy, 90% (95% CI, 72%-100%); and octreotide scintigraphy, 60% (95% CI, 35%-93%). In 9 patients, both octreotide scintigraphy and bone scintigraphy were performed. Of 45 bone lesions, 22 (49%) were visualized by both modalities, 13 (29%) were visualized with octreotide scintigraphy but not with bone scintigraphy, and 10 (22%) were visualized with bone scintigraphy but not with octreotide scintigraphy. In 2 patients, octreotide scintigraphy and bone scintigraphy provided complementary results. Markers of bone metabolism could not discriminate carcinoid patients from those without bone metastases. The markers of bone metabolism did not reflect the osteolytic or osteoblastic appearance of metastases. CONCLUSION: Pain is the principal symptom of bone metastases in patients with carcinoid tumors. Plain radiography and markers of bone metabolism do not contribute to the diagnosis of bone metastases. MRI has a high sensitivity for bone metastases. Both bone scintigraphy and octreotide scintigraphy have acceptable sensitivity and can provide complementary results.

http://www.ncbi.nlm.nih.gov/pubmed/10940687

Endoscopic ultrasonography of neuroendocrine tumours

Citation

Digestion, 2000, 62 (Suppl 1): 45-50.

Authors
Zimmer, GT., Scherübl, H., Stölzel, U., Riecken, E.O., & Wiedenmann, B.

Abstract
Neuroendocrine tumours (NETs) of the upper gastrointestinal tract are mainly located in the pancreas, stomach or duodenum. The aims of preoperative work-up are the localization of primary tumour(s), determination of local tumour invasion, of lymph node metastases and of the hormones secreted by the tumour. Endoscopic ultrasonography (EUS) offers ideal conditions to localize and stage NETs of the foregut. We report our results in localizing and staging NETs of the foregut in 40 patients examined between 1990 and 1997 by EUS, somatostatin receptor scintigraphy (SRS), computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasound (US). EUS shows the highest sensitivity in localizing insulinomas compared with SRS, US, CT and MRI. US and EUS should be the first-line diagnostics if insulinoma has been proven by a fasting test. Further diagnostic procedures are unnecessary in most cases. Further diagnostics such as CT or MRI to search for distant metastases are necessary in large tumours or local invasive tumours. EUS shows the highest accuracy to detect or exclude pancreatic gastrinomas, but fails to detect extrapancreatic gastrinomas in about 50%. The combination of EUS and SRS gives additional information. First-line diagnostics in gastrinoma patients should be SRS and CT or MRI. If no metastases are detected, EUS should be the next preoperative imaging procedure. In nonfunctional NETs, EUS provides the best information on local tumor invasion and regional lymph node involvement.

http://www.ncbi.nlm.nih.gov/pubmed/10932602

Intraoperative use of gamma-detecting probes to localize neuroendocrine tumors.

Citation
Quarterly Journal of Nuclear Medicine, 2000, 44(1): 59-67.

Authors
Adams, S, & Baum, R.P.

Abstract
Neuroendocrine tumors are characterized by the expression of different peptides and biogenic amines. These rare tumors tend to grow slowly and are notoriously difficult to localize, at least in the early stages. Surgical removal is the only definitive therapeutic option for neuroendocrine tumors and relief from hyperfunctional status. The effectiveness of surgical treatment is invariably dependent upon the complete surgical excision of all tumor tissue, because microscopic and occult disease not readily seen by the surgeon may remain in situ, leading to shortened survival. Therefore, pre- and intraoperative localization of the primary as well as of metastatic tumors is of utmost importance. Radioguided surgery (RGS) is an intraoperative technique that enables the surgeon to localize radiolabelled tissue based on the characteristics of the various tissues. Concerning gastroenteropancreatic tumors (GEP), intraoperative gamma probe examination is able to reveal small tumor sites accumulating (111In-DTPA-D-Phe1)-pentetreotide more efficiently (> 90%) than somatostatin receptor scintigraphy (68%-77%), because lesions with a size smaller than 5 mm in greatest dimension could be identified. Furthermore, RGS identified 57% more lesions when compared to the "palpating finger" of the surgeon. In medullary thyroid cancer (MTC), surgical removal of the

tumor is the first and most efficient treatment of the disease. Persistent or increasing serum calcitonin and carcinoembryonic antigen (CEA) levels imply tumor recurrence after thyroid ablation. For imaging recurrent MTC many radiopharmaceuticals have been used to visualize tumor sites, but none of them has shown excellent sensitivity. Preoperative somatostatin receptor scintigraphy and intraoperative RGS in patients with recurrent MTC demonstrate only part of the tumor sites and cannot visualize small tumor sites (less than 10 mm). In comparison, RGS using 99mTc(V)-DMSA detects metastases with a size of 5 mm in diameter, whereas the "palpating finger" of the surgeon localized metastases with a size of more than 1 cm in diameter. In patients with recurrent MTC, intraoperative gamma probe examination is able to localize over 30% more tumor lesions when compared with conventional preoperative imaging modalities and surgical findings. MIBG scintigraphy is the most sensitive technique for the detection and staging of neuroblastoma (sensitivity 92%; specificity nearly 100%). Intraoperative RGS with iodine labelled MIBG has been developed to improve the definition of tumor limits or to localize small, nonpalpable tumors. Comparison of 123I- and 125I-labelled MIBG revealed a sensitivity of 91% and 92%, respectively; the specificity of 125I (85%) was significantly higher than that of 123I (55%). In addition to scintigraphy of the adrenal glands by precusors of adrenal hormones, imaging with a radiolabelled somatostatin analogue is possible; however, (111In-DTPA-D-Phe1)-pentetreotide is not specific for any adrenal disease or function and the relatively high radioligand accumulation in the kidneys limited the use for detection of tumors in the area of the adrenal glands.

BIOCHEMICAL TESTING

OVERVIEW

http://ovidsp.tx.ovid.com.ezproxy1.library.arizona.edu/sp-2.3.1b/ovidweb.cgi?

Biochemical Testing for Neuroendocrine Tumors

Citation

Pancreas, 2009, 38(8): 876-889.

Authors
Vinik, A.I., Silva, M.P. Woltering, G., Go, W.L.W., Warner, R., & Caplin, M.

Abstract
In this review, we focus on the use of biochemical markers for the diagnosis of neuroendocrine tumors and exclusion of conditions that masquerade as neuroendocrine tumors. In addition, we outline the use of biochemical markers for follow-up, response to intervention, and determination of prognosis. Previous publications have focused only on markers specific to certain tumor types, but the uniqueness of this chapter is that it presents a new approach ranging from biochemical markers that relate to symptoms to the use of markers that facilitate decision making with regard to optimizing the choices of therapy from the complex arrays of intervention, The sequence of presentation in this chapter is first to provide the usual view, that is, biochemical markers of each tumor type and thereafter the diagnosis of the underlying condition or exclusion thereof and finally the algorithm for their use from the clinical presentation to the suspected diagnosis and the biochemical

markers to monitor progression and therapeutic choice. There is also a specific description of the properties of the most important biochemical markers and 2 complications, bone metastasis and carcinoid heart disease, from the biochemical point of view.

http://www.ncbi.nlm.nih.gov/pubmed/17382264

Biochemistry of neuroendocrine tumours.

Citation
Best Practice & Research in Clinical Endocrinology & Metabolism., 2007, 21(1): 33-41.

Authors
de Herder, W.W.

Abstract
Several circulating or urinary tumour markers can be used for the diagnosis and follow-up of functioning and clinically non-functioning neuroendocrine tumours of the pancreatic islet cells and intestinal tract. Among the specific tumour markers are serotonin and its metabolites--e.g. 5-hydroxyindoleacetic acid (5-HIAA)--in carcinoid tumours and the carcinoid syndrome, insulin and its precursors or breakdown products in insulinoma, and gastrin in gastrinoma. Plasma vasointestinal polypeptide (VIP) determinations have been used in the diagnosis of VIPoma, plasma glucagon for glucagonoma, and serum somatostatin for somatostatinoma. Among the tumour-non-specific markers are: chromogranins, neuron-specific enolase (NSE), alpha-subunits of the glycoprotein hormones, catecholamines, pancreatic polypeptide (PP), ghrelin and adrenomedullin.

STUDIES

http://www.ncbi.nlm.nih.gov/pubmed/20124939

Development of a Highly Sensitive and Specific Carboxy-Terminal Human Pancreastatin Assay to Monitor Neuroendocrine Tumor Behavior.
Citation
Pancreas, 2010, Jan 29. [Epub ahead of print]

Authors
O'Dorisio, TM., Krutzik, S.R., Woltering, E.A., Lindholm, E., Joseph, S., Gandolfi, A.E., Wang, Y.Z., Boudreaux, J.P., Vinik, A.I., Go, V.L., Howe, J.R., Halfdanarson, T., O'Dorisio, M.S., & Mamikunian, G.
Abstract
OBJECTIVE:: Pancreastatin is a fragment of the chromogranin A (CgA) molecule. Existing pancreastatin assays, which depend on antibodies that cross-react in varying percents with the larger prohormone, may lack sensitivity and specificity to detect small changes in neuroendocrine tumor volume. METHODS:: We developed a highly specific, sensitive pancreastatin assay. The antibody used recognizes the carboxyl terminal of the peptide hormone and was raised against a 17-amino acid porcine pancreastatin fragment with high homology with the carboxy-terminal amino acids 286-301 of the human CgA. RESULTS:: Our assay measures more than 95% of circulating pancreastatin levels; has little or no cross-reactivity with CgA, even at plasma concentrations of 1000 ng/mL; and can detect pancreastatin levels of 17 pg/mL. Interassay reproducibility for the pancreastatin radioimmunoassay was determined from results of 3 quality control pools in 15 consecutive

assays. Coefficients of variation for low, medium, and high pancreastatin levels were less than 20%. The sensitivity of serial pancreastatin assays to detect early liver tumor activity was demonstrated in 2 patients with slowly progressive neuroendocrine tumors and in patients undergoing surgical cytoreduction. CONCLUSIONS:: This highly specific, sensitive pancreastatin assay can detect small changes in liver tumor progression and is up to 100-fold more sensitive and specific than CgA assays in the United States.

http://www.ncbi.nlm.nih.gov/pubmed/19115463

Importance of gastrin in the pathogenesis and treatment of gastric tumors.

Citation
World Journal of Gastroenterology, 2009, 15(1): 1-16.

Authors
Burkitt, M.D., Varro, A., & Pritchard, D.M.

Abstract
In addition to regulating acid secretion, the gastric antral hormone gastrin regulates several important cellular processes in the gastric epithelium including proliferation, apoptosis, migration, invasion, tissue remodelling and angiogenesis. Elevated serum concentrations of this hormone are caused by many conditions, particularly hypochlorhydria (as a result of autoimmune or Helicobacter pylori (H pylori)-induced chronic atrophic gastritis or acid suppressing drugs) and gastrin producing tumors (gastrinomas). There is now accumulating evidence that altered local and plasma concentrations of gastrin may play a role during the development of various gastric tumors. In the absence of H pylori infection, marked hypergastrinemia frequently results in the development of gastric enterochromaffin cell-like neuroendocrine tumors and surgery to remove the cause of hypergastrinemia may lead to tumor resolution in this condition. In animal models such as transgenic INS-GAS mice, hypergastrinemia has also been shown to act as a cofactor with Helicobacter infection during gastric adenocarcinoma development. However, it is currently unclear as to what extent gastrin also modulates human gastric adenocarcinoma development. Therapeutic approaches targeting hypergastrinemia, such as immunization with G17DT, have been evaluated for the treatment of gastric adenocarcinoma, with some promising results. Although the mild hypergastrinemia associated with proton pump inhibitor drug use has been shown to cause ECL-cell hyperplasia and to increase H pylori-induced gastric atrophy, there is currently no convincing evidence that this class of agents contributes towards the development of gastric neuroendocrine tumors or gastric adenocarcinomas in human subjects.

http://www.ncbi.nlm.nih.gov/pubmed/18805126

Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease.

Citation
American Journal of Cardiology, 2008, 102(7): 938-942.

Authors
Bhattacharyya, S., Toumpanakis, C., Caplin, M.E., & Davar, J.

Abstract

We sought to investigate whether N-terminal pro-brain natriuretic peptide (NT-pro-BNP) can

be used as a biomarker for the detection of carcinoid heart disease (CHD); 200 patients with carcinoid syndrome were screened for CHD using transthoracic echocardiography. A carcinoid score was formulated to quantify severity of CHD. NT-pro-BNP was measured in all patients before echocardiography. Patients were categorised into New York Heart Association class. CHD was present in 39 patients (19.5%). NT-pro-BNP was significantly higher in those with CHD (median 1,149 pg/ml) than in those without CHD (median 101 pg/ml, $p < 0.001$). The sensitivity and specificity of NT-pro-BNP at a cut-off level of 260 pg/ml for detection of CHD were 0.92 and 0.91, respectively. NT-pro-BNP positively correlated both with carcinoid score ($r = 0.81$, $p < 0.001$) and New York Heart Association class ($p < 0.001$). The number of patients screened to diagnose 1 case of CHD decreased from 5.1 to 1.4. In conclusion, NT-pro-BNP seems to be an excellent biomarker of CHD. A high negative predictive value may allow it to provide a screening test for CHD.

http://www.ncbi.nlm.nih.gov/pubmed/18448176

Measurements of secretogranins II, III, V and proconvertases 1/3 and 2 in plasma from patients with neuroendocrine tumours.

Citation
Regulatory Peptides, 2008, 148(1-3):95-98

Authors
Stridsberg, M., Eriksson, B., & Janson, E.T.

Abstract
INTRODUCTION: Chromogranin (Cg) and secretogranin (Sg) are members of the granin family of proteins, which are expressed in neuroendocrine and nervous tissue. In recent publications we have presented generation of region-specific antibodies against CgA and CgB and also development of several region-specific radioimmunoassays for measurements of specific parts of the Cgs. In this study we describe generation of antibodies against SgII, SgIII, SgV and the proconvertases PC1/3 and PC2 and development of radioimmunoassays for measurements of these proteins. MATERIALS AND METHODS: Peptides homologous to defined parts of the secretogranin and proconvertase molecules were selected and synthesised. Antibodies were raised, radioimmunoassays were developed and circulating levels of the proteins in plasma samples from 22 patients with neuroendocrine tumours were measured in the assays. RESULTS: Increased plasma concentrations were recorded in 11, 4 and 3 of the patients with the SgII 154-165 (N-terminal secretoneurin), the SgII 172-186 (C-terminal Secretoneurin) and the SgII 225-242 assays respectively. The SgIII, SgV, PC1/3 and PC2 assays failed to detect increased concentrations in any of the patients. CONCLUSION: Increased concentrations of SgII, especially the N-terminal part of secretoneurin could be measured in plasma from patients with endocrine pancreatic tumours and in this case this assay was quite comparable to measurements of CgA and CgB. Even though secretoneurin was not as frequently increased as CgA and CgB in patients with carcinoid tumours or pheochromocytoma it may be a useful marker for endocrine pancreatic tumours.

http://www.ncbi.nlm.nih.gov/pubmed/18524798

Tachykinins in endocrine tumors and the carcinoid syndrome.

Citation
European Journal of Endocrinology, 2008, 159(3): 275-282.

Authors
Cunnigham, J. L., Janson, E.T., Agarwal, S., Grimelius, L., & Stridsberg, M.

Abstract
OBJECTIVE: A new antibody, active against the common tachykinin (TK) C-terminal, was used to study TK expression in patients with endocrine tumors and a possible association between plasma-TK levels and symptoms of diarrhea and flush in patients with metastasizing ileocecal serotonin-producing carcinoid tumors (MSPCs). METHOD: TK, serotonin and chromogranin A (CgA) immunoreactivity (IR) was studied by immunohistochemistry in tissue samples from 33 midgut carcinoids and 72 other endocrine tumors. Circulating TK (P-TK) and urinary-5 hydroxyindoleacetic acid (U-5HIAA) concentrations were measured in 42 patients with MSPCs before treatment and related to symptoms in patients with the carcinoid syndrome. Circulating CgA concentrations were also measured in 39 out of the 42 patients. RESULTS: All MSPCs displayed serotonin and strong TK expression. TK-IR was also seen in all serotonin-producing lung and appendix carcinoids. None of the other tumors examined contained TK-IR cells. Concentrations of P-TK, P-CgA, and U-5HIAA were elevated in patients experiencing daily episodes of either flush or diarrhea, when compared with patients experiencing occasional or none of these symptoms. In a Spearman partial rank test, the correlation of P-TK with daily diarrhea was independent of both U-5HIAA and CgA levels. CONCLUSION: We found that TK synthesis occurs in serotonin-IR tumors and that P-TK levels are significantly correlated with symptoms of flush and diarrhea in patients with MSPCs. This is, to our knowledge, the first report demonstrating an independent correlation of P-TKs with carcinoid diarrhea, a symptom that is customarily regarded as serotonin mediated. Further investigations may present opportunities for new therapeutic possibilities.

http://www.ncbi.nlm.nih.gov/pubmed/18577995

Alpha-fetoprotein and human chorionic gonadotrophin-beta as prognostic markers in neuroendocrine tumour patients.

Citation
British Journal of Cancer, 2008, 99(1): 72-77.

Authors
Shah, T., Srirajaskanthan, R., Bhogal, M., Toubanakis, C., Meyer, T., Noonan, A., Witney-Smith, C., Amin, T., Bhogal, P., Sivathasan, N., Warner, B., Hochhauser, D., & Caplin, M.E.

Abstract
Serum chromogranin A is the most useful general and prognostic tumour marker available for neuroendocrine tumour (NET) patients. The role of other tumour markers is less clear. In order to determine the diagnostic and prognostic value of serum alpha-fetoprotein (AFP) and human chorionic gonadotrophin-beta (hCGbeta) in NETs, a database containing biochemical, histological, and survival data on 360 NET patients was constructed. This data was statistically assessed, using Statistical Package for the Social Sciences, to determine the utility of commonly measured tumour markers with particular emphasis on AFP and hCGbeta. Alpha-fetoprotein and hCGbeta were raised in 9.5 and 12.3% of patients respectively and jointly raised in 9.1% of patients in whom it was measured. Alpha-fetoprotein levels associated strongly and positively with tumour grade, serum CgA and hCGbeta levels, and worse survival. Human chorionic gonadotrophin-beta levels also associated strongly and positively with serum CgA and AFP levels, and worsening survival. Alpha-fetoprotein and hCGbeta are elevated in high-grade NETs, with a rapidly progressive course and poorer

survival. They also correlate with chromogranin-A, which is known to be a marker of tumour burden and to have prognostic value. Thus AFP and hCGbeta are clinically important in NETs and when elevated are poor prognostic markers.

http://www.ncbi.nlm.nih.gov/pubmed/17585539

Selected markers (chromogranin A, neuron-specific enolase, synaptophysin, protein gene product 9.5) in diagnosis and prognosis of neuroendocrine pulmonary tumours.

Citation
Polish Journal of Pathology, 2007, 58(1): 23-33.

Authors
Kasprzak, A., Zabel., & Biczysko, W.

Abstract
Neuroendocrine tumours of lungs represent a subgroup of pulmonary tumours with typical morphofunctional traits. In light microscopy, the four principal types of the tumours (typical and atypical carcinoids, small cell lung cancer, large cell neuroendocrine carcinoma) demonstrate typical arrangement of cells (organoid nesting, palisading, a trabecular pattern, and rosette-like structures), variable number of mitoses, presence or absence of necrosis. In ultrastructure, neuroendocrine tumours manifest groups of cells with cytoplasmic granules (and the so called dense-core neurosecretory granules in particular). Neuroendocrine cells release hormones to circulation or in a paracrine manner. Some pulmonary tumours exhibit no neuroendocrine morphology at the level of light microscopy but demonstrate ultrastructural and/or immunohistochemical traits of neuroendocrine differentiation. Proteins the presence of which confirms neuroendocrine origin of the tumours have been found relatively early to include neuron-specific enolase (NSE), the group of chromogranins and synaptophysin. Present study aimed at summing up results of investigations conducted in, approximately, recent 30 years pertaining expression and/or serum concentrations of four neuroendocrine markers (chromogranin A, neuron-specific enolase, synaptophysin, protein gene product 9.5) and at an attempt to evaluate the role of such studies in extension of diagnostic and prognostic potential as related to neuroendocrine pulmonary tumours. Until now, the most sensitive and specific marker or marker combination for early detection of neuroendocrine subtypes of lung tumours has not been identified. All of the markers examined in present study were detected both in the typical neuroendocrine pulmonary tumours and in a certain proportion of non-endocrine tumours. In the case of chromogranin A improved sensitivity and specificity of immunocytochemical studies was obtained using a panel of antibodies directed to various epitopes of the protein. Both in endocrine and non-endocrine tumours, neuron-specific enolase (NSE) is thought to represent mainly a prognostic index, and only quantitation of serum concentrations of the protein or of the fraction of immunopositive cells may permit to differentiate between subtypes of the tumours. Synaptophysin is regarded to represent one of the most specific markers of neuroendocrine differentiation, manifesting a much higher sensitivity than chromogranin A and NSE. With increasing frequency, PGP 9.5 is regarded to provide a prognostic marker in diagnosis of non-small cell lung carcinomas rather than of typical neuroendocrine tumours.

http://www.ncbi.nlm.nih.gov/pubmed/17003646

Validation of serum versus plasma measurements of chromogranin a levels in patients with carcinoid tumors: lack of correlation between absolute chromogranin a levels and symptom frequency.

Citation
Pancreas, 2006, 33(3): 250-254.

Authors
Woltering, E.A., Hilton, R.S., Zolfoghary, C.M., Thomson, J., Zietz, S., Go, V.L., Vinik, A.I., Vinik, E., O'Dorisio, T.M., & Mamikunian, G.

Abstract
OBJECTIVE: Chromogranin A (CGA) levels are used to confirm the diagnosis and monitor the course of patients with neuroendocrine tumors. Chromogranin A levels are significantly reduced when patients are acutely treated with octreotide; however, limited data are available that correlates octreotide long-acting repeatable (LAR) dose or steady state octreotide blood levels to the absolute value of serum or plasma CGA. METHODS: Plasma, serum, and clinical information on carcinoid syndrome symptoms were collected anonymously from 40 patients treated with long-term octreotide LAR therapy for carcinoid syndrome. RESULTS: We found a strong positive linear relationship exists between serum and plasma CGA levels ($r = 0.9858$, $P < 0.0001$). No correlation existed between plasma octreotide levels or LAR dose and the static, absolute plasma/serum CGA levels. Although, higher mean CGA values were seen in the group whose diarrhea was "not under optimal control" than for the group "under optimal control," these results did not reach statistical significance ($P = 0.24$). Contrary to our hypotheses, a statistically significant inverse relationship was found between the frequency of flushing and the CGA levels ($P = 0.0372$). Higher mean CGA values were observed in the "under optimal control" group with flushing symptoms. CONCLUSIONS: Either serum or plasma can be used to measure CGA levels. Absolute (static) CGA levels do not positively correlate with symptom intensity during LAR therapy. Dynamic (serial) measurements of CGA are necessary to monitor the effectiveness of medical or surgical therapy.

http://www.ncbi.nlm.nih.gov/pubmed/15053236

Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors.

Citation
Journal of Endocrinology Investigation, 2004, 27(1): 6-11.

Authors
Panzuto, F., Severi, C., Cannizzaro, R., Falconi, M., Angeletti, S., Pasquali, A., Corleto, V.D., Annibale, B., Buonadonna, A., Pederzoli, P., & Delle Fave, G.

Abstract
BACKGROUND: Chromogranin A (CgA) is considered the most accurate marker in the diagnosis of gastro-entero-pancreatic (GEP) endocrine tumors. Pancreatic polypeptide (PP) has also been proposed to play this role, but then not used due to its low sensitivity. The aim of the present study was to determine whether the assessment of PP would improve the diagnostic reliability of CgA in patients with GEP tumors. PATIENTS AND METHODS: Both markers were assessed in 68 patients [28 functioning (F), 40 non functioning (NF)]. Twenty-seven patients disease-free (DF) after surgery, and 24 with non-endocrine tumors (non-ETs) were used as control groups. RESULTS: CgA sensitivity was: 96% in F, 75% in NF, 74% in

pancreatic, and 91% in gastrointestinal (GI) tumors. Specificity was 89% vs DF, and 63% vs non-ETs. PP sensitivity was: 54% in F, 57% in NF, 63% in pancreatic, and 53% in GI tumors. Specificity was 81% vs DF, and 67% vs non-ETs. By combining the two markers a significant gain in sensitivity vs CgA alone was obtained: overall in GEP tumors (96% vs 84%, p = 0.04), in NF (95% vs 75%, p = 0.02), and in pancreatic (94% vs 74%, p = 0.04). More specifically, a 25% gain of sensitivity was obtained in the subgroup of NF pancreatic tumors (93% vs 68%, p = 0.04). CONCLUSION: The combined assessment of PP and CgA leads to a significant increase in sensitivity in the diagnosis of GEP tumors, particularly in pancreatic NF.

http://www.ncbi.nlm.nih.gov/pubmed/14747448

Gastrin releasing peptide and gastrin releasing peptide receptor expression in gastrointestinal carcinoid tumours.

Citation
Journal of Clinical Pathology, 2004, 57(2): 189-192.

Authors
Scott, N., Millward, E., Cartwright, E.J., Preston, S.R., & Coletta, P.L.

Abstract
AIMS: To establish whether gastrin releasing peptide (GRP) and the GRP receptor (GRPR) are expressed together in gastrointestinal carcinoid tumours. METHODS: Twenty six carcinoid tumours from the stomach, small intestine, appendix, and colorectum were investigated by immunohistochemistry for GRP and GRPR. RESULTS: GRP was detected in nine of 19 tumours and GRPR in 22 of 26. Coexpression of both the ligand and receptor was seen in six of 19 cases. GRPR but not GRP was more strongly expressed in appendix and colonic tumours. CONCLUSIONS: GRP and GRPR are produced by a large number of gastrointestinal carcinoid tumours. An autocrine/paracrine pathway may exist for GRP stimulated cell proliferation in some of these neoplasms, analogous to that seen in small cell anaplastic carcinoma of the lung.

http://www.ncbi.nlm.nih.gov/pubmed/12564839

Serum peptide profiles in patients with carcinoid tumors.

Citation A
American Journal of Surgery, 2003, 186(1): 28-31.

Authors
Calhoun, K., Toth-Fejel, S., Cheek, J. & Pommier, R.

Abstract
BACKGROUND: Patterns of elevated serum peptides may reveal additional markers and permit better classification of tumors based on (secondary) peptide secretion. METHODS: Fasting peptide profiles were obtained from 31 carcinoid patients. vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), neurotensin, substance P, gastrin-releasing polypeptide (GRP), calcitonin, gastrin, and pancreastatin were measured. Peptide elevation patterns were correlated with disease sites, syndrome, and survival. RESULTS: Elevations in patients were as follows: VIP 0%, PP 13%, neurotensin 10%, substance P 20%, GRP 3%, calcitonin 10%, and gastrin 3%. There were no consistent patterns of elevated peptides with regard to site or syndrome. Pancreastatin was elevated in 81% of profiles and was the only

abnormal peptide in 57% of patients. CONCLUSION: Peptide profile results do not permit improved classification, predict syndrome development, or correlate with survival. In contrast, pancreastatin is elevated in most cases and may be utilized to monitor disease progression and evaluate response to therapy.

http://www.ncbi.nlm.nih.gov/pubmed/12746559

The chromogranins: their roles in secretion from neuroendocrine cells and as markers for neuroendocrine neoplasia

Citation
Endocrine Pathology. 2003, 14(1):3-23.

Authors
Feldman, S.A., & Eiden, L.E.

Abstract
Chromogranins are the major components of the secretory granules of most neuroendocrine cells. Within the secretory pathway, chromogranins are involved in granulogenesis, and in sorting and processing of secretory protein cargo prior to secretion. Once secreted, they have hormonal, autocrine, and paracrine activities. The chromogranin family includes chromogranins A (CgA) and B (CgB) and secretogranin II (SgII, once called chromogranin C). The related "granins" NESP55, 7B2, secretogranin III/1B 1075 (SgIII), and secretogranin IV/HISL-19 antigen (SgIV), are also sometimes included when considering the chromogranins. While it is useful to consider the granin proteins as a family with many common features, it is also necessary to examine the distinct features and properties of individual members of the granin family to understand fully their functions, employ them efficiently as tissue, serum, and urinary markers for neuroendocrine neoplasia, and develop an evolutionary-biologic perspective on their contribution to mammalian physiology. Recent advances in chromogranin research include establishing the role of CgA in granulogenesis and the role of CgB in nuclear transcription; new biologic activities for CgA-, CgB-, and SgII-derived peptides; and new marker functions for granins and their proteolytically processed products in endocrine neoplasias.

http://www.ncbi.nlm.nih.gov/pubmed/12655516

Carcinoid heart disease: the role of urinary 5-hydroxyindoleacetic acid excretion and plasma levels of atrial natriuretic peptide, transforming growth factor-beta and fibroblast growth factor.

Citation
Cancer, 2003, 97(7): 1609-1615.

Authors
Zuetenhorst, J.M., Bonfrer, J.M., Korse, C.M., Bakker, R., van Tinteren, H., & Taal, B.G.

Abstract
BACKGROUND: Serotonin excretion plays a role in the development of carcinoid heart disease (CHD), but the exact pathogenesis is not known. In the current study, the authors evaluated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion, as well as plasma levels of transforming growth factor-beta (TGF-beta), fibroblast growth factor (FGF), and atrial natriuretic peptide (ANP) in patients with and without CHD determined by ultrasound

examination. METHODS: Urine and plasma samples were obtained for 37 patients and cardiac ultrasound was performed during follow-up in 1999 and 2000. Median 5-HIAA excretion was calculated for the period between diagnosis and ultrasound examination. CHD was defined as the thickening of the tricuspid valve with additional III-IV/IV tricuspid valve regurgitation. RESULTS: CHD was found in 9 of 37 patients (24%). No significant differences were found for age, gender, presence, and duration of liver metastases. All CHD patients had symptoms of the carcinoid syndrome compared with 71% of the non-CHD patients (P = 0.159). Median 5-HIAA excretion was significantly higher in the CHD group compared with the non-CHD group: 576 micromol/24 hours versus 233 micromol/24 hours (P = 0.02). No difference in TGF-beta and FGF plasma levels was observed between both groups (P = 0.139 and P = 0.985, respectively), nor was there a correlation with morphology of the tricuspid valve or degree of dilatation of the right atrium/ventricle. However, the CHD group had higher median ANP levels than the non-CHD group: 48 ng/L and 25 ng/L, respectively (P = 0.026). CONCLUSIONS: High levels of 5-HIAA excretion and plasma ANP were found to be associated with CHD. No significant relation with TGF-beta or FGF was been found.

http://www.ncbi.nlm.nih.gov/pubmed/12842744

Evaluation of whole blood serotonin and plasma and urine 5-hydroxyindole acetic acid in diagnosis of carcinoid disease.

Citation
Annals of Clinical Biochemistry, 2002, 39(Pt 6): 577-582.

Authors
Carling R.S., Degg, T.J., Allen, K.R., Bax, N.D., & Barth, J.H.

Abstract
BACKGROUND: Carcinoid disease is an uncommon disorder resulting from tumours of the enterochromaffin cells. Current biochemical investigation usually involves the measurement of 5-hydroxyindole-3-acetic acid (5-HIAA) in 24-h urine collections. Because of the problems associated with urine collections (i.e. inconvenience, accuracy of collection and requirement for preservatives) two alternative markers, fasting plasma 5-HIAA and whole blood serotonin (5-hydroxytryptamine), have been studied. METHODS AND RESULTS: Whole blood serotonin concentration and plasma and urine 5-HIAA concentrations were measured by high-performance liquid chromatography in 31 patients suspected of having carcinoid and 26 known carcinoid patients. Receiver operator characteristic curve analysis of the data showed no statistical difference between the three markers (P>0.01) with regard to their discriminating function. However, fasting plasma 5-HIAA assay showed greater stability than whole blood serotonin assay and is more convenient for the patient than a 24-h urine collection. At a cut-off value of 118 nmol/L plasma 5-HIAA assay showed a sensitivity of 89%, a specificity of 97% and a test efficiency of 93%. Whole blood serotonin assay was further limited by its saturation in platelets at 40 nmol/10(9) platelets which made it less suitable for monitoring the treatment of carcinoid disease. CONCLUSION: Fasting plasma 5-HIAA concentration provides a more convenient screening test for carcinoid and overcomes the problems associated with 24-h urine collections, without any loss of diagnostic precision.

http://www.ncbi.nlm.nih.gov/pubmed/12144588

Prospective study of the ability of histamine, serotonin or serum chromogranin

A levels to identify gastric carcinoids in patients with gastrinomas.

Citation
Alimentary Pharmacology and Therapeutics, 2002, 16(7): 1367-1382.

Authors
Bashir, S., Gibril, F., Ojeaburu, J.V., Asgharian, B., Entsuah, L.K., Ferraro, G., Crafa, P., Bordi, C., & Jensen, R.T.

Abstract
BACKGROUND: Chronic hypergastrinaemia causes gastric enterochromaffin cell proliferation and carcinoid tumours. The only reliable means to diagnose enterochromaffin cell changes/carcinoids is by biopsy. AIM: To assess whether serum histamine, chromogranin A or serotonin and urinary N-methylimidazoleacetic acid or 5-hydroxyindoleacetic acid correlate with advanced enterochromaffin cell changes or gastric carcinoids in patients with gastrinomas. METHODS: Consecutive patients (n=145) had the above assays and endoscopy with gastric biopsies. RESULTS: Lower N-methylimidazoleacetic acid and chromogranin A levels (P < 0.0001) occurred in disease-free patients. In patients with active disease, the fasting serum gastrin levels correlated (P < 0.0001) with both chromogranin A and N-methylimidazoleacetic acid levels. Chromogranin A (P=0.005), but not N-methylimidazoleacetic acid, serotonin, 5-hydroxyindoleacetic acid or histamine levels, correlated with the enterochromaffin cell index. Carcinoids, but not advanced enterochromaffin cell changes only, were associated with higher chromogranin A and N-methylimidazoleacetic acid levels. CONCLUSIONS: Serum chromogranin A levels and urinary N-methylimidazoleacetic acid levels, but not serum histamine or serotonin or urinary 5-hydroxyindoleacetic acid, correlate with the presence of gastric carcinoids. However, no assay identified patients with advanced enterochromaffin cell changes only with high sensitivity/specificity. Thus, N-methylimidazoleacetic acid and chromogranin A levels are unable to identify patients with advanced changes in enterochromaffin cells and therefore neither can replace routine gastric biopsies.

http://www.ncbi.nlm.nih.gov/pubmed/11825654

Peptide YY and cancer: current findings and potential clinical applications.

Citation
Peptides, 2002, 23(2): 389-395.

Authors
Tseng, W.W., & Liu, C.D.

Abstract
Peptide YY (PYY) is a naturally occurring gut hormone with mostly inhibitory actions on multiple tissue targets. PYY has been identified in several carcinoid tumors and a decreased expression of PYY may be relevant to the development and progression of colon adenocarcinoma. Treatment with PYY decreases growth in pancreatic and breast tumors, most likely through a reduction in intracellular cAMP. In cancer patients, PYY may also improve malnutrition that results from iatrogenic causes or cachexia associated with advanced disease. PYY plays a significant role in multiple aspects of cancer from regulation of cell growth to potential therapeutic applications.

http://www.ncbi.nlm.nih.gov/pubmed/11017936

Discriminating capacity of indole markers in the diagnosis of carcinoid tumors.

Citation
Clinical Chemistry, 2000, 46(10): 1588-1596.

Authors
Meijer, W.G., Kema, I.P., Volmer, M., Willemse, P.H., & de Vries, E.G.

Abstract
BACKGROUND: We evaluated the discriminating capacity of the indole markers urinary 5-hydroxyindoleacetic acid (5-HIAA), urinary serotonin, and platelet serotonin in the diagnosis of carcinoid tumors. METHODS: Indole markers were measured in 688 patients with suspected carcinoid disease. The initial values of indole markers from patients in whom a carcinoid tumor was confirmed during follow-up (n = 98) were used for ROC analysis. Two groups served as reference populations. The first consisted of 45 healthy individuals ("healthy controls"). The second was a random sample of 40 patients, drawn from the 590 (688 minus 98) patients with carcinoid-like symptoms but without a carcinoid tumor ("clinically suspected patients"). RESULTS: ROC curve analysis showed platelet serotonin to have the highest discriminating capacity, especially in foregut carcinoids. Cutoff values for platelet serotonin obtained from ROC analysis with healthy controls as reference group (5.4 nmol/10(9) platelets) gave a sensitivity of 74%, specificity of 91%, positive predictive value of 63%, and negative predictive value of 95% when applied to the initial 688 patients. Using the cutoff value with the clinically suspected patients as the reference group (9.3 nmol/10(9) platelets) gave a sensitivity of 63%, specificity of 99%, positive predictive value of 89%, and negative predictive value of 93%. Indole markers were increased in 169 (25%) of 688 patients. In 76 (45%) of these 169 patients, a carcinoid tumor was present. Slight increases of markers were associated with non-carcinoid neuroendocrine tumors, non-neuroendocrine tumors, and disturbed bowel motility. CONCLUSIONS: ROC curve analysis shows that platelet serotonin is the most discriminating indole marker for the diagnosis of carcinoid tumors. Platelet serotonin especially improves the diagnosis of carcinoids producing small amounts of serotonin.

http://www.ajcn.org/cgi/content/abstract/42/4/639

Serotonin content of foods: effect on urinary excretion of 5- hydroxyindoleacetic acid.

Citation
American Journal of Clinical Nutrition, 1985, 42: 639-643.

Authors
Feldman, J.M., & Lee, E.M.

Abstract
Using a highly specific radioenzymatic assay we determined the serotonin concentration in 80 types of foods. The following fruits had a high serotonin concentration (mean +/- SEM) expressed in micrograms/g weight: plantain 30.3 +/- 7.5; pineapple 17.0 +/- 5.1; banana 15.0 +/- 2.4; Kiwi fruit 5.8 +/- 0.9; plums 4.7 +/- 0.8; and tomatoes 3.2 +/- 0.6. Only nuts in the walnut or hickory family had a high serotonin concentration expressed in micrograms/g weight; butternuts 398 +/- 90; black walnuts 304 +/- 46; English walnuts 87 +/- 20; shagbark hickory nuts 143 +/- 23; mockernut hickory nuts 67 +/- 13; pecans 29 +/- 4; and sweet pignuts 25 +/- 8. Ingestion of these fruits and nuts resulted in an increase in urinary 5-

hydroxyindoleacetic acid excretion with no change in platelet serotonin concentration. The above foods should not be eaten while a urine is being collected for 5-hydroxyindoleacetic acid analysis.

IMMUNOSTAINING

http://www.ncbi.nlm.nih.gov/pubmed/20414099

PAX8 Expression in well-differentiated pancreatic endocrine tumors: correlation with clinicopathologic features and comparison with gastrointestinal and pulmonary carcinoid tumors.

Citation
American Journal of Surgical Pathology, 2010, 34(5): 723-729.

Authors
Long, K.B., Srivastava, A., Hirsch, M.S., & Hornick, J.L.

Abstract
PAX (paired box) genes encode a family of transcription factors that regulate organogenesis and cell-lineage specification in multiple organ systems. In the pancreas, PAX proteins play a critical role in islet cell differentiation. We recently observed that islet cells show strong, diffuse staining for PAX8 by immunohistochemistry. However, PAX8 expression has not previously been examined in pancreatic endocrine tumors (PETs). The purpose of this study was to evaluate PAX8 expression in PETs, and to correlate expression with clinical and pathologic features and behavior. PAX8 expression in other well-differentiated neuroendocrine tumors (WDNETs) was also studied. In total, 190 tumors were evaluated: 156 primary WDNETs (63 PETs, 31 ileal, 5 duodenal, 5 gastric, 19 appendiceal, 13 rectal, and 20 pulmonary carcinoid tumors) and 34 liver metastases (18 PETs and 16 ileal carcinoid tumors). PAX8 was positive in 42/63 (67%) primary PETs. Expression of PAX8 was significantly associated with WHO category 1.1 ("benign" behavior) compared with category 1.2 (uncertain behavior) or 2 (well-differentiated endocrine carcinoma) (positive in 100%, 64%, and 52% of tumors, respectively; $P<0.05$). PAX8-positive PETs were also significantly smaller and more often clinically functional; PAX8-negative tumors were more frequently associated with liver metastases. PAX8 expression was not associated with patient age, gender, MIB1 index, or lymph node metastases. PAX8 expression was detected in 0/20 (0%) pulmonary, 1/5 (20%) gastric, 5/5 (100%) duodenal, 0/31 (0%) ileal, 4/19 (21%) appendiceal, and 11/13 (85%) rectal carcinoid tumors. Among the liver metastases, PAX8 was positive in 9/18 (50%) metastatic PETs compared with 0/16 (0%) metastatic ileal carcinoid tumors. In summary, PAX8 is expressed in normal pancreatic islet cells and in a high proportion of primary and metastatic PETs. In the GI tract, PAX8 is positive in the majority of duodenal and rectal carcinoid tumors, and in a minor subset of appendiceal and gastric carcinoids. PAX8 expression is absent in ileal and pulmonary carcinoid tumors. PAX8 immunostaining may be helpful in determining the primary site for a WDNET metastatic to the liver, as ileal (PAX8 negative) and pancreatic (PAX8 positive) tumors most often present as a metastasis from an occult primary. PAX8 may also be a prognostic marker in PETs, as loss of expression is associated with malignant behavior.

http://www.ncbi.nlm.nih.gov/pubmed/20381114

DNA methyltransferases 1, 3a, and 3b overexpression and clinical significance in gastroenteropancreatic neuroendocrine tumors.

Citation
Human Pathology, 2010 Apr 7. [Epub ahead of print]

Authors
Rahman, M.M., Qian, Z.R., Lu Wang, E., Yoshimoto, K., Nakasono, M., Sultana, R., Yoshida, T., Hayashi, T., Haba, R., Ishida, M., Okabe, H., & Sano, T.

Abstract
The alteration of DNA methylation is one of the most common epigenetic changes in human cancers. Three genes, namely, DNA methyltransferase 1, 3a, and 3b, which code for DNA methyltransferases that affect promoter methylation status, are thought to play an important role in the development of cancers and may be good anticancer therapy targets. The methylation of tumor suppressor genes has been reported in gastroenteropancreatic neuroendocrine tumors; however, there have been no studies about DNA methyltransferase protein expression and its clinical significance in gastroenteropancreatic neuroendocrine tumors. In this study, the expression of DNA methyltransferase 1, 3a, and 3b was studied in 63 gastroenteropancreatic neuroendocrine tumors by immunohistochemistry. The expression of DNA methyltransferase 1, 3a, and 3b was frequently detected in gastroenteropancreatic neuroendocrine tumors (87%, 81%, and 75%, respectively). The DNA methyltransferase 3a expression level was significantly higher in poorly differentiated neuroendocrine carcinomas than in well-differentiated neuroendocrine tumors or well-differentiated neuroendocrine carcinomas ($P < .01$ and $P < .05$, respectively). The expression of DNA methyltransferase 1, 3a, and 3b showed significantly higher levels in stage IV tumors than in stage I or II tumors. In addition, the expression levels of DNA methyltransferase 1, 3a, and 3b were positively correlated with the MIB-1 labeling index in gastroenteropancreatic neuroendocrine tumors ($R = 0.293$, $P = .019$; $R = 0.457$, $P = .001$; and $R = 0.249$, $P = .049$; respectively). In addition, the expression levels and positive immunostaining frequencies of DNA methyltransferase 3a and 3b were significantly lower in midgut neuroendocrine tumors than in foregut or hindgut neuroendocrine tumors. Our findings suggest that the overexpression of DNA methyltransferase 1, 3a, and 3b is related to tumorigenesis and the progression of gastroenteropancreatic neuroendocrine tumors

http://www.ncbi.nlm.nih.gov/pubmed/19065104

Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors.

Citation
American Journal of Surgical Pathology, 2009, 33(4): 626-632.

Authors
Srivastava, A., & Hornick, J.L.

Abstract
Well-differentiated neuroendocrine tumors (WDNET) of the gastrointestinal tract, pancreas, and lung are histologically similar. Thus, predicting the site of origin of a metastasis is not possible on morphologic grounds. Prior immunohistochemical studies of WDNET have yielded conflicting results, and pancreatic and duodenal homeobox factor-1 (PDX-1) has not

previously been evaluated in this context. We therefore analyzed the expression of CDX-2, PDX-1, TTF-1, and neuroendocrine secretory protein-55 (NESP-55), a recently described member of the chromogranin family, in primary and metastatic WDNET. In total, 64 gastrointestinal carcinoids (5 stomach; 5 duodenum; 31 ileum; 11 appendix; and 12 rectum); 39 pancreatic endocrine tumors (PET); and 20 pulmonary carcinoid tumors were studied. PET were positive for NESP-55 (16/39) and PDX-1 (11/39); 3/31 also showed heterogeneous positivity for CDX-2. Ileal carcinoids were exclusively positive for CDX-2 (30/31) and negative for all other markers. Appendiceal carcinoids were uniformly positive for CDX-2 (11/11). All rectal carcinoids were negative for CDX-2 and TTF-1; 2/12 were positive for PDX-1, and 1/12 for NESP-55. The gastric and duodenal carcinoids were only positive for PDX-1 (7/10). TTF-1 positivity was confined to pulmonary carcinoids (7/20); 1/20 was positive for NESP-55; and all were negative for CDX-2 and PDX-1. NESP-55 and PDX-1 positivity, in the presence of negative CDX-2 and TTF-1, was 97% specific for PET. The sensitivity and specificity of CDX-2 positivity for predicting an ileal primary, when PDX-1, NESP-55, and TTF-1 were negative, was 97% and 91%, respectively. TTF-1 positivity was confined to pulmonary carcinoids in our study but was present in only about a third of cases. A panel of these 4 markers may be useful in predicting the primary site of metastatic WDNET.

http://www.ncbi.nlm.nih.gov/pubmed/15809513

Nuclear survivin is a powerful novel prognostic marker in gastroenteropancreatic neuroendocrine tumor disease.

Citation
Neuroendocrinology, 2005, 81(1): 1-9.

Authors
Grabowski, P., Griss, S., Arnold, C.N., Hörsch, D., Göke, R., Arnold, R., Heine, B., Stein, H., Zeitz, M., & Scherübl, H.

Abstract
Gastroenteropancreatic neuroendocrine tumors represent a heterogeneous tumor entity. The growth pattern ranges from very slowly to fast growing, aggressive types of tumors. Survivin, a member of the family of apoptosis inhibitors, is a bifunctional protein that suppresses apoptosis and regulates cell division. In this study we determined the prognostic value of survivin in this tumor entity. Tumor specimens from 104 patients (38 foregut, 53 midgut, 13 hindgut) were studied immunohistochemically for cytoplasmic and nuclear survivin expression as well as for ki-67 antigen expression. 5-year-follow-up was complete in 89 patients. 29 patients with localized, well-differentiated gastroenteropancreatic neuroendocrine tumors (WDET, WHO class 1) had been curatively treated by surgical or endoscopic tumor resection. 50 patients suffered from well-differentiated endocrine carcinomas (WDEC, WHO class 2), 10 patients were diagnosed with poorly differentiated neuroendocrine carcinomas (PDEC, WHO class 3). Survivin expression was correlated with survival for the 50 patients with metastatic WDEC disease. All 29 WDETs were negative for nuclear survivin, whereas all 10 PDECs stained positive for nuclear survivin. In the 50 patients with metastatic WDECs, 5/50 (10%) tumors were nuclear survivin positive. Those 5 patients had a statistically significant worse prognosis (survival of 41 vs. 103 months, p=0.01). ki-67 was not a prognostic factor in this subgroup of patients. Nuclear survivin expression thus appears to be upregulated during progression of gastroenteropancreatic neuroendocrine tumors. The analysis of nuclear survivin expression identifies subgroups in metastatic disease (WHO class 2) with good (survivin-) or with less favorable prognosis (survivin+). We propose

that the determination of nuclear survivin expression could be used to individualize therapeutic strategies in this tumor entity in the future

http://www.ncbi.nlm.nih.gov/pubmed/16001632

The significance of CD44 expression in gastrointestinal neuroendocrine tumors.

Citation
Hepatogastroeneterology, 2005, 52(64): 1071-1076.

Authors
Lai, C.H., Shan, Y.S., Sy, E.D., Hsieh, Y.H., Tsai, H.W., Lee, J.C., & Lin, P.W.

Abstract
BACKGROUND/AIMS: Expression of CD44 and its isoforms has been demonstrated to be a prognostic marker in many neoplasms. Gastrointestinal neuroendocrine tumor is a slow-growing neoplasm, whose behavior is determined by site of occurrence, size or specific histologic growth pattern. In this study, the feasibility of using CD44 as a prognostic marker in gastrointestinal neuroendocrine tumor is evaluated. METHODOLOGY: Representative paraffin-embedded sections of gastrointestinal neuroendocrine tumor from 22 patients were studied by immunohistochemical staining using monoclonal antibodies against CD44, Ki-67, and p53 retrospectively. The correlation between these markers and clinical behavior of the tumors was analyzed. RESULTS: Positive expression of CD44 was observed in 15 cases (68%) of gastrointestinal neuroendocrine tumor. Expression of CD44 showed significant inverse correlation with lymph node status (P=0.049), distant metastasis (p<0.001) and mortality (p=0.002). Neither p53 nor Ki-67 correlated with lymph node status, distant metastasis and overall survival. Both lymph node status and distant metastasis showed strong correlation to survival after multivariate analysis. Patients with the tumor growing from the hindgut had better survival (p=0.024). The patients with stronger CD44 immunoreactivity (> or = 2+) tumors had significantly favorable survival (p=0.004) compared with those with weaker immunoreactivity (< or = 1+) tumors. CONCLUSIONS: Expression of CD44 in gastrointestinal neuroendocrine tumor inversely correlates with tumor metastasis, associates with a favorable outcome and may serve as one of the prognostic indicators.

http://www.ncbi.nlm.nih.gov/pubmed/12560757

Proliferation of antigen MIB-1 in metastatic carcinoid tumours removed at liver transplantation: relevance to prognosis.

Citation
European Journal of Gastroenterology & Hepatology, 2003, 15(2): 139-143

Authors
Amarapurkar, A.D., Davies, A., Ramage, J.K., Stangou, A.J., Wight, D. G., & Portmann, B.C.

Abstract
BACKGROUND: Metastatic carcinoid tumours are difficult to manage. In spite of a multidisciplinary approach, including orthotopic liver transplantation, the recurrence rate is high with a poor prognosis. Histopathology generally fails to provide prognostic information, hence it is essential to try to identify markers of prognosis in these tumours before considering orthotopic liver transplantation. The MIB-1 antibody, which detects cell proliferative activity, has been shown to be a useful prognostic marker for a variety of

neoplasms. AIMS: To assess the value of MIB-1 immunostaining as a prognostic marker of the duration to recurrence and the survival of patients undergoing orthotopic liver transplantation for metastatic carcinoid/neuroendocrine tumours of the liver. METHODS: Fourteen patients were included in the study. Formalin-fixed, paraffin-embedded tissue sections of the tumours were stained with routine haematoxylin and eosin and chromogranin. The cell proliferative activity was assessed by MIB-1 antibody labelling using the immunoperoxidase method. Results were correlated with the time of tumour recurrence and the length of patients' survival after transplantation. RESULTS: No correlation was found between MIB-1 labelling index and age, gender, clinical and histological type of tumour (i.e. carcinoid, APUDOMA, secreting or non-secreting). The patients with higher MIB-1 indices (5%) showed a trend toward earlier recurrence and poorer survival than those with low MIB-1 indices (5%). The predictive value of a MIB-1 index of 2 indicating patient survival of 24 months was 83% (five out of six patients). CONCLUSIONS: The correlation between MIB-1 index and patients' survival suggests that a high proliferative rate, as assessed by MIB-1 immunostaining, may detect those tumours with more aggressive biological behaviour. Prospective studies on a larger number of patients will be needed to determine if, in any individual tumour, this method will provide an additional parameter for a rational approach to therapy.

http://www.ncbi.nlm.nih.gov/pubmed/12389996

Different beta-catenin immunoexpression in carcinoid tumors of the appendix in comparison to other gastrointestinal carcinoid tumors.

Citation
Pathology, Research and Practice, 2002, 198(8): 531-536.

Authors
Barshack, I., Goldberg, I., Chowers, Y., Horowitz, A., & Kopolovic, J.

Abstract
Carcinoid tumor of the appendix is an endocrine tumor that is histologically similar to, but biologically less aggressive than carcinoids arising from other parts of the gastrointestinal tract. In this study, we examined E-cadherin, beta-catenin, DCC, p53 and Ki67 immunoexpression in cases of carcinoid of the appendix and made a comparison with non-appendiceal carcinoid tumors. Nine cases of appendiceal carcinoid and 11 biopsies of carcinoid of other parts of the gastrointestinal tract, five cases of the small intestine and six of the stomach were immunohistochemically evaluated for Ki67, p53, DCC, E-cadherin and beta-catenin. Two main patterns of beta-catenin staining were observed. The first pattern was characterized as membranous and cytoplasmic, and was seen mainly in the peripheral cells of the nests. The second pattern was diffuse, predominantly membranous. Most (five of seven) appendiceal carcinoids and only three of 11 non-appendiceal cases showed the first staining pattern ($p < 0.05$). Immunoexpression of E-cadherin and DCC was similar in both groups. p53 and Ki-67 immunostaining revealed stronger nuclear positivity in the non-appendiceal carcinoid tumors (statistically not significant). We found a pattern of beta-catenin immunostaining in typical carcinoid tumors of the appendix that was different from the pattern seen in non-appendiceal carcinoid tumors. This alteration suggests that carcinoid of the appendix may represent a different subtype of carcinoid tumors with different immunohistochemical and biological behavior.

http://www.ncbi.nlm.nih.gov/pubmed/11462912

Importance of proliferation markers in gastrointestinal carcinoid tumors: a clinicopathologic study.

Citation
Hepatogastroenterology, 2001, 48(39): 720-723.

Authors
Sökmensüer, C., Gedikogulu, G., & Uzanalimoglu, B.

Abstract
BACKGROUND/AIMS: Carcinoid tumors are common tumors in the gastrointestinal tract. Certain criteria such as the depth of invasion, the localization, the tumor size, the mitotic index and the pattern of ploidy are used to determine the potential biological behavior of these tumors some of which might be malignant. The goal of this study was to assess the prognostic significance of proliferation markers (Ki67 and PCNA) in carcinoid tumors by using immunohistochemistry. METHODOLOGY: An immunostaining in 37 carcinoid tumors arising in various locations of the gastrointestinal tract was performed. The best stained area was selected and 1000 neoplastic cells were counted in order to determine the proliferation index in each case. RESULTS: The results of proliferation index were compared with the depth of invasion, the embryologic type, the tumor size, the presence of metastases and disease-free survival by using statistical methods. The Ki67 tumor proliferation index in the tumors > 2.1 cm was significantly different from the tumors < or = 2 cm (P = 0.032). CONCLUSIONS: The presence of significant correlation between Ki67 positivity and the tumor size might suggest that Ki67 antibody can be useful for the determination of potential behavior of gastrointestinal carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/10747315

The spectrum of neuroendocrine differentiation among gastrointestinal carcinoids: importance of histologic grading, MIB-1, p53, and bcl-2 immunoreactivity.

Citation
Archives of Pathology and Laboratory Medicine, 2000, 124(4): 570-576.
Authors
Moyana, T.N., Xiang, J., Senthilselvan, A., & Kulaga, A.
Abstract
CONTEXT: The advent of panneuroendocrine markers has helped to better depict the heterogeneity of gastrointestinal carcinoids. Consequently, it has been proposed that these tumors constitute a histologic spectrum that includes well-, moderately, and poorly differentiated carcinoids. However, the reproducibility of this grading system and its prognostic importance have sometimes been called into question. OBJECTIVE: To investigate the potential utility of cell proliferation and oncoprotein markers in augmenting the histologic classification. DESIGN AND SETTING: Retrospective study; tertiary care teaching hospital. METHODS: Fifty-eight patients with 41 well-differentiated, 12 moderately differentiated and 5 poorly differentiated carcinoids from various topographic sites of the gastrointestinal tract were selected and immunostained for panneuroendocrine markers, MIB-1, p53, and bcl-2. MAIN OUTCOME MEASURES: Degree of association between histologic grading, MIB-1, p53, and bcl-2 immunoreactivity and carcinoid metastatic behavior. RESULTS: The group comprised 30 males and 28 females whose mean age was 52.7 years (range, 14-81). Mean

follow-up time was 85.8 months. All 58 patients tested positive for chromogranin A and/or synaptophysin. The group was divided into nonmetastatic (42/58, or 72.4%) and metastatic (16/58, or 27.6%) cases. Histologic grading tended to be associated with metastatic spread, but this occurrence of metastases did not attain statistical significance (P =.08). Positivity for MIB-1 (P =.004) and p53 (P =.04) was significantly associated with metastatic behavior, whereas bcl-2 was not (P = 0. 63). CONCLUSIONS: Although an organoid pattern and neuroendocrine immunophenotype help to define the spectrum of gastrotestinal carcinoids, this study suggests that the histologic grading of these tumors has some limitations with respect to predicting metastatic behavior. However, MIB-1 and p53 can compliment histologic grading as prognostic indicators in this regard while bcl-2 appears to be less useful.

http://www.ncbi.nlm.nih.gov/pubmed/9744317

Immunohistologic analysis of gastrointestinal and pulmonary carcinoid tumors.

Citation

Human Pathology, 1998, 29(9):992-999.

Authors

Al-Khafaji, B., Noffsinger, .E., Miller, M.A., DeVoe, G., Stemmermann, G.N., & Fenoglio-Preiser, C.

Abstract

Carcinoid tumors are potentially malignant neoplasms that arise in various body sites, including the lung and gastrointestinal tract. Those that appear cytologically atypical are more likely to behave aggressively than more typical carcinoid tumors. However, in the absence of cytological atypia or large tumor size, it is difficult to predict the biology of an individual tumor, because some lesions metastasize, whereas others do not. This study had four aims: (1) To study the expression pattern of p53, Ki-67, NCAM, and S-100 in carcinoid tumors and to relate these expression patterns to classical histopathologic features and to tumor location. (2) To identify nonhistological markers that might more accurately predict the early behavior of carcinoid tumors. (3) To determine whether sustentacular cells are present in carcinoid tumors arising in tissues derived from different embryological derivatives. (4) To determine the synaptophysin and chromogranin immunoreactivity in neuroendocrine tumors arising in various locations. The immunostaining reactions were quantitatively scored by three observers. Only 3 of the 39 tumors (all histologically atypical) were strongly positive for Ki-67; two of these were also strongly p53 immunoreactive. NCAM immunostaining differed according to the site of origin: 76.5% of foregut lesions, 58% of the midgut lesions, and 20% of hindgut lesions were positive. S-100 immunostaining ranged from 41% in foregut lesions to 50% in both the hindgut- and midgut-derived tumors. S-100-positive sustentacular cells were present in 20.5% of carcinoid tumors. All tumors stained with antibodies against synaptophysin. In contrast, 100% of midgut, 60% of hindgut, and 88% of foregut tumors were chromogranin positive. Carcinoid tumors tend to have low proliferative rates. p53 immunostaining tends to be strongly positive in tumors that are histologically atypical, but it is negative in typical carcinoid tumors arising in the gastrointestinal tract and lungs. Immunostaining reactions with antibodies to NCAM, S-100, and chromogranin differ depending on the site of origin. Synaptophysin stains 100% of carcinoid tumors regardless of their site of origin. In contrast, antibodies to chromogranin fail to stain 40% of hindgut tumors and 12% of foregut carcinoid tumors. S-100-positive sustentacular cells are present in foregut and midgut tumors but not in hindgut tumors.

http://www.ncbi.nlm.nih.gov/pubmed/3010302

Synaptophysin: a marker protein for neuroendocrine cells and neoplasms.

Citation
The Proceedings of the National Academy of Sciences USA, 1986, 83(10), 3500-3504.

Author
Wiedenmann, B., Franke, V.W., Kuhn, C., Moll, R., & Gould, V.E.

Abstract
Synaptophysin is an integral membrane glycoprotein (Mr 38,000) that occurs in presynaptic vesicles of neurons and in similar vesicles of the adrenal medulla. By using a monoclonal antibody to this protein (SY38), we have found, by immunohistochemistry and immunoblotting, that an identical or similar protein is also expressed in neuroendocrine tumors of neural type, such as pheochromocytomas and paragangliomas. In addition, this protein occurs in certain neuroendocrine epithelial cells, such as pancreatic islet cells; in a variety of neuroendocrine epithelial tumors, including isletcell adenomas and carcinomas and several carcinoids and neuroendocrine carcinomas of the gastrointestinal and the bronchial tracts; and in medullary carcinomas of the thyroid. Our results show that synaptophysin, and the vesicles that contain it, can occur in normal and neoplastic neuroendocrine cells of neural type, as demonstrated by colocalization with neurofilaments, as well as in those of epithelial type, as shown by colocalization with cytokeratin filaments and desmoplakins. We conclude that synaptophysin is expressed independently of other neuronal differentiation markers and propose that it be used as a differentiation marker in tumor diagnosis.

STAGING/GRADE

http://www.ncbi.nlm.nih.gov/pubmed/18953609
A proposed staging system for gastric carcinoid tumors based on an analysis of 1,543 patients.
Citation
Annals of Surgical Oncology, 2009, 16(1): 51-60.

Authors
Landry, C.S., Brock, G., Scoggins, C.R., McMasters, K.M., & Martin, R.C. 2Nd .

Abstract
The lack of a clinically relevant staging system for gastric carcinoid tumors creates a persistent challenge for clinicians trying to provide patients with meaningful prognostic information. The purpose of this study was to identify the clinicopathologic factors that affect survival for patients diagnosed with gastric carcinoid, and use this information to create a staging system. A search of 15,983 patients with carcinoid tumors from the Surveillance Epidemiology and End Results (SEER) database identified 1,543 patients with gastric carcinoid tumors from 1973 to 2004. Patients were analyzed according to various clinicopathologic factors, and a tumor (T1, T2, T3), lymph node (N0, N1), and metastasis (M0, M1) staging system was created according to these parameters. Gastric carcinoid was the only primary malignancy in 74% of patients; 24% presented with one additional primary malignancy, and 2.7% had two or more additional malignancies. On multivariate analysis, age and depth of invasion were significant for patients with one tumor. Four stages were created according to statistically significant prognostic factors: 60% of patients were classified into stage I, 7.6% into stage II, 6.5% into stage III, and 26% into stage IV. Five-year survival rates were 82, 63, 21, and 5.5% for stages I-IV, respectively. We conclude that this tumor-node-metastasis (TNM) staging

system accurately discriminates prognosis for all types of gastric carcinoid tumors, with size, depth of invasion, lymph node involvement, and distant metastasis having the greatest impact on survival. Incorporation of this staging system into clinical practice will allow better study of outcomes and development of stage-specific treatment.

http://www.ncbi.nlm.nih.gov/pubmed/19368957

Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors.

Citation
Human Pathology, 2009, 40(9):1262-1268.

Authors
Strosberg, J., Nasir, A., Coppola, D., Wick, M., & Kvols, L.

Abstract
Three-tiered grading systems (low, intermediate, and high grade) have been proposed for neuroendocrine tumors. These classifications have not been rigorously evaluated in neuroendocrine malignancies of the digestive tract. We performed a retrospective chart analysis of 83 patients with metastatic gastroenteropancreatic neuroendocrine tumors, correlating tumor grade with overall survival. We also analyzed available biopsy specimens (on 40 patients), examining hematoxylin and eosin stains for mitotic rate and immunostaining for measurement of the Ki-67 index. Tumor grades were assigned based on the mitotic rate and the Ki-67 index, and the prognostic validity of each grading method was assessed. A highly significant correlation existed between the reported tumor grade and overall survival. Five-year survival rates for patients with low-, intermediate-, and high-grade tumors were 87%, 38%, and 0%, respectively. On biopsy specimen analysis, both mitotic rates and Ki-67 indexes correlated strongly with overall survival. We conclude that a 3-tiered grading classification for gastroenteropancreatic neuroendocrine tumors correlates with survival in the metastatic setting. Both mitotic rates and Ki-67 indexes are inversely associated with survival and can be analyzed independently for assignment of grade.

http://www.ncbi.nlm.nih.gov/pubmed/18978555

The IASLC Lung Cancer Staging Project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer.

Citation
Journal of Thoracic Oncology, 2008, 3(11): 1213-1223.

Authors
Travis, W.D., Giroux, D.J., Chansky, K., Crowley, J., Asamura, H., Brambilla, E., Rami-Porta, R., Rusch, V.W., Goldstraw, P.

Abstract
OBJECTIVE: In the 2003 Supplement for tumor, node, metastasis (TNM) Staging classification it states that TNM staging "applies to all types of carcinoma including small cell carcinoma; however, it does not apply to carcinoids." Despite this caveat, most publications on typical and atypical carcinoids use the TNM staging system for nonsmall cell carcinoma and are able to demonstrate prognostic significance for the different stages. For this reason, as the next TNM Staging proposal is being considered, we sought to investigate the carcinoid

cases submitted to the International Association for the Study of Lung Cancer (IASLC) database, as well as the National Cancer Institute Surveillance Epidemiology and End Results (SEER). MATERIALS AND METHODS: In the data collected for the IASLC Staging Project database over the time period 1990 to 2000, there were 513 broncho-pulmonary carcinoids. A total of 1619 broncho-pulmonary carcinoid cases diagnosed over the period 1990-2002 were analyzed from the SEER database, including 1437 surgical cases. Pathologic slides were not available for histologic review. RESULTS: Most of tumors in both the IASLC and SEER databases were Stage I (82% and 78%, respectively), as defined by the IASLC proposals for the 7th edition of TNM staging system. T status was a statistically significant predictor of survival for both the SEER data ($p < 0.0001$) and the IASLC database ($p = 0.0156$), though for different reasons. N status showed significant survival correlations in both data sets ($p < 0.0001$). The effect of M status was significant ($p < 0.0001$) within the SEER data and not studied in the IASLC cases, which were almost exclusively M0. We found that all three T, N, and M categories as defined for non-small cell lung cancer are generally useful for staging of pulmonary carcinoid tumors. Significant differences in survival for overall stages I versus II versus III/IV were identified in both data sets. Patients with multiple same lobe nodules had a 100% 5-year survival, which may be a reason to reevaluate their status in the IIB category in future analyses. CONCLUSIONS: In summary, the IASLC proposals for the 7th edition of TNM are helpful in predicting prognosis for broncho-pulmonary carcinoid tumors. It is the recommendation of the IASLC Staging project that TNM be applied to broncho-pulmonary carcinoid tumors. A prospective collection of data through an International Registry of Pulmonary Neuroendocrine Tumors planned by the IASLC will allow for further detailed analysis of staging data for broncho-pulmonary carcinoids.

http://www.ncbi.nlm.nih.gov/pubmed/18481499

Proposed staging system for gastrointestinal carcinoid tumors.

Citation

American Surgeon, 2008, 74(5): 418-422.

Authors

Landry, C.S., McMasters, K.M., Scoggins, C.R., & Martin, R.C. 2nd.

Abstract

Gastrointestinal carcinoid tumors are rare neuroendocrine tumors with no staging system in existence. The goal of this study was to establish a staging system consistent with the American Joint Commission on Cancer Staging Systems using the TNM strategy. A retrospective review of our prospective database of 990 hepatopancreaticobiliary patients and our tumor registry identified 108 patients with gastrointestinal carcinoid tumors from June 1990 to September 2006. Tumors were classified into our staging system by depth of penetration, size of primary tumor, nodal status, and the presence/absence of distant metastasis. Patients were staged as Stage 1, 22 per cent; Stage II, 29 per cent; Stage 3, 12 per cent; and Stage 4, 35 per cent. There were 41 men and 57 women with a median age of 58.5 years (range, 19-86 years). Primary tumors included 52 small bowel, 12 colon, 19 rectum, nine stomach, and seven of unknown primary origin. The use of our initial staging system demonstrated a trend in differences in survival across all four stages. The use of our initial staging proposal delineates the biology of the disease with accurate overall survival estimates. The addition of a dedicated American Joint Commission on Cancer staging system is needed for gastrointestinal carcinoids. Widespread use of this staging system may contribute to the future management and treatment of gastrointestinal carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/18707046

A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients.

Citation Surgery, 2008, 144(3): 460-466.

Authors
Landry, C.S., Brock, G., Scoggins, C.R., McMasters, K.M., & Martin, R.C. 2Nd .

Abstract
BACKGROUND: The lack of a clinically relevant staging system for carcinoid tumors of the rectum creates a persistent challenge for clinicians trying to provide patients with meaningful prognostic information. The purpose of this study was to identify the clinicopathologic factors that affect survival for patients diagnosed with carcinoid of the rectum, and to use this information to create a staging system. METHODS: A search of 15,983 patients with carcinoid tumors from the National Cancer Institute's SEER (Surveillance Epidemiology and End Results) database identified 4701 patients with rectal carcinoid tumors from 1973 to 2004. Patients were analyzed according to various clinicopathologic factors and a tumor (T1, T2, T3), lymph node (N0, N1), and metastasis (M0, M1) staging system was created according to these parameters. The staging system was developed using log rank tests and the Cox proportional hazards model. RESULTS: Of the 4701 patients, 2329 females and 2372 males were identified with a median age of 56 years (14-94). Median size of primary tumor was 0.6 cm (0.1-25). Lymph node metastasis was found in 111 (4%), and distant metastatic disease was present in 97 (2.4%) patients. Rectal carcinoid was the only primary malignancy in 82% of patients; 17% presented with 1 additional primary malignancy, and 1% had two or more additional malignancies. Age, size, depth of invasion, lymph node involvement, and distant metastasis were significant predictors of survival. Four stages were created according to statistically significant prognostic factors: 83% of patients were classified into Stage I, 6.5% into Stage II, 2.8% into Stage III, and 7.4% into Stage IV. Five-year survival rates were 97%, 84%, 27%, and 20% for Stages I through IV, respectively. CONCLUSION: The newly developed TNM staging system accurately discriminates prognosis for carcinoid tumors of the rectum. Size of primary tumor, depth of invasion, lymph node involvement, and distant metastasis have the greatest impact on survival. Incorporation of this staging system into clinical practice will allow better study of outcomes and development of stage-specific treatment recommendations.

http://www.ncbi.nlm.nih.gov/pubmed/19095106

A proposed staging system for small bowel carcinoid tumors based on an analysis of 6,380 patients.

Citation
American Journal of Surgery, 2008, 196(6):896-903; discussion 903.

Authors
Landry, C.S., Brock, G., Scoggins, C.R., McMasters, K.M., & Martin, R.C. 2Nd .

Abstract
BACKGROUND: Little is known about the long-term prognosis of small bowel carcinoids because currently no staging system exists. METHODS: A search of the Surveillance, Epidemiology and End Results (SEER) database identified 6,380 patients with small bowel carcinoid tumors from 1977 to 2004. Patients were analyzed according to various clinicopathologic factors and a tumor (T1, T2, T3), lymph node (N0, N1), and metastasis (M0, M1) staging system was created according to these parameters. RESULTS: Among the 6,380 patients, 2,985 women and 3,395 men, with a median age of 66 years (range 14-98), the median tumor size was 1.9 cm (range .1-30 cm). Multivariate analysis demonstrated that age,

size of the primary tumor, and depth of invasion were significant factors. Four stages were created according to statistically significant prognostic factors: 13% of patients were classified into stage I, 31% into stage II, 16% into stage III, and 40% into stage IV. Five-year survival rates were 96%, 87%, 74%, and 43% for stages I through IV, respectively. CONCLUSIONS: The newly developed TNM staging system accurately discriminates prognosis for small bowel carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/19183534

Proposed staging system for colon carcinoid tumors based on an analysis of 2,459 patients.

Citation

Journal of the American College of Surgeons, 2008, 207(6): 874-881.

Authors

Landry, C.S., Brock, G., Scoggins, C.R., McMasters, K.M., & Martin, R.C. 2Nd .

Abstract

BACKGROUND: Colon carcinoid remains an uncommon finding during screening endoscopy or operation, with little known about the longterm prognosis. The reason for this uncertainty is that no staging system exists to appropriately risk stratify or follow these patients for overall survival. We sought to investigate prognostic factors associated with colon carcinoid tumors and create a predictive staging system to accurately estimate prognosis. STUDY DESIGN: A search of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database identified 15,983 patients with carcinoid tumors, with 2,459 from the colon, from 1973 to 2004. Patients were analyzed to various clinicopathologic factors and a tumor (T1, T2, T3), lymph node (N0, N1), and metastasis (M0, M1) staging system was created according to these parameters. RESULTS: Of the 2,459 patients, 1,287 (52%) women and 1,172 (48%) men were identified, with a median age of 63 years (range, 12 to 96 years). Lymph node metastasis was found in 820 (48%), and distant metastatic disease was present in 522 (24%) patients. On multivariate analysis, age, size, depth of invasion, lymph node involvement, distant metastasis, and location were significant. Four stages were created to statistically significant prognostic factors: 13% into stage I, 32% into stage II, 12% into stage III, and 43% into stage IV. Five-year survival rates were 97%, 69%, 21%, and 17% for stages I through IV ($p = 0.001$). CONCLUSIONS: The newly developed TNM staging system accurately discriminates prognosis for carcinoid tumors of the colon. Incorporation of this staging system into clinical practice will allow better study of outcomes and development of stage-specific treatment recommendations.

http://www.ncbi.nlm.nih.gov/pubmed/18645109

Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system.

Citation

Archives of Surgery, 2008, 143(7): 664-670; discussion 670.

Authors

Landry, C.S., Woodall, C., Scoggins, C.R., McMasters, K.M., & Martin, R.C2nd.

Abstract

BACKGROUND: Appendiceal carcinoid tumors (ACTs) are rare, and little is known about the

long-term prognosis for these tumors because no staging system exists. Therefore, we sought to investigate prognostic factors associated with ACTs and to create a predictive staging system to accurately estimate prognosis. HYPOTHESIS: In patients with ACTs, TNM staging will accurately predict prognosis. DESIGN: Retrospective review of 15 983 patients with carcinoid tumors in the Surveillance Epidemiology and End Results (SEER) database from January 1, 1977, to December 31, 2004. SETTING: SEER database study. PARTICIPANTS: Nine hundred patients with ACTs (552 females and 348 males; mean age, 47.1 years [age range, 9-89 years]; mean size of the primary tumor, 2.4 cm [range, 0.1-11.5 cm]). Main Outcome Measure Clinicopathologic features in patients with ACTs that affect prognosis using a newly created TNM staging system incorporating these parameters. RESULTS: Lymph node metastasis was found in 137 patients (24%), and distant metastatic disease in 89 patients (10%). Stage-specific survival was statistically significant between stages (P < .001) but not within stages. At multivariate analysis, patient age, primary tumor size, histologic features, lymph node involvement, and distant metastasis were significant factors predicting survival. CONCLUSIONS: Our newly developed TNM staging system accurately predicts prognosis in patients with ACTs. A TNM staging system for ACTs will be helpful not only for physician education about factors that affect the outcome with this disease but also to observe trends in prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/18506737

Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors.

Citation
Cancer, 2008, 113(2): 256-265.

Authors
Pape, U.F., Jann, H., Müller-Nordhorn, J., Bockelbrink, A., Berndt, U., Willich, S.N., Koch, M., Röcken, C., Rindi, G., & Wiedenmann, B.

Abstract
BACKGROUND: Neuroendocrine tumors (NETs) of the gastroenteropancreatic (GEP) system comprise a rare but challenging group of malignant neoplasms and occur at virtually any site of the GEP system. In 2006, a new TNM classification system was proposed for the staging and grading of upper GEP NETs. METHODS: The prognostic relevance of the TNM classification system was analyzed retrospectively in 202 patients from a referral center with histologically proven foregut NET. Patients were classified according to previous classification systems and the TNM classification. Survival data were acquired and statistical analyses were performed by using log-rank and Cox regression testing. RESULTS: Primary tumors were gastric (n = 48), duodenal (n = 23), and pancreatic (n = 131). During the observation period, 21% of patients died. The overall 5- and 10-year survival rates were 75% and 64%, respectively. Previous classification systems discriminated between low-grade and high-grade malignant NETs but did not allow further prognostic differentiation. In contrast, the proposed TNM classification was able to differentiate significantly between different tumor stages (stages I-III vs stage IV; P < .01) and cellular proliferation rates according to Ki-67 labeling (grade 1 vs grade 2, P = .04; grade 1 vs grade 3 and grade 2 vs grade 3, P < .01). Cox regression analysis confirmed an increased risk of reduced survival for patients with stage III or IV NET and grade 2 or 3 NET. CONCLUSIONS: The current results demonstrated the prognostic relevance of the newly proposed TNM classification system for foregut NETs with statistical significance for the subgroups of both the staging classification and the grading system. Thus,

the new classification system provides a valid and powerful tool for prognostic stratification of GEP NETs in clinical practice and research.

http://www.springerlink.com/content/7rjg872752462r55/

TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system.

Citation
Virchows Archiv, 2007, 451(1): 757-762.

Authors
Rindi,G., Klöppel, G., Couvelard,A., Komminoth, P., Körner, M., Lopes, J.M., McNicol, A-M., Nilsson, O., Perren, A., Scarpa, A., Scoazec, J-Y., & Wiedenmann, B.

Abstract
Criteria for the staging and grading of neuroendocrine tumors (NETs) of midgut and hindgut origin were established at the second Consensus Conference in Frascati (Rome) organized by the European Neuroendocrine Tumor Society (ENETS). The proposed tumor–node–metastasis (TNM) classifications are based on the recently published ENETS Guidelines for the Diagnosis and Treatment of gastroenteropancreatic NETs and follow our previous proposal for foregut tumors. The new TNM classifications for NETs of the ileum, appendix, colon, and rectum, and the grading system were designed, discussed, and consensually approved by all conference participants. These proposals need to be validated and are meant to help clinicians in the stratification, treatment and follow-up of patients

http://www.ncbi.nlm.nih.gov/pubmed/16967267

TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system.
Citation
Virchows Archiv, 2006, 449(4): 395-401.
Authors
Rindi, G., Klöppel, G., Alhman, H., Caplin, M., Couvelard, A., de Herder, W.W., Eriksson, B., Falchetti, A., Falconi, M., Kamminoth, P., Körner, M., Lopes. J.M., McNicol, A.M., Nilsson, O., Perren, A., Scarpa, A., Scoazec, J.Y., Wiedenmann, B., & all Frascati Consensus participants (ENETS).

Abstract
The need for standards in the management of patients with endocrine tumors of the digestive system prompted the European Neuroendocrine Tumor Society (ENETS) to organize a first Consensus Conference, which was held in Frascati (Rome) and was based on the recently published ENETS guidelines on the diagnosis and treatment of digestive neuroendocrine tumors (NET). Here, we report the tumor-node-metastasis proposal for foregut NETs of the stomach, duodenum, and pancreas that was designed, discussed, and consensually approved at this conference. In addition, we report the proposal for a working formulation for the grading of digestive NETs based on mitotic count and Ki-67 index. This proposal, which needs to be validated, is meant to help clinicians in the stratification, treatment, and follow-up of patients.

TREATMENT

GUIDELINES

http://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf
Citation
Neuroendocrine Tumors v.2.2010
NCCN Clinical Practice Guidelines in Oncology.

http://content.karger.com/ProduktеDB/ProduktNr=223855
ENETS Consensus Guidelines for the Management of Patients with Rare Metastases from Digestive Neuroendocrine Tumors: Rationale and Working Framework.
Citation
Neuroendocrinology, 2010, 91(4): 324-325. (no abstract available.)
Authors:
O'Toole, D., Rindi, G., Plöckinger, U., & Wiedenmann, B.

http://content.karger.com/ProduktеDB/produkte.asp?ProduktNr=22385
ENETS Consensus Guidelines for the Management of Peritoneal Carcinomatosis from Neuroendocrine Tumors.
Citation
Neuroendocrinology, 2010, 91(4): 333-340. (no abstract available.)
Authors
Kianmanesh, R., Ruszniewski, P., Rindi, G., Kwekkeboom, D., Pape, U-E., Kulke, M., Sevilla Gracia, I., Scoazec, J-Y., Nilsson, O., Fazio, N., Lesurtel, M., Chen, Y-J., Eriksson, B., Cioppi, F., & O'Toole, D.

http://content.karger.com/ProduktеDB/produkte.asp?Doi=287255
ENETS Consensus Guidelines for the Management of Bone and Lung Metastases from Neuroendocrine Tumors.
Citation
Neuroendocrinology. 2010, 91(4): 341-350(no abstract available.)
Authors
Kos-Kudła, B., O'Toole, D., Falconi, M., Gross, D., Klöppel, G., Sundin, A., Ramage, J., Oberg, K., Wiedenmann, B., Komminoth, P., Van Custem, E., Mallath, M., Papotti, M., & Caplin, M.

http://content.karger.com/ProduktеDB/produkte.asp?Doi=287277
ENETS Consensus Guidelines for the Management of Brain, Cardiac and Ovarian Metastases from Neuroendocrine Tumors.
Citation
Neuroendocrinology, 2010, 91(4): 326-332 (no abstract available.)
Authors
Pavel, M., Grossman, A., Arnold, R., Perren, A., Kaltsas, G., Steinmüller, T., de Herder, W., Nikou, G., Plöckinger, U., Lopes, J. M., Sasano, H., Buscombe, J., Lind, P., O'Toole, D., & Oberg, K.

http://www.online.karger.com/ProduktеDB/produkte.asp?Doi=183751

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biotherapy.

Citation
Neuroendocrinology, 2009, 90(2): 209-213 (no abstract available.)

Authors
Oberg, K., Ferone, D., Kaltsas, G., Knigge, U. P., Taal, B., Plöckinger, U, & other Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society.

http://www.ncbi.nlm.nih.gov/pubmed/19454438
Neuroendocrine bronchial and thymic tumors: ESMO clinical recommendation for diagnosis, treatment and follow-up.
Citation
Annals of Oncology, 2009, 20 (Suppl 4): 147-149.

Authors
Oberg, K., Jelic, S., & ESMO Guidelines Working Group.

http://www.ncbi.nlm.nih.gov/pubmed/18097129
Consensus guidelines for the management of patients with digestive neuroendocrine tumors--well-differentiated jejunal-ileal tumor/carcinoma.
Citation
Neuroendocrinology, 2008, 87(1): 8-19. (no abstract available.)
Authors
Eriksson, B., Klöppel, G., Krenning E., Ahlman, H., Plöckinger, U., Wiedenmann, B., Arnold, R., Auerhammer, C., Körner, M., Rindi, G., Wildi, S.: Frascati Conference Participants.

http://web.ebscohost.com.ezproxy2.library.arizona.edu/ehost/pdfviewer/pdfviewer?
Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours: A Consensus Statement on Behalf of the European Neuroendocrine Tumour Society (ENETS).
Citation
Neuroendocrinology, 2004, 80(6): 394-424.(no abstract available.)
Authors
Plöckinger, U., Rindi, G., Arnold, R., Eriksson, B., Krenning, E.P., de Herder, W.W., Goede, A., Caplin, M., Wiedenmann, B., Oberg, K., Reubi, J.C., Nilsson, O., Delle Fave, G., Ruszniewski, P., & Ahlman, H.

SURGICAL TREATMENT

PRIMARY TUMOR RESECTION

http://www.ncbi.nlm.nih.gov/pubmed/20437863
Surgical management of bronchopulmonary carcinoid tumors: experience over 8 years and review of the literature.
Citation
Tumori, 2010, 96(1): 84-89.
Authors
Belak, J., Kudlac, M., Zak, V., Cavarga, I., Kocan, P. Böör, A., Stebnicky, M., Somos, A., &

Tkacova, T.

Abstract

AIMS AND BACKGROUND: An increased incidence of neuroendocrine tumors in the last decade has been noticed worldwide. Our purpose was to study the characteristics, surgical approaches and outcome in patients with primary bronchopulmonary carcinoid tumors. METHODS: Between 2001 and 2007, bronchopulmonary carcinoid tumors were removed in 11 of a total of 287 patients who underwent surgery for primary lung malignancies in our tertiary referral center. RESULTS: The patient group consisted of 3 men and 8 women (mean age 52.9 +/- 5.2 years, range 19-76 years). At presentation, 10 of 11 patients were symptomatic, with cough, pneumonia, breathlessness and hemoptysis being the most frequent symptoms. Histological findings revealed typical carcinoid in 10 patients and atypical carcinoid in one. The surgical approach included 8 lung resections (6 lobectomies, 1 bilobectomy, 1 segmentectomy), and 3 bronchoplastic tumor removals. In 2008, clinical examination and chest X-ray revealed no recurrence of the carcinoid and no long-term postoperative complications in any patient. CONCLUSIONS: In the light of our study and the review of the literature we conclude that early recognition of primary bronchopulmonary carcinoid tumors followed by adequate surgical removal of the malignancy are essential for complete remission of the disease.

http://www.ncbi.nlm.nih.gov/pubmed/20087092

Endoscopic treatment of rectal carcinoid tumors.

Citation

Diseases of the Colon & Rectum, 2010, 53(2): 169-176.

Authors

Onozato, Y., Kakizaki, S., Iizuka, H., Sohara, N., Mori, M., & Itoh, H.

Abstract

BACKGROUND: Various methods have been reported for the endoscopic treatment of rectal carcinoid tumors. The present study was designed to identify the optimal treatment strategy for an endoscopic resection. METHODS: Forty rectal carcinoid tumors of 38 patients were treated endoscopically. The indication criteria, complete resection rate, selection of treatment, local recurrence, distant metastases, and complications were analyzed. All tumors were estimated to measure 1 cm or less in diameter, without muscular invasion, atypical features, and lymph node metastases to the pararectal region. RESULTS: Complete resection of the lesions was obtained in 75.0% (30/40). The complete resection rates were 20.0% (1/5) by conventional polypectomy, 84.6% (22/26) by a two-channel endoscopic mucosal resection, and 77.8% (7/9) by endoscopic submucosal dissection. The 10 cases that did not show a clear submucosal layer after initial endoscopic treatment received additional endoscopic microwave coagulation therapy. There were no local or distant recurrences in the followed-up periods (median, 6.4 years). No difference was observed in the complete resection rate between two-channel endoscopic mucosal resection and endoscopic submucosal dissection. CONCLUSIONS: Small carcinoid tumors measuring less than 1 cm in diameter can therefore be managed endoscopically with no recurrence or spread. The selection of endoscopic treatment should be made after taking such factors as cost-effectiveness, expertise, and experience into careful consideration.

http://www.ncbi.nlm.nih.gov/pubmed/20421108

Laparoscopic Antrectomy for the Treatment of Type I Gastric Carcinoid Tumors.

Citation

Journal of Surgical Research, 2010, Feb. 4, [Epub ahead of print]

Authors
Ozao-Choy, J., Buch, K., Strauchen, J.A., Warner, R.R., & Divino, C.M.

Abstract
BACKGROUND: While the optimal treatment for type I gastric carcinoid tumors remains controversial, there is evidence to suggest that in multifocal disease, antrectomy may not only control local disease but also may lead to enterochromaffin-like cell (ECL) hyperplasia regression compared to medical and endoscopic treatments. MATERIALS AND METHODS: A single institution retrospective review of eight consecutive patients with multifocal type I gastric carcinoid tumor patients with no evidence of metastatic disease was performed from 2005 to 2006. All of these patients underwent laparoscopic antrectomy with Billroth II reconstruction. Patients' preoperative gastrin, chromogranin A levels, and biopsy and surgical specimen slides were compared with postoperative laboratory and biopsy slides. Pathology slides were reanalyzed by a blinded pathologist from our institution for evidence of tumor and ECL hyperplasia regression. RESULTS: All patients tolerated the procedure well with no reoperations or mortalities. Six of eight patient complained of mild reflux which was treated medically. One of eight had a mild wound infection which resolved with a course of cephalexin. Gastrin levels significantly decreased (98.9%) in all patients (P = 0.001). Furthermore, chromogranin A levels also significantly decreased (81.4%). Eight of eight patients showed no evidence of carcinoid tumor after surgery at mean biopsy follow-up of 17 mo (range 2-35 mo), however there was ECL hyperplasia after resection. Four of eight patients (50%) showed regression of ECL hyperplasia on postop biopsy, while the remaining four of eight showed no evidence of regression. CONCLUSIONS: This is the largest case series to investigate the surgical, clinical, and histologic outcomes of laparoscopic antrectomy in type I gastric carcinoid. Our data suggest that laparoscopic antrectomy is a safe and minimally invasive approach to treat nonmetastatic type I gastric carcinoid. All patients had no evidence of gross or microscopic disease at follow-up biopsy and almost half had regression of ECL hyperplasia at follow-up suggesting that antrectomy may be sufficient to prevent tumor recurrence. However, continued regular endoscopic surveillance and medical follow-up of patients with ECL hyperplasia are recommended.

http://www.ncbi.nlm.nih.gov/pubmed/20385369

Typical carcinoids and neuroendocrine carcinomas of the stomach: differing clinical courses and prognoses.

Citation
American Journal of Surgery, 2010 Apr 10. [Epub ahead of print]

Authors
Kim, B.S., Oh, S.T., Yook, J.H., Kim, K.C., Kim, M.G., Jeong, J.W., & Kim, B.S.

Abstract
BACKGROUND: Gastric endocrine tumors are usually classified as 3 types of well-differentiated endocrine tumors (typical carcinoids or carcinoids) and poorly differentiated carcinomas (neuroendocrine carcinomas [NECs]). METHODS: From 1993 to 2008, 97 patients (73 men and 24 women) were diagnosed with gastric neuroendocrine tumors at the Asan Medical Center. RESULTS: Of the 45 patients with typical carcinoids, 37 underwent surgery (eg, endoscopic resection). Of the 52 patients with NECs, 43 underwent surgery (eg, radical gastrectomy). One patient died of recurrence of the typical carcinoids, whereas 26

patients with NECs died of related diseases (P < .05). The rates of survival and recurrence did not significantly differ by type of typical carcinoid (P > .05). CONCLUSIONS: Regardless of the type, carcinoids that are not yet advanced can be effectively treated with minimal endoscopic or laparoscopic surgery. However, all NECs and advanced carcinoids should be treated with radical gastrectomy.

http://www.ncbi.nlm.nih.gov/pubmed/20333796

Surgically treated primary malignant tumor of small bowel: a clinical analysis.

Citation
World Journal of Gastroenterology, 2010 Mar, 16(12): 1527-1532.

Authors
Han, S.L., Cheng, J., Zhou, H.Z., Guo, S.C., Jia, Z.R., & Wang, P.F.

Abstract
AIM: To evaluate the clinical presentation, treatment and survival of patients with primary malignant tumor of small bowel (PMTSB). METHODS: Clinicopathologic data about 141 surgically treated PMTSB patients (91 males and 50 females) at the median age of 53.5 years (range 23-79 years) were retrospectively analyzed. RESULTS: The most common initial clinical features of the patients were intermittent abdominal discomfort or vague abdominal pain (67.4%), abdominal mass (31.2%), bowel obstruction (24.1%), hemotochezia (21.3%), jaundice (16.3%), fever (14.2%), coexistence of bowel perforation and peritonitis (5.7%), coexistence of gastrointestinal bleeding and shock (5.0%), and intraabdominal bleeding (1.4%). Ileum was the most common site of tumor (44.7%), followed by jejunum (30.5%) and duodenum (24.8%). PMTSB had a nonspecific clinical presentation. Segmental bowel resection (n = 81) was the most common surgical procedure, followed by right hemi-colectomy (n = 15), pancreaticoduodenectomy (n = 10), and others (n = 19). Twenty-seven adenocarcinoma patients and 13 malignant lymphoma patients received adjuvant chemotherapy with 5-fluorouracil and cyclophosphamide, adriamycin, vincristine and prednisone, respectively. Information about 120 patients was obtained during the follow-up. The median survival time of PMTSB patients was 20.3 mo. The 1-, 3- and 5-year survival rate was 75.0% (90/120), 40.0% (48/120) and 20.8% (25/120), respectively. Adenocarcinoma was found in 73.7% (42/57), 21.1% (12/57) and 15.8% (9/57) of the patients, respectively. Gastrointestinal stromal tumor was observed in 80.0% (20/25), 72.0% (18/25) and 36.0% (9/25) of the patients, respectively. Carcinoid was detected in 100.0% (15/15), 80.0% (12/15) and 46.7% (7/15) of the patients, respectively. Malignant lymphoma was demonstrated in 69.2% (9/13), 30.8% (4/13) and 0% (0/13) of the patients, respectively. CONCLUSION: En bloc resection is the principal therapy for most PMTSB and chemotherapy is the important treatment modality for malignant lymphoma and other malignant tumors of small bowel which cannot be radically removed.

http://www.ncbi.nlm.nih.gov/pubmed/19886158

Pancreatic neuroendocrine tumors: presentation, management, and outcomes.

Citation
American Surgeon, 2009, 75(10): 1025-1029.

Authors

Nissen, N.N., Kim, A.S., Yu, R., Wolin, E.M., Friedman, M.L., Lo, S.K., Wachsman, A.M., & Colquhoun, S.D.

Abstract
Pancreatic neuroendocrine tumors (pNETs) are an uncommon pancreatic neoplasm. We reviewed the presentation, management, and outcome of patients with pNETs treated at a single center by a multidisciplinary approach between 2004 and 2008. Over this time period, 154 patients with carcinoid and neuroendocrine tumors were treated, which included 46 patients (30% of total) with pNETs. The most common presentations included abdominal pain (20 of 46 [43%]), systemic symptoms such as hypoglycemia (15 of 46 [33%]), and incidental mass (7 of 46 [15%]). Fourteen patients had functional tumors. At the time of diagnosis, 22 patients (48%) presented without metastases and 24 (52%) had metastatic disease. Median follow up for the entire group was 42 months. All patients with nonmetastatic pNET underwent pancreatic resection with 95 per cent postoperative survival. Overall survival in this group at 3 years was 86 per cent and disease-free survival was 81 per cent. In patients presenting with metastatic pNET, multiple treatment modalities were used, including liver resection or ablation (n = 15), hepatic chemoembolization (n = 17), pancreatic resection (n = 12), and systemic treatments (n = 7). Three-year survival was 70 per cent. Pancreatic resection results in greater than 80 per cent 3-year survival in nonmetastatic pNET. In patients presenting with metastatic pNET, excellent survival rates are also achievable using a multidisciplinary multimodal approach.

http://www.ncbi.nlm.nih.gov/pubmed/20169101

Long-term follow-up of flexible bronchoscopic treatment for bronchial carcinoids with curative intent.

Citation
Diagnostic and Therapeutic Endoscopy, 2009: 782961. Epub 2010 Feb 7 .

Authors
Fuks, L., Fruchter, O., Amital, A., Fox, B.D., Rahman, A., & Kramer, M.R.

Abstract
Background. Typical pulmonary carcinoids represent less than 5% of primary lung tumors. In patients with typical bronchial carcinoid, formal surgical resection still remains the gold-standard treatment. Data regarding long-term outcome in using flexible bronchoscope-based modalities under conscious sedation is very limited. Objectives. We sought to investigate, over extended follow-up period, the effectiveness of endobronchial resection for carcinoid tumors with curative intent using flexible bronchoscopy. Methods. Nd:YAG laser photoresection using flexible bronchoscope under conscious sedation. Follow-up included repeat bronchoscopy every 6 months and chest CT every year. Results. Ten patients aged 24 to 70 years with endobronchial carcinoid were treated. The tumor location was variable: 2 left Main bronchus, 1 left upper lobe bronchus, 2 right main bronchus, 2 right middle lobe bronchus and 3 right lower lobe bronchus. No major complications were observed. The patients required between 2 and 4 procedures. Patients were followed for a median period of 29 months with no evidence of tumor recurrence. Conclusions. Endobronchial laser photoresection of typical bronchial carcinoids using flexible bronchsocopy under conscious sedation is an effective treatment modality for a subgroup of patients that provides excellent long-term results that are similar to outcome obtained by more invasive procedures.

http://www.ncbi.nlm.nih.gov/pubmed/19727959

Defining surgical indications for type I gastric carcinoid tumor.

Citation
Annals of Surgical Oncology, 2009, 16(11): 3154-3160.

Authors
Gladdy, R.A., Strong, V.E., Coit, D., Allen, P.J., Gerdes, H., Shia, J., Klimstra, D.S., Brennan, M.F., & Tang, L.H.

Abstract
BACKGROUND: Most gastric carcinoid tumors (GC) (type I) occur in association with achlorhydria, hypergastrinemia, atrophic gastritis and exhibit low-grade histopathology. The management of this indolent disease is controversial. The aim of this study was to evaluate endoscopic surveillance (ES) compare with surgical resection (SR) for type I GC. METHODS: Between 1985 and 2007, 65 patients with type IGC were identified. Data analysis included: demographics, biochemical and endoscopic assessment, type of operation performed, and pathologic evaluation. The primary endpoints were disease-specific survival (DSS) in both groups and recurrence-free survival (RFS) in SR patients. RESULTS: Median follow-up was 30 months (range 1-176 months); most patients were female (83%) with median age of 58 years (range 29-91 years). Type I GC was diagnosed by evidence of hypergastrinemia and/or positive autoimmune antibodies with histopathologic confirmation. Patients underwent ES with polypectomy (n=46) or gastric resection (n=19). SR was performed with larger tumor size, increased depth of invasion, and solitary tumors. Although the 5-year RFS in SR patients was 75%, the DSS in both groups was 100%. However, concomitant adenocarcinoma was identified in 4/19 resected cases; 2/4 were detected on preoperative biopsies. All cases with coexisting gastric adenocarcinoma had larger carcinoid tumors and more advanced carcinoid disease. CONCLUSIONS: The DSS is excellent for type I GC patients treated with either ES or SR. SR should be considered with more advanced carcinoid disease given its association with an increased risk of adenocarcinoma. ES is appropriate to assess both the status of carcinoid disease and dysplasia or adenocarcinoma that can develop in association with type I GC.

http://www.ncbi.nlm.nih.gov/pubmed/18490556

Rectal carcinoid tumors: review of results after endoscopic and surgical therapy.

Citation
Archives of Surgery, 2008, 143(5): 471-475.

Authors
Kwaan, M.R., Goldberg, J.E., & Bleday, R.

Abstract
OBJECTIVE: To assess whether endoscopic treatment can clear local disease in patients with carcinoid tumor. DESIGN: Retrospective cohort study. SETTING: Tertiary care academic medical center. PATIENTS: All patients diagnosed as having a neuroendocrine tumor or carcinoid tumor of the rectum who were evaluated at our institution between January 1, 1990, and December 31, 2006. MAIN OUTCOME MEASURE: Margin status of tumor resection. RESULTS: Eighty-five patients were identified (median age at diagnosis, 55 years). Thirty-three tumors (39%) were asymptomatic and diagnosed during screening colonoscopy. Eleven tumors (13%) were metastatic at presentation. Of the 85 tumors, 48 (56%) were smaller than 1.0 cm. Endoscopic therapy was performed in 46 patients (54%). Of these, 38 patients (83%)

had tumors with positive or indeterminate margins on histologic examination; of whom 6 (16%) had residual tumor on subsequent endoscopy and 1 (3%) had recurrence as metastatic disease. One patient who had a negative margin had residual tumor on follow-up. Thirty-one patients (36%) underwent surgical resection; of these, 23 (74%) underwent transanal excision or transanal endoscopic microsurgery, 6 (19%) underwent low anterior resection, and 2 (6%) underwent abdominoperineal resection. Eight patients who did not receive local clearance of tumor had metastases on presentation, had another active malignant neoplasm, or refused further surgical treatment. Among the 85 patients, 4 metastases occurred during follow-up, including 2 from tumors smaller than 1.0 cm at presentation. CONCLUSIONS: Endoscopic treatment is sufficient for tumors that are small, for tumors limited to the mucosa, and when a margin is negative for tumor. Transanal excision should be considered when margins of endoscopic resection are positive. We recommend rectal resection for tumors that are 1.0 to 1.9 cm and have high-risk features.

http://journals.lww.com/bronchology/Abstract/2007/01000/Endobronchial_Ablation_of_Typical_Carcinoid_Tumor.4.aspx

Endobronchial Ablation of Typical Carcinoid Tumor With Photodynamic Therapy.

Citation

Journal of Bronchology & Interventional Pulmonology, 2007, 14 (1): 10-14.

Authors

Downie, G.H., Qureshi, A.M.B., Loewen, G., Cuenca, R., Allison, R., & Sibata, C.

Abstract

Introduction: Typical endobronchial carcinoids are uncommon tumors. Standard of care has been surgical resection with survival and local control reported at 75% to 90% in several series. However, local endobronchial ablation with laser, photodynamic therapy (PDT), electrocautery, or brachytherapy may have the potential for similar outcomes based on initial small case series. We report outcomes of selected typical carcinoid tumors treated with PDT. Methods: Seven patients (4 males, 3 females), ages 28 to 76, with typical carcinoid tumors were treated with PDT using porfimer sodium 2 mg/kg and 630 nm laser at 200 J/cm. Response was determined visually and with biopsy at 1 month posttreatment as: none [no visible reaction, (+) biopsy], partial response [PR>50% reduction in tumor (+) biopsy], or complete response [CR 100% reduction in tumor (-) biopsy] and surveillance with bronchoscopy and computed tomography scan every 3 months for the first year and then yearly. Results: Six of 7 (86%) had CR, of the 6 patients with CR, 2 are 2 years, 2 are 3 years, and 2 are 5 years post-PDT. One CR patient required balloon dilatations for bronchial stenosis with success, no other significant side effects were seen. The sole PR had visualized distal margins in the anterior subsegment of the right upper lobe but had an unsuspected origin in the posterior subsegment and was unable to be completely treated with any local ablation technique. Conclusions: Employing selection criteria, we report CR in 86% of patients. There were no sustained significant side effects. Endobronchial treatments are effective, safe, and surgery sparing in selected patients.

http://www.ncbi.nlm.nih.gov/pubmed/18338494

Appendectomy or right hemicolectomy in the treatment of appendiceal carcinoid tumors?

Citation

Tumori, 2007, 93(6): 587-590.
Authors
Fornaro, R., Frascio, M., Sticchi, C., De Salvo, L., Mandolfino, F., Ricci, B., & Gianetta, E.

Abstract
AIMS AND BACKGROUND: Carcinoids of the appendix continue to be of interest, despite their low incidence. There is still considerable controversy surrounding these tumors, especially with regard to the role of right hemicolectomy in the surgical management. The aim of this work was to explicate the current therapeutic knowledge and to review the criteria for the indications of appendectomy or hemicolectomy. METHODS: The records of patients who underwent appendectomies from 1990 to 2000 were analyzed. Seven patients were included in the study. The clinical data were reviewed for demographic details, tumor size, localization in the appendix, histological patterns and surgical procedures. All patients underwent appendectomy including removal of the mesenteriolum, and in one of them a right hemicolectomy was performed 3 weeks later. The mean follow-up was 7 years (range, 4-14). Follow-up data included symptoms, urinary 5-hydroxyindoleacetic acid, ultrasound examination, computerized tomography, and octreotide scanning. RESULTS: Seven patients (0.9% of all appendectomies) were reported to have carcinoid tumors of the appendix. They were 3 men and 4 women with a mean age of 29 years. All patients were admitted for appendicitis. None suffered from the carcinoid syndrome. The site of the tumor was the apex of the appendix in 4 cases, the body in 2 cases and the base in 1 case. Mean tumor diameter was 8 mm (range, 5-29 mm); in 6 patients it was <2 cm. Treatment was appendectomy in all cases; additional right hemicolectomy was necessary in one case because of a tumor of more than 2 cm with invasion of the mesoappendix and lymph nodes. The 7-year survival rate is 100%. Six patients are without disease, while 1 patient (the one who underwent a right hemicolectomy) developed metastases in the liver 6 years after the operation. This patient, who was treated with a liver resection, is still alive. CONCLUSIONS: According to current guidelines, an appendectomy may be performed for small carcinoid tumors (<1 cm). Reasons for more extensive surgery than appendectomy are tumor size >2 cm, lymphatic invasion, lymph node involvement, spread to the mesoappendix, tumor-positive resection margins, and cellular pleomorphism with a high mitotic index. The criteria that direct us towards major (hemicolectomy) or minor surgery (appendectomy) are controversial. Tumor size is still considered the most important prognostic factor, with a presumed increase in the risk of metastasis for tumors greater than 2.0 cm. The accepted treatment of such tumors is a right hemicolectomy. However, there is no evidence demonstrating a survival benefit for right hemicolectomy over simple appendectomy in patients with carcinoids greater than 2.0 cm in diameter.

http://www.ncbi.nlm.nih.gov/pubmed/17188135

Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival.

Citation
Surgery, 2006, 140(6): 891-897; discussion 897-898.

Authors
Givi, B., Pommier, S.J, Thompson, A.K., Diggs, B.S., & Pommier, R.F.

Abstract
BACKGROUND: It is unclear whether there is a benefit to resection of primary

gastrointestinal carcinoid neoplasm with hepatic metastases. We investigated whether primary tumor resection in this setting led to a significant difference in outcomes. METHODS: A retrospective review of patients with abdominal carcinoid neoplasms between 1995 and 2006 was performed. Data collected on patients with proven carcinoid liver metastases at initial diagnosis included whether the primary neoplasm was resected, time to progression of liver metastases, and status at last follow-up. Progression-free survival and survival were calculated by the method of Kaplan-Meier and compared by the log-rank test. RESULTS: There were 84 patients, 60 of whom had their primary neoplasm resected. The resected group had a greater median progression-free survival of 56 months, compared with 25 months for the primary nonresected group (P < .001). Median survival time for the resected group was longer at 159 months, compared with 47 months for the nonresected group (P < .001). CONCLUSIONS: Resection of the primary neoplasm is associated with better progression-free survival and overall survival in patients with abdominal carcinoid neoplasms. Therefore, localization and resection of the primary neoplasm should be considered, even among patients in whom the primary neoplasm is asymptomatic.

http://www.ncbi.nlm.nih.gov/pubmed/16618891

Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified?

Citation
Archives of Surgery, 2006, 141(4): 349-52; discussion 352.

Authors
Bamboat, Z.M., & Berger, D.L.

Abstract
HYPOTHESIS: We believe right hemicolectomy (RHC) is not necessary in patients with an appendiceal carcinoid greater than 2.0 cm. DESIGN: A retrospective review of patients with a histologically confirmed appendiceal carcinoid from April 1, 1980, to February 28, 2005, and an analysis of the literature. SETTING: Tertiary care referral center. PATIENTS: Forty-eight patients (34 females and 14 males) with a histologically confirmed diagnosis of appendiceal carcinoid were included in the study. Appendiceal carcinoid was diagnosed incidentally in all 48 patients. Patient ages ranged from 11 to 86 years (mean age, 41 years). Postoperative follow-up and disease-free survival were confirmed in 33 patients via medical record review. MAIN OUTCOME MEASURES: We assessed the relationship between survival, tumor size, and the role of RHC vs appendectomy alone. RESULTS: Four patients in our series underwent secondary RHC and lymph node dissection for tumors greater than 2.0 cm, and none had positive lymph nodes. Following review of the literature, we were unable to find any recent evidence of distant metastasis from carcinoids in patients already treated by appendectomy. There seem to be no conclusive data to support the notion that RHC confers a survival benefit over appendectomy for carcinoids greater than 2.0 cm. CONCLUSION: Appendiceal carcinoids greater than 2.0 cm can be managed effectively with simple appendectomy, given their low malignant potential and slow growth, obviating the need for RHC in this group of patients without affecting overall survival.

http://www.ncbi.nlm.nih.gov/pubmed/15912033
Surgical treatment of advanced-stage carcinoid tumors: lessons learned.
Citation
Annals of Surgery, 2005, 241(6): 839-845.

Authors
Boudreaux, J.P., Putty, B., Frey, D.J., Woltering, E., Anthony, L., Daly, I., Ramcharan, T., Lopera, J., & Castaneda, W.
Abstract
OBJECTIVE: To evaluate clinical outcomes in a large group of advanced-stage carcinoid patients (stage IV) following multimodal surgical therapy. SUMMARY BACKGROUND DATA: Patients with advanced-stage carcinoid have traditionally experienced poor 5-year survival (18%-30%). Few recent series have evaluated a large number of patients treated with aggressive surgical rescue therapy. METHODS: This single-center retrospective review analyzes the records of 82 consecutive carcinoid patients treated by the same 2 surgeons, from August 1998 through August 2004 with a 3- to 72-month follow-up. RESULTS: Surprisingly, one third of 26 (32%) patients were found to have intestinal obstructions; 10 being moribund at presentation. Mesenteric encasement with intestinal ischemia was successfully relieved in 10 of 12 cases. Five of eighty-two "terminal" patients were rendered free of macroscopic disease. Karnofsky performance scores improved from 65 to 85 ($P < 0.0001$). Two- and four-year survival for patients with no or unilateral liver metastases ($n = 23$) was 89%, while 2- and 4-year survival for patients with bilateral liver disease ($n = 59$) was 68% and 52% ($P = 0.072$), respectively. CONCLUSION: We think that all patients with advanced-stage carcinoid should be evaluated for possible multimodal surgical therapy. Primary tumors should be resected, even in the presence of distant metastases to prevent future intestinal obstruction. The "wait and see" method of management of this slow-growing cancer no longer has merit. We offer an algorithm for the surgical evaluation and management of these patients.

http://www.carcinoid.org/medpro/docs/ENET2003Surgery.pdf

Surgery for midgut carcinoid

Citation
Endocrine Related Cancer , 2003, 10, 469–481.

Authors
Sutton, R., Doran, H.E., Williams, E.M., Vora, J., Vinjamuri, S., Evans, J., Campbell, F., Raraty, M.G.T., Ghaneh, P., Hartley, M., Poston, G.J., & Neoptolemos, J.P.

Abstract

Many clinicians prefer to avoid surgery in patients with carcinoid neoplasia, because of its slow growth and relatively favourable prognosis. Nevertheless, the commonest cause of death in patients with carcinoid is advanced metastatic disease, and both clinical and epidemiological data indicate that the more effectively the disease is ablated, the more long-lasting the benefit. Multidisciplinary management of patients with carcinoid must consider inherited risk, possible multiple carcinoids and/or synchronous non-carcinoid cancer, and the use of a range of investigations that also evaluate the 10% of patients with carcinoid syndrome with or without valvular heart disease. Although primary size is correlated with the presence of nodal with or without liver metastases, carcinoid tumours < 1 cm in diameter may be metastatic at presentation, particularly those arising within the small intestine. In the jejunum and ileum, resection of all sizes of carcinoid with local and regional nodes is preferred, to prevent nodal dissemination causing mesenteric ischaemia with or without infarction. Resection of nodal metastases should be undertaken in those with persistent or recurrent nodal disease if possible. Appendiceal and right colonic carcinoids are most effectively treated by right hemicolectomy with local and regional nodal clearance, as for adenocarcinoma. However, for most appendiceal carcinoids which are < 1 cm in diameter and non-invasive, appendicectomy alone is sufficient. For appendiceal carcinoids 1–2 cm in

diameter, histopathological assessment helps to determine the need for hemicolectomy. Liver resection has been followed by prolonged 5 year survival in several series and is recommended in appropriate patients to attempt cure or to debulk metastatic disease. Liver transplantation has had only qualified success in highly selected patients without extra-hepatic disease in whom other therapies have failed.

http://www.ncbi.nlm.nih.gov/pubmed/12912744

Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors.

Citation
Archives of Surgery, 2003, 138(8): 859-866.

Authors
Norton, J.A., Kivlen, M., Li, M., Schneider, D., Chuter, T., & Jensen, R.T.

Abstract
BACKGROUND: There is considerable controversy about the treatment of patients with malignant advanced neuroendocrine tumors of the pancreas and duodenum. Aggressive surgery remains a potentially efficacious antitumor therapy but is rarely performed because of its possible morbidity and mortality. HYPOTHESIS: Aggressive resection of advanced neuroendocrine tumors can be performed with acceptable morbidity and mortality rates and may lead to extended survival. DESIGN: The medical records of patients with advanced neuroendocrine tumors who underwent surgery between 1997 and 2002 by a single surgeon at the University of California, San Francisco, were reviewed in an institutional review board-approved protocol. MAIN OUTCOME MEASURES: Surgical procedure, pathologic characteristics, complications, mortality rates, and disease-free and overall survival rates were recorded. Disease-free survival was defined as no tumor identified on radiological imaging studies and no detectable abnormal hormone levels. Proportions were compared statistically using the Fisher exact test. Kaplan-Meier curves were used to estimate survival rates. RESULTS: Twenty patients were identified (11 men and 9 women). Of these, 10 (50%) had gastrinoma, 1 had insulinoma, and the remainder had nonfunctional tumors; 2 had multiple endocrine neoplasia type 1, and 1 had von Hippel-Lindau disease. The mean age was 55 years (range, 34-72 years). In 10 patients (50%), tumors were thought to be unresectable according to radiological imaging studies because of multiple bilobar liver metastases (n = 6), superior mesenteric vein invasion (n = 3), and extensive nodal metastases (n = 1). Tumors were completely removed in 15 patients (75%). Surgical procedures included 8 proximal pancreatectomies (pancreatoduodenectomy or whipple procedure), 3 total pancreatectomies, 9 distal pancreatectomies, and 3 tumor enucleations from the pancreatic head. Superior mesenteric vein reconstruction was done in 3 patients. Liver resections were done in 6 patients, and an extended periaortic node dissection was performed in 1. The spleen was removed in 11 patients, and the left kidney was removed as a result of tumor metastases in 2. Eighteen patients had primary pancreatic tumors, and 2 had duodenal tumors; 2 patients with multiple endocrine neoplasia type 1 had both pancreatic and duodenal tumors. The mean tumor size was 8 cm (range, 0.5-23 cm). Of the patients, 14 (70%) had lymph node metastases and 8 (40%) had liver metastases. The mean postoperative hospital stay was 11.5 days (range, 6-26 days). Six patients (30%) had postoperative complications. There was a significantly greater incidence of pancreatic fistulas with enucleations compared with resections (P =.04). There were no operative deaths. The mean follow-up period was 19 months (range, 1-96 months); 18 patients (90%) are alive, 2 died of progressive tumor, and 12 (60%) are disease-free. The actuarial overall survival rate is 80% at 5 years, and disease-free survival rates

indicate that all tumors will recur by the 7-year follow-up visit. CONCLUSIONS: Aggressive surgery including pancreatectomy, splenectomy, superior mesenteric vein reconstruction, and liver resection can be done with acceptable morbidity and low mortality rates for patients with advanced neuroendocrine tumors. Although survival rates following surgery are excellent, most patients will develop a recurrent tumor. These findings suggest that conventional contraindications to surgical resection, such as superior mesenteric vein invasion and nodal or distant metastases, should be reconsidered in patients with advanced neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/12016480

Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases.

Citation

World Journal of Surgery, 2003, 26(8): 991-997.

Authors Hellman, P., Lundström, T., Ohrvall, U., Eriksson, B., Skogseid, B., Oberg, K., Tiensuu Jansen, E., & Akerström, G.

Abstract

We have evaluated survival and tumor-related symptoms in the presence of mesenteric lymph node and liver metastases in relation to surgical procedures in 314 patients (148 women, mean age at diagnosis 61 years; 249 with liver metastases) treated for midgut carcinoid tumors. Of the operated patients, 46% presented with severe abdominal pain and intestinal obstruction and were operated on before the diagnosis. Medical treatment (somatostatin analogs, interferon-a) was initiated in 67% and 86%, respectively. Surgical attempts included small intestine or ileocecal/right-sided colon resection with excision of mesenteric lymph node metastases. Most of the patients (n = 286) had mesenteric lymph node metastases; 33% of them had unresectable mesenteric lymph node metastases and underwent surgery without mesenteric dissection. Patients who underwent resection for the primary tumor had a longer survival than those with no resection (median survival 7.4 vs. 4.0 years; $p < 0.01$). Patients who underwent successful excision of mesenteric metastases had a significantly longer survival than those with remaining lymph node metastases. Patients operated on for a primary tumor but with remaining lymph nodes but no liver metastases and who subsequently received interferon and somatostatin analog treatment had a median survival of 7.4 years. Resection of the primary tumor and the mesenteric lymph node metastases led to a significant reduction in tumor-related symptoms. Surgery to remove the primary intestinal tumor including mesenteric lymph node metastases is supported by the present results, even in the presence of liver metastases. Liver metastases and significant preoperative weight loss are identified as major negative prognostic factors for survival.

http://www.ncbi.nlm.nih.gov/pubmed/12354709

Carcinoid heart disease: impact of pulmonary valve replacement in right ventricular function and remodeling.

Citation

Circulation, 2002, 106(12 Suppl 1): I51-I56.

Authors

Connolly, H.M., Schaff, H.V., Mullany, C.J., Abel, M.D., & Pellikka, P.A.

Abstract

BACKGROUND: Carcinoid heart disease characteristically affects tricuspid (TV) and pulmonary valves (PV), and TV replacement is helpful in selected patients. There is uncertainty, however, regarding optimal surgical management of PV regurgitation. METHODS AND RESULTS: We reviewed 22 patients having operation for carcinoid heart disease and compared those having TV and PV replacement (n=12), to those who underwent TV replacement and excision of the PV (n=10). Pre- and postoperative right ventricular (RV) size and dysfunction were assessed by consensus of 2 echocardiographers blinded to type of surgical treatment. RV dysfunction was graded as none (0), mild (1), moderate (2), or severe (3). RV size was graded as normal (0), or mild (1), moderate (2), or severe (3) enlargement. Preoperatively, RV size (2.2+/-0.8 [no PVR]versus 2.7+/-0.6 [with PVR], P=0.15), RV dysfunction (0.9+/-0.9 [no PVR]versus 1.4+/-0.7 [with PVR], P=0.14), and NYHA class were similar in the 2 groups. Postop RV size decreased inpatients with PVR, 2.7+/-0.6 to 1.7+/-1.0 (P=0.008), but did not change appreciably in those without PVR, 2.2+/-0.8 to 2.3+/-0.8 (P=0.67). There was no significant change in RV dysfunction after surgery, 1.4+/-0.7 to 1.8+/-0.9 with PVR (P=0.26) and 0.9+/-0.9 to 1.6+/-0.9 without PVR (P=0.07). CONCLUSIONS: PV replacement appears to have a beneficial effect on RV size in patients after surgery for carcinoid heart disease. This may have important implications for RV remodeling after PV replacement.

http://www.ncbi.nlm.nih.gov/pubmed/11828290

Bronchial carcinoid tumors: surgical management and long-term outcome.

Citation
Journal of Thoracic & Cardiovascular Surgery, 2002, 123: 303-309.

Authors
Filosso, P.L., Rena, O., Donati, G., Casadio, C., Ruffini, E., Papalia, E., Oliaro, A.. & Maggi, G.

Abstract

OBJECTIVE: We sought to determine the variables influencing long-term survival of patients treated for bronchial carcinoid tumors. METHODS: A retrospective, mono-institutional review of patients subjected to surgical treatment since 1977 was conducted. RESULTS: Over 22 years, 126 patients with a final histologic diagnosis of bronchial carcinoid tumors were assessed for surgery. The group comprised 72 men (57%) and 54 women (43%) with a mean age at presentation of 47 +/- 16 years (range 11-77 years). Symptoms were present in 65 (53%) patients. Operations included lobectomy or bilobectomy in 88 (with 4 bronchoplastic procedures), pneumonectomy in 15, segmentectomy in 3, wedge resection in 16, and bronchial sleeve resection in 3 patients. One patient (0.7%) died in the perioperative period. Eighty-two patients (65%) had typical and 44 (35%) had atypical carcinoid tumors. Postoperative staging was complete for 113 of 126 patients (13 patients did not undergo lymphadenectomy): 90 patients had stage I disease, 6 had stage II, 15 had stage III, and 2 had stage IV disease. A typical subtype was stage I in 70 and more advanced (II-IV) in 5, whereas an atypical subtype was stage I in 20 and more advanced in 18 (P <.05). Mean follow-up was 99 +/- 73 months (range 6-282 months) during which 19 (15%) patients died (12 of recurrent disease). Recurrent tumor developed in 4 (5.5%) of 72 patients affected by typical subtypes and 8 (19.5%) of 41 by atypical subtypes with complete follow-up. Overall survival at 15 years was 74%; survival related to histologic type and nodal status at 15 years was significant (P <.05). CONCLUSIONS: Biologic behavior and prognosis for bronchial carcinoid tumors are better than for other lung cancers. Surgical treatment requires radical excision and lymph node sampling. Survival and long-term outcome are significantly related to the histologic type, nodal status, and pathologic stage.

http://circ.ahajournals.org/cgi/content/abstract/104/suppl_1/I-36

Surgical Management of Left-Sided Carcinoid Heart Disease.

Citation
Circulation, 2001, 104: I36-I40.

Authors
Connolly, H.M., Schaff, H.V., Mullany, C.J., Rubin, J., Abel, M.D., & Pellikka, P.A.

Abstract
BACKGROUND: Carcinoid involvement of left-sided heart valves has been reported in patients with a patent foramen ovale, carcinoid tumor of the lung, and active carcinoid syndrome with high levels of serotonin. The present study details the clinical features and surgical management of patients with carcinoid heart disease affecting both left- and right-sided valves. METHODS AND RESULTS: Eleven patients (7 men, 4 women) with symptomatic carcinoid heart disease underwent surgery for left- and right-sided valve disease between 1989 and 1999. Mean age was 57+/-9 years, and median preoperative NYHA class was 3. All patients had metastatic carcinoid tumors and were on somatostatin analog. Of 11 patients, 5 (45%) had a patent foramen ovale; 1 of these also had a primary lung carcinoid tumor. Surgery included tricuspid valve replacement in all patients, pulmonary valve replacement in 3 and valvectomy in 7, mitral valve replacement in 6 and repair in 1, aortic valve replacement in 4 and repair in 2, CABG in 2, and patent foramen ovale closure in 5. One myocardial metastatic carcinoid tumor was removed. There were 2 perioperative deaths. At a mean follow-up of 41 months, 4 additional patients were dead. All but 1 surgical survivor initially improved >/=1 functional class. No patient required reoperation. CONCLUSIONS: Carcinoid heart disease may affect left- and right-sided valves and occurred without intracardiac shunting in 55% of this surgical series. Despite metastatic disease that limits longevity, operative survivors had improvement in functional capacity. Cardiac surgery should be considered for select patients with carcinoid heart disease affecting left- and right-sided valves.

http://www.ncbi.nlm.nih.gov/pubmed/11517130

Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours.

Citation
British Journal of Anaesthesia, 2001, 87(3):447-452.

Authors
Kinney, M.A., Warner, M.E., Nagorney, D.M., Rubin, J., Schroeder, D.R., Maxson, P.M., & Warner, M.A.

Abstract
Patients with metastatic carcinoid tumours often undergo surgical procedures to reduce the tumour burden and associated debilitating symptoms. These procedures and anaesthesia can precipitate a life-threatening carcinoid crisis. To assess perioperative outcomes, we studied retrospectively the medical records of adult patients from 1983 to 1996 who underwent abdominal surgery for metastatic carcinoid tumours. Preoperative risk factors, intraoperative complications and complications occurring in the 30 days after surgery were recorded.

Perioperative complications or death occurred in 15 of 119 patients (12.6%, exact confidence interval 7.2-19.9). None of the 45 patients who received octreotide intraoperatively experienced intraoperative complications compared with eight of the 73 patients (11.0%) who did not receive octreotide (P=0.023). The presence of carcinoid heart disease and high urinary output of 5-hydroxyindoleacetic acid preoperatively were statistically significant risk factors for perioperative complications.

METASTATIC DISEASE

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/15709214

Metastatic Carcinoid Tumors: A Clinical Review.
Citation
The Oncologist, 2005,10: 123-131.
Authors
Zuetenhorst, J.M., & Taal, B.G.

Abstract
Carcinoid tumors are neuroendocrine tumors derived from enterochromaffin cells, which are widely distributed in the body. They can originate from any location in the body, but they are traditionally described as originating from the foregut, midgut, and hindgut. Although the overall incidence of carcinoid tumors appears to have increased in the past decades, the prognosis for patients with metastatic carcinoid tumors has improved during the last decade. Due to longer survival times, complications, such as carcinoid heart disease, and new metastatic patterns, like skin and bone metastases, may become more important features of carcinoid disease. Therapy focused on these complications should be part of the management. Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in better quality of life and longer survival times. The increasing number of therapeutic options and diagnostic procedures requires a multidisciplinary approach, with decisions made in multidisciplinary meetings focused on "tailor-made" therapy based on patients' specific conditions. Because carcinoid tumors are uncommon, effort should be made to treat these patients in specialized centers and for these centers to join together in multicenter studies.

SURGERY

http://www3.interscience.wiley.com.ezproxy2.library.arizona.edu/cgi-bin/fulltext/123417649/PDFSTART

Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review.

Citation
Transplant International, 2010, 23(7): 668-678.

Authors

Bonaccorsi-Riani, E., Apestegui, C., Jouret-Mourin, A., Sempoux, C., Goffette, P., Ciccarelli, O., Borbath, I., Hubert, C., Gigot, J. F., Hassoun, Z., & Lerut, J.

Abstract
Neuroendocrine tumor (NET) metastases represent at this moment the only accepted indication of liver transplantation (LT) for liver secondaries. Between 1984–2007, nine (1.1%) of 824 adult LTs were performed because of NET. There were five well differentiated functioning NETs (four carcinoids and one gastrinoma), three well differentiated non functioning NETs and one poorly differentiated NET. Indications for LT were an invalidating unresectable tumor (4×), and/or a diffuse tumor localization (3×) and/or a refractory hormonal syndrome (5×). Median post-LT patient survival is 60.9 months (range 4.8–119). One-, 3- and 5-year actuarial survival rates are 88%, 77% and 33%; 1, 3 and 5 years disease free survival rates are 67%, 33% and 11%. Due to a more rigorous selection procedure, results improved since 2000; three out of five patients are alive disease-free at 78, 84 and 96 months. Review of these series together with a review of the literature reveals that results of LT for this oncological condition can be improved using better selection criteria, adapted immunosuppression and neo- and adjuvant surgical as well as medical treatment. LT should be considered earlier in the therapeutic algorithm of selected NET patients as it is the only therapy that can offer a cure.

http://www.ncbi.nlm.nih.gov/pubmed/20207070

Surgical management of carcinoid tumors metastatic to the spine: Report of three cases.

Citation
Clinical Neurology & Neurosurgery, 2010, 112(5): 443-445.

Authors
Arnold, P. M., Floyd, H.E., Anderson, K. K., & Newell, K. L.

Abstract
BACKGROUND: Carcinoid tumors are rare, slow-growing neuroendocrine tumors that most frequently arise from the gastrointestinal tract or the lungs. Common sites of carcinoid metastases include lymph nodes, liver, lungs, and bone, with rare metastasis to the spine. We report three patients who presented with spinal cord compression secondary to carcinoid metastases to the spine. METHODS: Three patients presented with symptoms characteristic of spinal cord compression, including neck pain, radiculopathy, thoracic pain, weakness and numbness. All three patients underwent radiographic work-up and surgical treatment. RESULTS: One patient continued to have decreased strength in her right upper extremity, but was able to participate in physical therapy; another patient's numbness eventually resolved after completion of physical therapy; and the third patient's pain dramatically improved after surgery. One patient died more than two years post-surgery due to widespread metastasis; the other two remain alive more than two years post-surgery. CONCLUSIONS: Carcinoid tumor metastases rarely cause spinal cord compression, but should be considered when patients present with neurological symptoms consistent with cord compression. Work-up should include magnetic resonance imaging (MRI), computed tomography (CT) of the spine, and perhaps CT-guided biopsy. Surgery is indicated for symptomatic spinal cord compression in patients with carcinoid tumors.

http://journals.lww.com/pancreasjournal/Citation/2010/03000/Surgical_Management_of_Neuroendocrine_Tumors.38.aspx

Surgical Management of Neuroendocrine Tumors Metastatic to the Liver.

Citation

Pancreas, 2010, 39(2): 272

Authors

Celinski, S., Steel, J., Nguyen, K.T., Wallis, J.W., Geller, D.A,, Raizmann, R., Tsung, A., & Clark, G.T.

Abstract

Background: Neuroendocrine tumors (NET) frequently metastasize to the liver. Aggressive management of metastatic disease has been advocated due to the indolent course of NET. We sought to evaluate factors affecting survival in surgically treated hepatic metastases from NET. Methods: Clinicopathologic data was retrospectively gathered from the records of 34 patients at our center who underwent liver surgery for NET. Chi-square and Analysis of Variances was performed to test differences between groups. Survival was assessed using Kaplan-Meier analysis. Results: Median survival of the entire sample was 70.7 months. Resection alone was performed in 68%, and 32% had resection coupled with RFA. Liver disease was synchronous with the primary in 68%, and bilobar in 85% of patients. There was no difference in survival based on primary site (p = 0.53), tumor histology (p = 0.66), or synchronicity (p = 0.48). R0/R1 resection was achieved in 65%. There was no significant difference in survival comparing R0/R1 (87 months; 95% CI 10 - 164 months) and R2 resections (71 months; 95% CI 32 - 108 months; p = 0.65). Recurrence occurred in 41% of patients undergoing R0 or R1 resection in a mean of 23.8 months, with no difference in time to recurrence between R0 and R1 resection (p = 0.73). Patients 51-69 years old had the best survival (115 months; 95% CI 26-204 months) followed by those G51 (31 months; 95% CI 15-137 months) and those >69 (39 months; 95% CI 15-64 months; p = 0.04). Conclusions: Surgical resection of NET hepatic metastases may result in long term survival. Long term survival was only influenced by age at resection. In those achieving R0 and R1 status, positive microscopic margins did not adversely affect survival, suggesting that surgical debulking may have a positive effect on survival. Our cohort and survival data underscores the need for a multicenter investigation of NET surgical management.

http://www.ncbi.nlm.nih.gov/pubmed/19470616

Clinical and imaging follow-up after exhaustive liver resection of endocrine metastases: a 15-year monocentric experience.

Citation

Endocrine-Related Cancer, 2009, 16(3): 977-990.

Authors

Scigliano, S., Lebtahi, R., Maire, F., Stievenart, J.L., Kianmanesh, R., Sauvanet, A., Vullierme, M.P., Couvelard, A., Belghiti, J., Ruszniewski, P., & Le Guludec, D.

Abstract

Liver metastases are common in gastroenteropancreatic neuroendocrine tumors and significantly impair survival. Hepatic resection is the only potential curative treatment. The records of 41 consecutive patients undergoing exhaustive resection of liver-only endocrine metastases and followed between 1992 and 2006 were reviewed. Patient's outcome and diagnostic accuracy of somatostatin receptor scintigraphy (SRS) and morphological imaging (MI) for detection of recurrences during post-operative follow-up were assessed. All identified primary had been resected. MI studies including abdominal computed tomography (CT)

and/or liver magnetic resonance imaging and thoracic CT if indicated were performed every 6 months; SRS timing was decided by referring clinician. Tumor recurrences were confirmed by pathology or subsequent imaging studies. The results of 136 MI and SRS examinations performed within a 30-day interval from each other were retrospectively compared. Median post-operative follow-up was 51 months (7-165). Recurrences developed in 32 patients (78%), mainly in the liver (n=24) after a median of 19 months (2-79). Five-year overall and disease-free survival rates were 79 and 3% respectively. For recurrence detection, sensitivity, specificity, and accuracy were 89, 94, and 91% for SRS, 68, 91, and 74% for MI respectively. In 11 out of 32 patients (34%), abdominal or extra-abdominal metastases were detected 15.5 months earlier by SRS than MI. In conclusion, despite exhaustive liver surgery for endocrine metastases, hepatic or extra-hepatic recurrences are frequent and develop early. SRS is highly accurate for the detection of recurrences during post-operative follow-up and permitted early diagnosis in one third of patients; therapeutic implications of this early diagnosis remain to be determined.

http://www.ncbi.nlm.nih.gov/pubmed/18324347

Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors.

Citation
World Journal of Surgery, 2008, 32(5): 930-938.

Authors
Eriksson, J., Stålberg, P., Nilsson, A., Krause, J., Lundberg, C., Skogseid, B., Granberg, D., Eriksson, B., Akerström, G., & Hellman, P.

Abstract
BACKGROUND: Many neuroendocrine tumors (NETs) have a tendency to metastasize to the liver. In case of limited number of metastases, liver surgery or radiofrequency ablation (RFA) may result in apparently total clearance of metastases. However, it is not clear whether such therapy will provide symptom reduction or increased survival. METHODS: Seventy-three patients with foregut (n=6) or midgut carcinoids (n=37) or endocrine pancreatic tumors (n=28), and two patients with NETs without discernable origin were studied. Symptoms were evaluated using a Symptom Severity Score. Liver surgery was performed in 42 operations and RFA on 205 lesions. RESULTS: Apparently total clearance of liver metastases was attained in 1 of 6 patients with foregut carcinoids, 15 of 37 with midgut carcinoids, and 13 of 28 with EPT. Symptom improvement was noted in 12 of 17 (70.6%) patients with carcinoid syndrome, and 75% also reduced their 5-HIAA and P-CgA by at least 50%. Patients with nonfunctioning EPT generally had no improvement of symptoms after surgical/RFA liver treatment, but eight patients had functioning EPT, and four of these reduced their biochemical markers by at least 50%. NETs with higher Ki67 index tended to recur more often. Complications occurred in 9 of 45 open surgery procedures, and in 8 of 203 RFA procedures. CONCLUSIONS: Treatment of liver metastases is successful in midgut carcinoid patients with limited liver metastases. Patients with foregut carcinoid and EPTs recur more often, possibly related to higher Ki67 index, and treatment of liver lesions less often reduces symptoms. Liver resections and RFA may be safely performed, and RFA is associated with few complications.

http://www.ncbi.nlm.nih.gov/pubmed/18241623

Role of hepatic resection for patients with carcinoid heart disease.

Citation
Mayo Clinic Proceedings, , 2008, 83(2): 143-150.

Authors
Bernheim, A.M., Connolly, H.M., Rubin, J., Møller, J.E., Scott, C.G., Nagorney, D.M., & Pellikka, P. A.

Abstract
OBJECTIVE: To evaluate the effects of resection of hepatic carcinoid metastases on progression and prognosis of carcinoid heart disease. PATIENTS AND METHODS: From our database of 265 consecutive patients diagnosed as having carcinoid heart disease from January 1, 1980, through December 31, 2005, we calculated survival from first diagnosis of cardiac involvement. Hepatic resection during follow-up was entered as a time-dependent covariable in a multivariable analysis. In patients with serial echocardiograms more than 1 year apart without intervening cardiac surgery, a previously validated cardiac severity score was calculated. A score increase that exceeded 25% was considered relevant progression. RESULTS: Hepatic resection was performed in 31 patients (12%) during follow-up. Five-year survival was significantly higher in these patients (86.5%; 95% confidence interval [CI], 73.5%-100.0%) than in patients without hepatic resection (29.0%; 95% CI, 23.3%-36.1%; univariable hazard ratio for hepatic resection, 0.25; 95% CI 0.12-0.53; P<.001). Hepatic resection remained strongly associated with improved prognosis in multivariable analysis (hazard ratio, 0.31; 95% CI, 0.14-0.66; P=.003). Among 77 patients (29%) with serial echocardiograms, 10 (13%) underwent hepatic resection during follow-up; resection was independently associated with decreased risk of cardiac progression (odds ratio, 0.29; 95% CI, 0.06-0.75; P=.03). CONCLUSION: Despite the limitations of this retrospective nonrandomized study, our data suggest that patients with carcinoid heart disease who undergo hepatic resection have decreased cardiac progression and improved prognosis. Eligible patients should be considered for hepatic surgery.

http://www.ncbi.nlm.nih.gov/pubmed/18362629

Two-step surgery for synchronous bilobar liver metastases from digestive endocrine tumors: a safe approach for radical resection.

Citation
Annals of Surgery, 2008, 247(4): 659-665.

Authors
Kianmanesh, R., Sauvanet, A., Hentic, O., Couvelard, A., Lévy, P., Vilgrain, V., Ruszniewski, P., & Belghiti, J.

Abstract
OBJECTIVE: We describe the early and distant results of a 2-step surgical strategy that enables complete resection in selected patients with primary digestive endocrine tumors (DET) and synchronous bilobar liver metastases (LM). BACKGROUND: Frequent synchronous and bilobar liver involvement limits indications of surgery in LM from DET. STUDY DESIGN: From 1996 to 2004, of 41 patients with synchronous bilobar LM from DET, 23 (56%) were selected for 2-step surgery. The first step included resection of the primary tumor and limited (nonanatomic) resection of left LM (segments 1-4) associated with a right portal vein ligation. After 8 weeks, following hypertrophy of the cleared left liver, a right or extended right hepatectomy was planned. RESULTS: At the first step, all primary tumors (bowel = 12, distal pancreas = 10, rectal = 1) were resected and LM were resected in 20 patients (87%). One

patient did not have second-step due to tumor progression. The second step (n = 19; 83%) was performed after a median interval of 8 weeks (range, 6-13) and a 54 +/- 21% mean left liver hypertrophy rate. Postoperatively, 4 (17%) and 4 (21%) patients developed nonlethal complications and the median hospital stay was 11 (range, 7-26) and 13 (range, 9-17) days after the first and the second step, respectively. The median number of resected LM was 4 (range, 1-9) and 7 (range, 4-17), respectively. With a median follow-up of 64 months (range, 6-122), of the 19 patients who had complete 2-step surgery, all except one are alive. The 2-, 5-, and 8-year Kaplan-Meier overall and disease-free survival rates were 94%, 94%, 79% and 85%, and 50% and 26%, respectively. CONCLUSIONS: This 2-step surgery approach enables complete resection with no mortality, acceptable morbidity, and good long-term survival in selected patients with synchronous bilobar LM from DET.

http://www.ncbi.nlm.nih.gov/pubmed/18847650

The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors.

Citation

Surgery, 2008, 144(4): 645-651; discussion 651-653.

Authors

Chambers, A.J., Pasieka, J.L., Dixon, E., & Rorstad, O.

Abstract

BACKGROUND: Metastatic neuroendocrine tumors (NETs) can present with complications of gastrointestinal tract obstruction or ischemia and carcinoid syndrome (CS). The purpose of this study was to assess whether aggressive surgical intervention of metastatic NETs provides effective palliation from these symptoms. METHODS: Sixty-six patients with metastatic gastrointestinal tract NETs that presented with either CS and/or obstructive symptoms were retrospectively reviewed. All patients were managed according to a standardized protocol that involved initial surgical resection of regional and/or hepatic disease followed by appropriate medical therapy. RESULTS: Symptoms of obstruction or ischemia were present in 24 patients (36%) and CS in 56 (85%). All patients with obstructive symptoms undergoing operative therapy had complete symptomatic relief. Hepatic cytoreduction was performed in 30 (45%). Overall symptoms of CS improved in 42 patients (75%); 86% of patients that underwent hepatic cytoreduction and 64% of those receiving medical therapy alone (P = .064). Postoperative morbidity was 22% with no mortality. Mean follow-up was 47 months (range, 6-156). Overall 5-year survival rate was 74%. CONCLUSIONS: Surgical resection is highly effective in relieving symptoms of intestinal obstruction and ischemia. Hepatic cytoreduction seems to enhance the ability to control the symptoms of carcinoid syndrome. A surgically aggressive approach in patients with metastatic NETs provides effective palliation in carefully selected patients.

http://www.ncbi.nlm.nih.gov/pubmed/18345317

Hepatic resection for metastatic gastrointestinal and pancreatic neuroendocrine tumours: outcome and prognostic predictors.

Citation

HPB (Oxford), 2007, 9(5): 345-351.

Authors

Gomez, D., Malik, H.Z., Al-Mukthar, A., Menon, K.V., Toogood, G.J., Lodge, J.P. & Prasad, K.R.

Abstract
BACKGROUND: Treatment modalities for hepatic metastases from neuroendocrine tumours (NETs) include surgery, somatostatin analogues and arterial embolization. The aims of this study were to evaluate the outcome of patients following surgery and to identify prognostic predictors of recurrent disease. PATIENTS AND METHODS: This was a retrospective clinico-pathological analysis of patients managed with hepatic NET metastases over a 13-year period (January 1994 to December 2006). RESULTS: Eighteen patients with hepatic metastases from NET were identified with a median age of 53 years (range 31-75). The localization of the primary tumour was the terminal ileum (n=8), pancreas (n=7), appendix (n=2) or duodenum (n=1). Twelve patients had synchronous disease and six patients developed metachronous hepatic tumours over a median period of 20 months (range 6-144). Presenting symptoms included abdominal pain (n =13), recurrent diarrhoea (n=7) and flushing (n=7). Fifteen patients underwent surgery with complete cytoreduction and three patients had partial cytoreduction. The overall 2- and 5-year actuarial survival rates were 94% and 86%, respectively. The 2- and 5-year disease-free rates following hepatic resection with complete cytoreduction were both 66%. Partial or complete control of endocrine-related symptoms was achieved in all patients with functioning tumours following surgery. Recurrent disease occurred in four patients following complete cytoreductive surgery. Resection margin involvement was associated with developing recurrent disease (p=0.041). CONCLUSION: Surgical resection for hepatic NET metastases results in good long-term survival in selected patients and resection margin involvement was associated with recurrent disease.

http://www.ncbi.nlm.nih.gov/pubmed/16511671

Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors.

Citation
Annals of Surgical Oncology, 2006, 13(4): 572-581.

Authors
Osborne, D.A., Zervos, E.E., Strsberg, J., Boe, B.A., Rosemurgy, A.S., Yeatman, T.J., Carey, L., Duhaine, L., & Kvols, L.K.

Abstract
BACKGROUND: Few data exist regarding outcomes after resection versus embolic treatment of symptomatic metastatic carcinoid and neuroendocrine tumors. The purpose of this study was to determine whether cytoreduction provides any benefit over embolic management of diffuse neuroendocrine tumors. METHODS: A prospective database of 734 patients treated at our institution was retrospectively queried for symptomatic metastatic tumors treated with embolization or cytoreduction. Patients were compared with regard to pretreatment performance status, relief of symptoms, and survival. RESULTS: A total of 120 patients were identified: 59 undergoing embolization and 61 undergoing cytoreduction. Twenty-three patients had palliative cytoreduction (gross residual disease). Pretreatment performance status (Eastern Cooperative Oncology Group) was similar for both groups: .7+/-.70 (embolization) versus .8+/-.72 (cytoreduction; P=.27). Complete symptomatic relief was observed in 59% and partial relief in 32% of patients who underwent embolization, with a mean symptom-free interval of 22+/-13.6 months. A total of 69% of patients who underwent cytoreduction had complete symptomatic relief, and 23% had partial relief (P=.08 vs. embolization). The mean duration of relief was 35+/-22.0 months (P<.001 vs. embolization). The mean survival for the patients who underwent embolization was 24+/-15.8 months versus

43+/-26.1 months for those who underwent cytoreduction (P<.001). Survival in patients who underwent palliative cytoreduction was 32+/-18.9 months (P<.001 vs. embolization), whereas it was 50+/-27.6 months in patients who underwent curative resection (P<.001 vs. embolization; P<.001 vs. palliative). CONCLUSIONS: Cytoreduction for metastatic neuroendocrine tumors resulted in improved symptomatic relief and survival when compared with embolic therapy in this nonrandomized study. Cytoreduction should be pursued whenever possible even if complete resection may not be achievable.

http://www.ncbi.nlm.nih.gov/pubmed/15968542

Palliative management strategies of advanced gastrointestinal carcinoid neoplasms.

Citation

Lagenbeck's Archives of Surgery, 2005, 390(5): 391-396.

Authors

Sartori, P., Mussi, C., Angellini, C., Crippa, S, Caprotti, R., & Uggeri, F.

Abstract

BACKGROUND/AIMS: Optimal management of gastrointestinal carcinoid neoplasms that metastasize to the liver is controversial. Although operative resection seems to be the most effective approach to metastatic disease, hepatic metastases are usually multicentric and often non-resectable. We investigated the effectiveness of several forms of palliative tumor cytoreduction followed by administration of somatostatin analogues in advanced carcinoid neoplasms. METHODS: We reviewed our experience with 34 patients with gastrointestinal carcinoid neoplasms. Eighteen patients had metastases and 14 had hormonal symptoms. Twenty-two patients underwent radical surgery, ten with multiple liver metastases were treated with a combination of debulking (resection, radiofrequency ablation, chemoembolization), followed by medical treatment with long-acting octreotide and eventually by radiolabelled somatostatin analogues, and two patients with intractable disease received only biotherapies. RESULTS: The six patients with metastatic disease who underwent radical curative liver resection had a median survival of 52 months, compared with a median survival of 48 months in the ten patients who underwent palliative debulking. Symptomatic improvement was observed in all the patients after debulking procedures. The two patients who underwent only medical treatment died after 9 and 18 months. CONCLUSIONS: Aggressive tumor debulking should be performed in patients with liver metastases already at diagnosis even when complete resection is not feasible because the combination of cytoreductive procedures followed by biotherapies may provide good long-term survival and achieves symptom control in most patients with advanced disease.

http://www.ncbi.nlm.nih.gov/pubmed/14668741

Aggressive surgery for metastatic liver neuroendocrine tumors.

Citation

Surgery, 2003, 134(6): 1057-1063; discussion 1063-1065.

Authors

Norton, J.A., Warren, R.S., Kelly, M.G., Zuraek, M.B., & Jensen, R.T.

Abstract

BACKGROUND: Neuroendocrine tumors of the gastrointestinal tract (carcinoids, pancreatic endocrine tumors) have low malignant potential but can decrease survival rates if they spread to the liver (LNET). METHODS: The records of 16 patients with LNET primarily from

gastrointestinal carcinoids treated surgically were retrospectively reviewed. RESULTS: There were 12 women and 4 men. Median age was 56 years (range 25 to 75). Thirteen (81%) had a carcinoid tumor and 5 had gastrinoma. Two patients with multiple endocrine neoplasia type 1 had both a gastric carcinoid and a jejunal gastrinoma. Eight patients (50%) had the carcinoid syndrome. Each patient had all identifiable LNET either resected or ablated. Ten patients had liver wedge resections, 1 right trisegmentectomy, 5 left hepatic lobectomies, and 2 radiofrequency ablations. Thirteen (81%) patients had concomitant bowel resections. Two patients had concomitant total gastrectomies to remove stomach primaries. The final patient had an extraintestinal pelvic primary or a liver primary. There were no operative deaths, and all 8 (100%) patients with the carcinoid syndrome had amelioration of symptoms. The 5-year actuarial survival rate was 82% with a median follow-up of 32 months. CONCLUSIONS: This study demonstrates that liver and concomitant extrahepatic surgery can be performed safely in patients with liver metastases because of carcinoids or pancreatic endocrine tumors. It results in excellent long-term survival and amelioration of symptoms. Surgery should be the first-line therapy for patients with LNET.

http://www.ncbi.nlm.nih.gov/pubmed/12831921

Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival.

Citation
Journal of the American College of Surgeons, 2003, 197(1): 29-37.

Authors
Sarmiento, J.M., Heywood, G., Rubin, J., Ilstrup, D.M.,Nagorney, D.M., & Que, F.G.

Abstract
BACKGROUND: Hepatic metastases from neuroendocrine tumors have a protracted natural history and are associated with endocrinopathies. Resection is indicated for symptom control. Previous reports have suggested improvement in survival for patients undergoing debulking procedures. STUDY DESIGN: The records of all consecutive patients undergoing resection of hepatic metastases from neuroendocrine tumors between 1977 and 1998 were reviewed. Tumors were classified according to histology, endocrine activity, and primary location. Patients lost to followup before 1 year were excluded. Followups were based on outpatient evaluations and were updated by correspondence. The Kaplan-Meier method was used to generate survival and recurrence curves, and the log-rank test was used for comparison. RESULTS: A total of 170 patients fulfilled the inclusion criteria, of whom 73 were men. Mean age (+/-SD) was 57 (+/-11.5) years. Carcinoid (n = 120) and nonfunctioning islet cell tumors (n = 18) predominated; the ileum (n = 85) and the pancreas (n = 52) were the most common primary sites. Major hepatectomy (one or more lobes) was performed in 91 patients (54%). The postoperative complication rate was 14%, and two patients died (1.2%). Operation controlled symptoms in 104 of 108 patients, but the recurrence rate at 5 years was 59%. Operation decreased 5-hydroxyindoleacetic acid levels considerably, and no patient experienced carcinoid heart disease postoperatively. Recurrence rate was 84% at 5 years. Overall survival was 61% and 35% at 5 and 10 years, respectively, with no difference between carcinoid and islet cell tumors. CONCLUSIONS: Hepatic resection for metastatic neuroendocrine tumors is safe and achieves symptom control in most patients. Debulking extends survival, although recurrence is expected. Hepatic resection is justified by its effects on survival and quality of life.

http://www.ncbi.nlm.nih.gov/pubmed/12717354

Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-year single center prospective study.

Citation
Surgery, 2003, 133(4): 375-382.

Authors
Elias, D., Lasser, P., Ducreux, M., Duvillard, P., Ouellet, J.F., Dromain, C., Schlumberger, M., Pocard, M., Boige, V., Miquel, C., & Baudin, E.

Abstract
BACKGROUND: The timing and benefits of hepatectomy remain controversial for metastatic well-differentiated endocrine neoplasms, which are generally considered slow growth tumors. However, surveillance alone yields only a 22% 5-year survival when metastases occur. The aim of this study was to determine the results of hepatic and extra hepatic resections and to clarify the indications of surgery. METHODS: To define the role of hepatic resection, a database regrouping all patients (n = 47) who underwent hepatectomy with curative intent (R0 status) for well-differentiated endocrine neoplasms in the Gustave-Roussy Institute was constructed in 1984. New prognostic factors such as tumor growth and liver tumor mitotic index were studied. Median follow-up was 62 months. RESULTS: Hepatectomy was associated with extrahepatic tumor resection in 77% of the patients (primary tumor in 51%, lymph nodes in 21%, peritoneal carcinomatosis in 25%, and other in 6%). Resection was curative (R0) only in 53% of the patients, despite removing at least 97% of the tumor in each patient. Mortality was 5%, and morbidity was 45%. Median survival was 91 months, 5-year and 10-year overall survival rates were 71% and 35%, respectively. Liver recurrence rate was 75% at 10 years. No prognostic factor was correlated with overall survival in this population in which at least 97% of the tumor load was resected. The completeness of surgery, the presence of bilateral liver metastases, the number of liver metastases (>10) and a primary tumor from pancreatic origin were all significantly correlated with the disease-free survival. Preoperative tumor growth rate, mitotic index, and Ki67 expression were not predictive of prognosis. No significant prognostic factors could be found by the comparison of the patients who did and did not recur during the 3 years after hepatectomy. CONCLUSION: Hepatectomy for liver metastases from well-differentiated endocrine neoplasms is indicated when all visible intra- and extra hepatic lesions can be resected safely. The number, size, and localization of the tumor sites are less important than performing a complete (or near-complete) resection.

http://www.ncbi.nlm.nih.gov/pubmed/11602899

Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors.

Citation
Surgery, 2001, 130(4): 677-682; discussion 682-685.

Authors
Yao, K.A., Talamonti, M.S., Nemeck, A., Angelos, P., Chrisman, H., Skarda, J., Benson, A. B., Rao, S., & Joehl, R.J.

Abstract

BACKGROUND: We reviewed 36 patients with liver metastases from islet cell tumors of the pancreas (n = 18) and carcinoid tumors (n = 18) who were treated with surgical resection (n = 16) or hepatic chemoembolization (n = 20). METHODS: All resections were complete and included 4 lobectomies, 6 segmental resections, and 6 wedge resections. There were no operative deaths. RESULTS: Median survival has not yet been reached, and the actuarial 5-year survival rate is 70%. Prognostic variables associated with improved disease-free survival included prior resection of the primary tumor and 4 or fewer metastases resected (P <.05). With an average of 3 chemoembolization procedures per patient, 17 of 20 patients (90%) demonstrated either a significant radiographic response (n = 5), stabilization of tumor mass (n = 2), or improvement of clinical symptoms (n = 10). Factors related to a sustained response (more then 1 year) included surgical resection of the primary tumor, 4 or more chemoembolization procedures, and liver metastases of 5 cm or smaller. Median survival after treatment was 32 months (range, 7-63 months), and the actuarial 5-year survival rate was 40%. CONCLUSIONS: Surgical resection of metastatic neuroendocrine tumors provides the best chance for extended survival. Chemoembolization effectively improves clinical symptoms and, in selected patients, may provide sustained tumor control.

http://www.ncbi.nlm.nih.gov/pubmed/11038214

Method for dissection of mesenteric metastases in mid-gut carcinoid tumors.

Citation
World Journal of Surgery, 2000, 24(11): 1402-1408.

Authors
Ohrvall, U., Eriksson, B., Juhlin, C., Karacagil, S., Rastad, J., Hellman, P., & Akerström, G.

Abstract

With adequate medical management the midgut carcinoid tumor generally is an indolent malignancy associated with substantial life expectancy and appreciable life quality, even in the presence of liver metastases and significant tumor burden. Abdominal complications may occur in this entity of carcinoids owing to entrapment of intestines and encasement of mesenteric vessels by mesenteric metastases and associated marked mesenteric fibrosis. This may be the cause of abdominal pain, disabling diarrhea, weight loss to the extent of malnutrition, and eventually the risk of death with acute or chronic intestinal obstruction or intestinal gangrene. Operative removal of the mesentericointestinal lesion is often indicated to prevent or treat these complications but may be technically difficult when mesenteric metastases extend in the vicinity of major vessels in the mesenteric root. At laparotomy 56 patients with advanced midgut carcinoids underwent removal of the mesenteric tumor with a method for preserving the mesenteric vessels. This was feasible by mobilizing and releasing the right colon and mesenteric root from posterior adhesions, identifying the mesenteric artery below the pancreas, and free-dissecting this artery on the tumor capsule in the mobilized mesentery. Dissection was successful even with tumors initially judged inoperable unless tumor growth completely surrounded the mesenteric vessels or extended retroperitoneally. One patient was subjected to distal intestinal artery bypass. Symptom relief was been substantial and often of long duration after mesenteric tumor removal in patients who prior to surgery often had threatening intestinal ischemia. Patients with advanced midgut carcinoids may benefit markedly from dissectional removal of mesenteric tumors, which (conceivably better than conventional wedge resection) preserves the length of the remaining intestine.

http://www.ncbi.nlm.nih.gov/pubmed/10757381

Hepatic neuroendocrine metastases: does intervention alter outcomes?

Citation
Journal of the American College of Surgeons, 2000, 190(4): 432-445.

Authors
Chamberlain, R.S., Canes, D., Brown, K.T., Saltz, L., Jarnagin, W., Fong, Y., & Blumgart, L.H.

Abstract
BACKGROUND: In most instances, advanced neuroendocrine tumors follow an indolent course. Hepatic metastases are common, and although they can cause significant pain, incapacitating endocrinopathy, and even death, they are usually asymptomatic. The appropriate timing and efficacy of interventions, such as hepatic artery embolization (HAE) and operation, remain controversial. STUDY DESIGN: The records of 85 selected patients referred for treatment of hepatic neuroendocrine tumor metastases between 1992 and 1998 were reviewed from a prospective database. A multidisciplinary group of surgeons, radiologists, and oncologists managed all patients. Overall survival among this cohort is reported and prognostic variables, which may be predictive of survival, are analyzed. RESULTS: There were 37 men and 48 women, with a median age of 52 years. There were 41 carcinoid tumors, 26 nonfunctional islet cell tumors, and 18 functional islet cell tumors. Thirty-eight patients had extrahepatic metastases, and in 84% of patients, the liver metastases were bilobar. Eighteen patients were treated with medical therapy or best supportive care, 33 patients underwent HAE, and 34 patients underwent hepatic resection. Both the HAE-related mortality and the 30-day operative mortality rates were 6%. By univariate analysis, earlier resection of the primary tumor, curative intent of treatment, and initial surgical treatment were associated with prolonged survival ($p < 0.05$). On multivariate analysis, only curative intent to treat remained significant ($p < 0.04$). Patients with bilobar or more than 75% liver involvement by tumor were least likely to benefit from surgical resection. One-, 3-, and 5-year survival rates for the entire group were 83%, 61%, and 53%, respectively. The 1-, 3-, and 5-year survivals for patients treated with medical therapy, HAE, and operation were 76%, 39%, and not available; 94%, 83%, and 50%; and 94%, 83%, and 76%, respectively. CONCLUSIONS: Hepatic metastases from neuroendocrine tumors are best managed with a multidisciplinary approach. Both HAE and surgical resection provide excellent palliation of hormonal and pain symptoms. In select patients, surgical resection of hepatic metastases may prolong survival, but is rarely curative.

LOCOREGIONAL ABLATIVE THERAPIES

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/19346815
Minimally Invasive Techniques in Management of Hepatic Neuroendocrine Metastatic Disease
Citation
American Journal of Clinical Oncology, 2009, 32(2): 200-215.

Authors
Liu, D.M., Kennedy, A., Turner, D., Rose, S.C., Kee, S.T., Whiting, S., Murthy, R., Nutting, C., Heran, M., Lewandowski, R., Knight, J., & Salem, R.

Abstract
The development of new technologies and therapies provides an exciting new chapter in the management of neuroendocrine disease. Fundamentally (albeit through an extensive array of retrospectively based studies), the use of cytoreductive therapies (whether it be through open surgery, laparoscopic approaches, percutaneous, or endovascular) have clearly demonstrated the ability to control symptoms, decrease tumor burden, and in selected series, translate into survival benefit. However, this situation is not without challenge, as overall strategy and consensus has not been reached as to the optimal therapy.

MICROWAVE ABLATION

http://www.ncbi.nlm.nih.gov/pubmed/19707829

Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience.

Citation
Annals of Surgical Oncology, 2010, 17(1): 171-178.

Authors
Martin, R.C., Scoggins, C.R., & McMasters, K.M.

Abstract
BACKGROUND: This study was designed to evaluate the safety, efficiency, effectiveness, and overall long-term outcome in patients treated with microwave thermal ablation of hepatic tumors. Microwave ablation technology represents the next generation in ablative techniques for the treatment of hepatic malignancies. Currently there have been no large reports of its use in the United States with appropriate long-term follow-up. METHODS: An institutional review board-approved prospective phase II study of microwave ablation of hepatic malignancies from January 2004 to January 2009 was performed. All complications were recorded up to 90 days from operation and reported using an established five-point grading scale. RESULTS: One hundred patients underwent 270 ablations for hepatic malignancies. The most tumor types were as follows: metastatic colorectal cancer (50%), hepatocellular carcinoma (17%), metastatic carcinoid (11%), and other metastatic disease (22%). A majority of patents (53%) underwent combination hepatic resection and microwave ablation; 38% underwent ablation alone, 9% underwent ablation and additional organ resection, with 68% open procedures. Median tumor size was 3.0 (range, 0.6-6.0) cm, median number of tumors was 2 (range, 1-18), and median total ablation time was 13 (range, 5-45) min. Overall 90-day mortality was 0% and morbidity was 29%. One patient developed a hepatic abscess and no patients experienced bleeding complications. After a median follow-up of 36 months, 5 patients (5%) had incomplete ablation, 2 (2%) had local recurrence at the ablated site, and 37 (37%) developed intrahepatic recurrence at nonablated sites. CONCLUSIONS: Microwave ablation of hepatic tumors is a safe and effective method for treating unresectable hepatic tumors, with a low rate of local recurrence.

RADIOFREQUENCY ABLATION

http://www.ncbi.nlm.nih.gov/pubmed/17629995

Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival.

Citation
Surgery, 2007, 142(1): 10-19.

Authors
Mazzaglia, P.J., Berber, E., Milias, M., & Siperstein, A.E.

Abstract

BACKGROUND: A decade ago we reported the first use of laparoscopic radiofrequency thermal ablation (RFA) for the treatment of neuroendocrine hepatic metastases. This study analyzes our 10-year experience and determines characteristics predictive of survival. METHODS: Eighty RFA sessions were performed in 63 patients with neuroendocrine hepatic metastases in a prospective trial. All patients had unresectable disease with computed tomography (CT) documented lesion and/or symptom progression. Perioperative morbidity, symptom relief, disease progression, and long-term survival were analyzed. Data are expressed as mean +/- standard error of the mean (SEM). RESULTS: There were 22 women and 41 men, age 54.4 +/- 1.5 years followed for 2.8 +/- 0.3 years (range, 0.1 to 7.8). Tumor types included 36 carcinoid, 18 pancreatic islet cell, and 9 medullary thyroid cancer. RFA was performed 1.6 +/- 0.3 years after the diagnosis of liver metastases. Number of lesions treated was 6 +/- 0.5 (range, 1 to 16). Forty-nine patients underwent 1 ablation session, and 14 (22%) had repeat sessions caused by disease progression. Mean hospital stay was 1.1 days. Perioperative morbidity was 5%, with no 30-day mortality. Fifty-seven percent of patients exhibited symptoms. One week postoperatively 92% of these reported at least partial symptom relief, and 70% had significant or complete relief. Duration of symptom control was 11 +/- 2.3 months. CT follow-up demonstrated 6.3% local tumor recurrence. Larger dominant liver tumor size and male gender adversely impacted survival (P < .05). Median survival times were 11.0 years postdiagnosis of primary tumor, 5.5 years postdiagnosis of neuroendocrine hepatic metastases, and 3.9 years post-1st RFA. Survival for patients undergoing repeat ablation sessions was not significantly lower. CONCLUSIONS: This study represents the largest series of neuroendocrine hepatic metastases treated by RFA. In this group of patients with aggressive neuroendocrine tumor metastases and limited treatment options, RFA provides effective local control with prompt symptomatic improvement.

http://www.ncbi.nlm.nih.gov/pubmed/17044296

The surgical approach for radiofrequency ablation of liver tumors.

Citation
Recent Results in Cancer Research, 2006, 167: 53-68.

Authors
Schumacher, G., Eisele, R., Spinelli, A., & Neuhaus, P.

Abstract

Radiofrequency ablation for the treatment of liver tumors is one of the best alternative treatment modalities when surgical resection is not possible. To find the right indication for the treatment, every patient should be treated in a high-volume center for the treatment of liver tumors in an interdisciplinary conference consisting of liver surgeons, interventional radiologists, medical oncologists, and gastroenterologists. With a multimodal approach including anatomic segmental and wedge resection of the liver, RFA, and chemotherapy, a median survival of 36 months was achieved in technically unresectable patients with

colorectal liver metastases (Elias et al. 2005). This survival doubles the survival rate of any other treatment modality in this group of patients. These interdisciplinary conferences also serve to determine the approach for RFA, whether it should be percutaneous, laparoscopic, or open surgery. The safest ablation with the fewest adverse events from RFA is the open surgical approach, followed by the laparoscopic approach. The approach with the highest risk of injury to organs in proximity to the liver is the percutaneous approach. Therefore, many variables must be evaluated before making definite decisions. After choosing RFA as the best alternative treatment option after evaluation of all variables for a particular patient, it offers a treatment option with a potential cure. A major advantage is the possible combination with liver resection, which extends the indication for surgical or ablative therapy.

http://www.ncbi.nlm.nih.gov/pubmed/15759207

Radiofrequency ablation of neuroendocrine liver metastases: the Middlesex experience.

Citation
Abdominal Imaging, 2005, 30(4): 435-441.

Authors
Gilliams, A., Cassoni, A., Conway, G., & Lees, W.

Abstract
BACKGROUND: Current treatment options for neuroendocrine liver metastases are not widely applicable or not that effective. Image-guided thermal ablation offers the possibility of a minimally invasive, albeit palliative, treatment that decreases tumor volume, preserves most of the normal liver, and can be repeated several times. We report our experience with image-guided thermal ablation in 25 patients with unresectable liver metastases. METHODS: Since 1990 we have treated 189 tumors at 66 treatment sessions in 25 patients (12 female, 13 male; median age, 56 years; age range, 26--78 years). Thirty treatments were performed with a solid-state laser, and 36 treatments were performed with radiofrequency ablation. All but one treatment was performed percutaneously under image guidance. Sixteen patients had metastases from carcinoid primaries, three from gastrinoma, two from insulinoma, and fou**r** from miscellaneous causes. Fourteen of 25 had symptoms from hormone secretion. RESULTS: Imaging follow-up was available in 19 patients at a median of 21 months (range, 4--75 months). There was a complete response in six patients, a partial response in seven, and stable disease in one; hence, tumor load was controlled in 14 of 19 patients (74%). Relief of hormone-related symptoms was achieved in nine of 14 patients (69%). The median survival period from the diagnosis of liver metastases was 53 months. One patient with end-stage cardiac disease died after a carcinoid crisis. There were eight (12%) complications: five local and three distant, four major and four minor. CONCLUSIONS: As a minimally invasive, readily repeatable procedure that can be used to ablate small tumors, preferably before patients become severely symptomatic, radiofrequency ablation can provide effective control of liver tumor volume in most patients over many years.

http://www.ncbi.nlm.nih.gov/pubmed/15024305

Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients.

Citation

Annals of Surgery, 2004, 239(4):450-458.

Authors
Curley, S.A., Marra, P., Beaty, K., Ellis, L.M., Vauthey, J.N., Abdalla, E.K., Scaife, C., Raut, C., Wolff, R., Choi, H., Lloyer, E., Vallone, P., Fiore, F., Scordino, F., De rosa, V., Orlando, R., Pignata, S., Daniele, B., & Izzo, E.

Abstract
BACKGROUND: Radiofrequency ablation (RFA) has become a common treatment of patients with unresectable primary and secondary hepatic malignancies. We performed this prospective analysis to determine early (within 30 days) and late (more than 30 days after) complication rates associated with hepatic tumor RFA. METHODS: All patients treated between January 1, 1996 and June 30, 2002 with RFA for hepatic malignancies were entered into a prospective database. Patients were evaluated during RFA treatment, throughout the immediate post RFA course, and then every 3 months after RFA to assess for the development of treatment-related complications. RESULTS: A total of 608 patients, 345 men (56.7%) and 263 women (43.3%), with a median age of 58 years (range 18-85 years) underwent RFA of 1225 malignant liver tumors. Open intraoperative RFA was performed in 382 patients (62.8%), while percutaneous RFA was performed in 226 (37.2%). The treatment-related mortality rate was 0.5%. Early complications developed in 43 patients (7.1%). Early complications were more likely to occur in patients treated with open RFA (33 [8.6%] of 382 patients) compared with percutaneous RFA (10 [4.4%] 226 patients, $P < 0.01$), and in patients with cirrhosis (25 [12.9%] complications in 194 patients) compared with noncirrhotic patients (31 [7.5%] complications in 414 patients, $P < 0.05$). Late complications arose in 15 patients (2.4%) with no difference in incidence between open and percutaneous RFA treatment. The combined overall early and late complication rate was 9.5%. CONCLUSIONS: Hepatic tumor RFA can be performed with low mortality and morbidity rates. Though relatively rare, late complications can develop and physicians performing hepatic RFA must be cognizant of these delayed treatment-related problems.

http://www.ncbi.nlm.nih.gov/sites/pubmed

Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes.

Citation
American Journal of Roentgenology, 2003, 181(4): 1005-1010.

Authors
Henn, A.R., Levine, E.A., McNulty, W., & Zagoria, R.J.

Abstract
OBJECTIVE: The purpose of this study was to evaluate the efficacy of percutaneous radiofrequency ablation of hepatic neuroendocrine metastases for symptomatic relief of neuroendocrine syndromes. CONCLUSION: Percutaneous radiofrequency ablation, a minimally invasive technique, is an effective and safe way to reduce systemic symptoms in patients with hepatic metastases from neuroendocrine neoplasms.

http://www.ncbi.nlm.nih.gov/sites/pubmed

Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine

tumors.

Citation
World Journal of Surgery, 2002, 26(8):1052-1056.

Authors
Hellman, P., Ladjevardi, S., Skogseid, B., Akerström, G., & Elvin, A.

Abstract
Tumors derived from hormone-producing cells are generally highly differentiated, and vast experience indicates benefit with combinations of surgical and medical treatment for metastatic disease. Tumor debulking surgery is an accepted approach for reducing hormonal symptoms and to establish better conditions for medical treatment. Radiofrequency treatment (RF), a novel method for destroying liver tumors, was used to treat 43 liver metastases in 21 patients with endocrine tumors (12 with midgut carcinoid disease; 4 with nonfunctional endocrine pancreatic tumors; 1 with a VIPoma; 1 with a glucagonoma; 1 with a gastrinoma; 2 with adrenal carcinomas). Among these patients we treated with intention to cure in 14 by RF alone or RF plus surgery. Ablation was performed either percutaneously or intraoperatively using a cooled-tip needle, applying 50 to 90 watts over 10 to 12 minutes under ultrasound guidance. Contrast-enhanced computed tomography, liver function tests, and tumor markers were followed before and after RF. There were two complications: One patient suffered from conservatively treated bile leakage, and another had pleural effusion and fever for 7 days post-RF. Two lesions developed signs of incomplete necrosis after 6 months, yielding a local recurrence rate of (4.6%). Of the 15 patients treated with curative intent, we attained cure (i.e., no residual macroscopic tumor) in 4 patients. We conclude that RF using cooled-tip needles is safe and efficient; it may be performed percutaneously and intraoperatively; and it may expand the indications for liver resection.

http://www.ncbi.nlm.nih.gov/pubmed/11120628
Radiofrequency ablation treatment of refractory carcinoid hepatic metastases.
Citation
Journal of Surgical Research, 2001, 95(1):8-12.
Authors
Wessels, F.J., & Schell, S.R.
Abstract
BACKGROUND: Our institution has experienced excellent success using hepatic artery embolization for treating symptoms and slowing tumor progression for patients with unresectable hepatic metastases for carcinoid tumors. Our previous treatment strategies used hepatic artery embolization alone, examining control of symptoms and dependence on octreotide therapy. However, some patients exhibit hepatic metastases that are unresponsive to embolization. This report describes the use of radiofrequency ablation (RFA) as salvage treatment for these refractory metastases. METHODS: Thirteen patients with unresectable bilobar hepatic metastases from biochemically confirmed carcinoid tumors were treated with selective hepatic artery embolization using Lipiodol/Gelfoam between 1994 and 2000. Three patients developed symptoms resistant to embolization treatment resulting from progression of existing metastases or development of new metastases. These patients underwent surgical exploration and intraoperative ultrasound of their refractory lesions, followed by treatment with RFA. Tumor size, symptoms of carcinoid syndrome, and octreotide requirements were monitored postoperatively. RESULTS: Median follow-up for the three patients treated with RFA was 6 months. During the first 3-month interval following RFA, all three patients

demonstrated decrease in the size of treated lesions. Using our previously developed symptom scoring system, all three patients demonstrated decreased symptoms following treatment. One patient was able to discontinue octreotide treatment, and the other two patients required decrease octreotide dosages. CONCLUSIONS: This study demonstrates that utilization of RFA treatment for carcinoid metastases refractory to hepatic artery embolization may represent a useful adjunct for symptomatic control, decreased octreotide dependence, and slowing of disease progression.

http://www.ncbi.nlm.nih.gov/pubmed/11005558

Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications.

Citation
Annals of Surgical Oncology, 2000, 7(8): 593-600.

Authors
Wood, T.F., Rose, D.M., Chung, M., Allegra, D.P., Foshag, L.J., & Bilchik, A.J.

Abstract
BACKGROUND: Radiofrequency ablation (RFA) is increasingly used for the local destruction of unresectable hepatic malignancies. There is little information on its optimal approach or potential complications. METHODS: Since late 1997, we have undertaken 91 RFA procedures to ablate 231 unresectable primary or metastatic liver tumors in 84 patients. RFA was performed via celiotomy (n = 39), laparoscopy (n = 27), or a percutaneous approach (n = 25). Patients were followed with spiral computed tomographic (CT) scans at 1 to 2 weeks postprocedure and then every 3 months for 2 years. RESULTS: Intraoperative ultrasound (IOUS) detected intrahepatic disease not evident on the preoperative scans of 25 of 66 patients (38%) undergoing RFA via celiotomy or laparoscopy. In 38 of 84 patients (45%), RFA was combined with resection or cryosurgical ablation (CSA), or both. RFA was used to treat an average of 2.8 lesions per patient, and the median size of treated lesions was 2 cm (range, 0.3-9 cm). The average hospital stay was 3.6 days overall (1.8 days for percutaneous and laparoscopic cases). Ten patients underwent a second RFA procedure (sequential ablations) and, in one case, a third RFA procedure for large (one patient), progressive (seven patients), and/or recurrent (three patients) lesions. Seven (8%) patients had complications: one skin burn; one postoperative hemorrhage; two simple hepatic abscesses; one hepatic abscess associated with diaphragmatic heat necrosis following sequential percutaneous ablations of a large lesion; one postoperative myocardial infarction; and one liver failure. There were three deaths, one (1%) of which was directly related to the RFA procedure. Three of the complications, including one RFA-related death, occurred after percutaneous RFA. At a median follow-up of 9 months (range, 1-27 months), 15 patients (18%) had recurrences at an RFA site, and 36 patients (43%) remained clinically free of disease. CONCLUSIONS: Celiotomy or laparoscopic approaches are preferred for RFA because they allow IOUS, which may demonstrate occult hepatic disease. Operative RFA also allows concomitant resection, CSA, or placement of a hepatic artery infusion pump, and isolation of the liver from adjacent organs. Percutaneous RFA should be reserved for patients at high risk for anesthesia, those with recurrent or progressive lesions, and those with smaller lesions sufficiently isolated from adjacent organs. Complications may be minimized when these approaches are applied selectively.

CRYOABLATION

http://www.ncbi.nlm.nih.gov/pubmed/9569305

Cryotherapy of metastatic carcinoid tumors.

Citation

Abdominal Imaging, 1998, 23(3):314-317.

Authors
Shapiro. R.S., Shafir, M., Sung, M., Warner, R., & Glajchen, N.

Abstract
BACKGROUND: To describe the use of hepatic cryotherapy to treat patients with symptomatic carcinoid metastates. METHODS: Hepatic cryotherapy was performed on five patients with carcinoid syndrome resulting from metastatic carcinoid tumors. Intraoperative ultrasound was used to guide the cryotherapy and to assess the adequacy of freezing. RESULTS: All five patients had relief of the carcinoid syndrome after treatment. In four of the five patients, the relief was prolonged (>3 months); in one patient, the relief of symptoms was transient (2 months). Four of five patients had a transient reduction in hormonal tumor markers (the fifth patient did not have hormonal-level follow-up). During a follow-up period of 2.5 years, four of the five patients died. The 6-month survival rate was 80%, the 1-year survival rate was 60%, the 2-year survival rate was 40%, and the 2.5-year survival was 20%. One patient is alive 30 months after treatment. CONCLUSION: Hepatic cryotherapy can provide symptomatic relief for patients with hepatic metastates producing the carcinoid syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/9426418

Cryosurgical palliation of metastatic neuroendocrine tumors resistant to conventional therapy.

Citation
Surgery, 1997, 122(6):1040-1047; discussion 1047-8.

Authors
Bilchik, A.J., Sarantou, T., Foshag, L.J., Giuliano, A.E., & Ramming, K. P.

Abstract
BACKGROUND: Hepatic cryosurgery is a well-recognized modality for hepatic colon metastases. We examined its potential use for refractory neuroendocrine tumors causing progressive symptoms. METHODS: Between July 1992 and February 1997, 19 patients (with islet cell, 7; carcinoid, 8; vasoactive intestinal peptide, 1; gastrinoma, 3) underwent cryosurgery with ultrasonography. The number of lesions frozen ranged from 1 to 16 (median, 8), and their diameters ranged from 2 to 15 cm with an average of 4 cm. Patients underwent resection of the primary tumor either before (37%) or concurrent with (32%) cryosurgery, and half underwent excision of metastases with cryosurgery. Before cryosurgery, patients received chemotherapy (63%), somatostatin (47%), interferon (10%), hepatic artery ligation (5%), radiation (10%), and/or omeprazole (16%). RESULTS: The reduction in tumor markers reached 90% (5-hydroxyindoleacetic acid), 80% (vasoactive intestinal peptide), 90% (gastrin), 90% (pancreatic polypeptide), and 80% (serotonin). At a median follow-up of 17 months, the

metastases had progressed in 11 patients (two underwent a second cryosurgical procedure that eliminated symptoms) and five had died. Subsequently an additional five patients received chemotherapy and three somatostatin. Median symptom-free and overall survival were 10 months and more than 49 months, respectively. CONCLUSIONS: Cryosurgery dramatically relieved symptoms with significant reduction in tumor markers. The reduced tumor burden may explain the subsequent response to systemic therapy. Cryosurgery is a useful adjuvant in symptomatic patients with refractory hepatic neuroendocrine metastases.

http://www.ncbi.nlm.nih.gov/pubmed/8625133

Cryotherapy treatment of patients with hepatic metastases from neuroendocrine tumors.

Citation
Cancer, 1995, 76(3):501-509.

Authors
Cozzi, P.J., Englund, R., & Morris, D.L.

Abstract
BACKGROUND: Liver metastases from neuroendocrine tumors often present with disabling symptoms due to syndromes of hormonal excess. A locally destructive technique such as hepatic cryotherapy not only alleviates symptoms but may improve survival in this group of patients. METHODS: Six patients with metastatic neuroendocrine tumors were treated with hepatic cryotherapy. Four patients were symptomatic and three of these had elevated tumor markers from ectopic hormone production. RESULTS: All patients are alive and asymptomatic, with a median follow-up of 24 months (range, 6 months to 6 years). All have had a complete radiologic response. All with elevated preoperative markers have had a greater than 89% decrease in tumor markers. Coagulopathy occurred in two patients necessitating additional surgery, but there was no other morbidity attributable to the cryotherapy. CONCLUSION: To the authors' knowledge, this study demonstrates for the first time that hepatic cryotherapy offers supportive treatment for patients with neuroendocrine tumors metastatic to the liver. Cryotherapy alleviates symptoms and may improve survival.

HEPATIC ARTERY EMBOLOTHERAPY

BLAND AND CHEMOEMBOLIZATION

http://ovidsp.tx.ovid.com.ezproxy1.library.arizona.edu/sp-2.3.1b/ovidweb.cgi

Transarterial Chemoembolization in Patients With Metastatic Carcinoid Amenable to Cytoreductive Hepatectomy Results in Improved Survival but Similar Regional Disease Control Compared to Those Deemed Inoperable.

Citation
Pancreas, 2010, 39(2): 272
Authors
Feria-Arias, E., Arrese, D., Hatzaras, I., Schidt, C., Shah, M., & Bloomston, M.

Abstract
Background**:** Metastatic carcinoid to the liver is often incurable but long-term survival is still possible. Transarterial chemoembolization (TACE) has traditionally been the locoregional therapy of choice for the management of patients with incurable carcinoid liver metastases. In this study, we reviewed the outcomes of patients who, in retrospect, may have been potential candidates for cytoreductive hepatectomy compared to those in whom surgery would never be offered. We hypothesize that patients with disease amenable to surgical debulking would have better tumor response, symptom control, and survival following TACE. Methods: We identified 98 patients from our carcinoid database that underwent TACE as primary treatment for incurable liver metastases between October 2000 and July 2008. Two independent liver surgeons reviewed the patients_ pre-TACE imaging studies to classify them as potentially resectable (defined as ability to remove at least 90% of tumor burden) or unresectable. Demographics, clinicopathologic characteristics, response to TACE, complications, and survival were compared. Results: The two groups were similar in terms of age, gender, histopathologic characteristics, and complications (p 9 0.05). Patients considered resectable (N = 28) were more likely to present with carcinoid syndrome and had a median survival of 62 months with five-year survival of 53%. Patients considered unresectable (N = 70) had a median survival of 21 months with five-year survival of 19% (p G 0.001 vs. resectable). No difference was seen between groups in radiographic, symptomatic, or serologic responses or the durability of response following TACE.
Conclusions: Patients with metastatic carcinoid amenable to cytoreductive hepatectomy experienced longer overall survival following TACE compared to those with clearly inoperable disease. However, these seemingly biologically favorable patients did not have better or more durable response to TACE compared to those with more advanced disease. From this study, we conclude that a clinical trial comparing TACE to cytoreductive hepatectomy in patients with resectable yet incurable carcinoid metastases is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/19358175

Prolonged survival after hepatic artery embolization in patients with midgut carcinoid syndrome.

Citation
British Journal of Surgery, 2009, 96(5): 517-521.
Authors
Swärd, C., Johanson, V., Nieveen van Dijkum, E., Jansson, S., Nilsson, O., Wänberg, B., Ahlman, H., & Kölby, L.
Abstract
BACKGROUND: Hepatic artery embolization (HAE) is a palliative treatment for patients with liver metastases from neuroendocrine tumours. HAE reduces hormonal symptoms, but its impact on survival has been questioned. METHODS: Biochemical responses and survival in consecutive patients with disseminated liver metastases from midgut carcinoid tumours were studied after HAE. Repeat HAE was performed in selected patients with radiological and biochemical signs of progression. RESULTS: Of 107 patients who had HAE, the median survival from the first procedure was 56 (range 1-204) months. Prolonged survival showed a strong correlation with reduction of urinary 5-hydroxyindoleacetic acid (P = 0.003) and plasma chromogranin A (P = 0.001) levels. The biochemical response to repeat HAE was similar to that for the first procedure (P = 0.002). The complication rate was low (7.5 per cent), as was the mortality rate (1.9 per cent) within 1 month of HAE. CONCLUSION: HAE is safe, provides good control of hormonal symptoms, and prolongs survival in biochemically

responsive patients. It is a valuable palliative option for patients with midgut carcinoid syndrome due to liver metastases and can be repeated in patients with a favourable response to the first procedure.

http://www.ncbi.nlm.nih.gov/pubmed/19040993

Hepatic artery chemoinfusion with chemoembolization for neuroendocrine cancer with progressive hepatic metastases despite octreotide therapy.

Citation

Surgery, 2008, 144(6):885-893; discussion 893-894.

Authors

Christante, D., Pommier, S., Givi, B., & Pommier, R.

Abstract

BACKGROUND: Hepatic metastases from neuroendocrine cancer dramatically reduce survival, introducing an important opportunity for intervention. Several treatment modalities have been examined, but an optimal treatment approach has been difficult to define. We evaluated a regimen combining hepatic artery chemoinfusion with chemoembolization. METHODS: Patients with neuroendocrine cancer and diffuse hepatic metastases were treated with hepatic artery chemoinfusion and chemoembolization when they demonstrated disease progression despite octreotide therapy. Four monthly cycles of 5-fluorouracil were administered via hepatic artery infusion with chemoembolization after the final 2 cycles. Response was defined by radiologic response or symptomatic improvement. RESULTS: Seventy-seven patients were treated; 18 received chemoinfusion only. The treatment-related mortality rate was 7%. The overall response rate was 80% for patients with carcinoid or islet cell neoplasms. Median progression-free survival was 19 months. Median disease-specific survival was 39 months from the first treatment; 1- and 5-year survival rates were 78% and 27%, respectively. CONCLUSION: Survival after initiating this regimen was over 3 years for the majority of patients exhibiting progression of extensive, unresectable hepatic disease despite octreotide therapy. The addition of hepatic artery chemoinfusion to chemoembolization offers a high probability of clinical benefit to patients who, otherwise, have severely limited therapeutic options and a dismal survival.

http://www.ncbi.nlm.nih.gov/pubmed/18503899

Transarterial chemoembolization of liver metastases from well differentiated gastroenteropancreatic endocrine tumors with doxorubicin-eluting beads: preliminary results.

Citation

Journal of Vascular and Interventional Radiology, 2008, 19(6): 855-861.

Authors

de Baere, T., Deschamps, F., Triitheau, C., Rao, P., Coengrapht, K., Schlumberger, M., Leboulleux, S., Baudin, E., & Hechelhammer, L.

Abstract

PURPOSE: To evaluate the feasibility, safety, and efficacy of transarterial chemoembolization (TACE) of progressive liver metastases from well differentiated gastroenteropancreatic endocrine (GEP) tumors with drug-eluting beads (DEBs). MATERIALS AND METHODS: From June 2004 to July 2005, eight men and 12 women aged 34 to 75 years (mean +/- SD, 59 y +/- 12), including 13 patients with bilobar disease and seven with unilobar disease,

underwent 34 sessions of TACE with DEBs (500-700 mum) loaded with doxorubicin. Morphologic response was evaluated with computed tomography (CT) at 1 and 3 months according to Response Evaluation Criteria In Solid Tumors. Clinical and laboratory data were also assessed. RESULTS: The complete dose of 4 mL of DEBs loaded with 100 mg doxorubicin was injected during 22 TACE sessions and 1-3.5 mL of DEBs was injected during 12 TACE sessions. Three months after TACE, 16 of 20 patients (80%) exhibited a partial response, three (15%) had stable disease, and one (5%) had progressive disease. The mean size of the largest metastasis in each patient decreased from 42 mm +/- 24 before treatment (median, 39.5 mm) to 33 mm +/- 23 (median, 29 mm) 1 month after treatment and 30 mm +/- 21 (median, 26.5 mm) 3 months after treatment. After a median follow-up of 15 months (range, 6-24 months), nine patients' disease remained controlled without tumor progression and 10 patients had progressive disease. The median time to progression was 15 months. Postembolization syndrome lasted less than 7 days in 23 sessions (67%) and more than 7 days in seven sessions (22%), and no symptoms at all were observed in four sessions (11%). Peak aspartate aminotransferase, alanine aminotransferase, and bilirubin levels after TACE were 35-490 IU (mean, 125 IU +/- 77; normal, <35 IU), 20-440 IU (mean, 149 IU +/- 155; normal, <45 IU), and 8-90 mol/L (mean, 26 IU +/- 25; normal, <17 IU), respectively, at 2-3 days. In five patients, follow-up CT at 1 month revealed TACE-induced peripheral liver necrosis. CONCLUSIONS: TACE with DEBs is well tolerated and appears effective. A comparative study with a standard TACE or transarterial embolization regimen is warranted to define the best protocol for transarterial treatment of GEP liver metastases.

http://www.ncbi.nlm.nih.gov/pubmed/17103105

Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies.

Citation Cardiovascular Interventional Radiology, 2007, 30(1): 6-25.

Authors
Marelli, L., Stigliano, R., Triantos, C,., Senzolo, M., Cholongitas, E., Davies, N., Tiballs, J., Meyer, T., Patch, D.W., & Burroughs, A.K.

Abstract

BACKGROUND: Chemoembolization (TACE) improves survival in cirrhotic patients with hepatocellular carcinoma (HCC). The optimal schedule, or whether embolization (TAE) alone gives the same survival advantage, is not known. PURPOSE: To evaluate whether specific patient characteristics and/or radiological transarterial techniques result in better outcomes. METHOD: A PubMed search was carried out for cohort and randomized trials (n = 175) testing transarterial therapies; meta-analysis was performed where appropriate. RESULTS: Anticancer drugs were used as sole agent in 75% of cases (double 15% and triple 6%): doxorubicin (36%), cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin (8%), and SMANCS (5%). Embolizing agents used were: gelatin sponge particles (71%), polyvinyl alcohol (PVA) particles (8%), degradable starch microspheres (DSM) (4%), and embospheres (4%). Sessions per patient were 2.5 +/- 1.5 (interval: 2 months). Objective response was 40 +/- 20%; survival rates at 1, 2, 3, and 5 years were: 62 +/- 20%, 42 +/- 17%, 30 +/- 15%, and 19 +/- 16%, respectively, and survival time was 18 +/- 9.5 months. The post-TACE complications were: acute liver failure, 7.5% (range 0-49%); acute renal failure, 1.8% (0-13%); encephalopathy, 1.8% (0-16%); ascites, 8.3% (0-52%); upper gastrointestinal bleeding; 3% (0-22%); and hepatic or splenic abscess, 1.3% (0-2.5%). Treatment-related mortality was 2.4% (0-9.5%), mainly due to acute liver failure. Our meta-analysis of nine randomized controlled

trials (RCTs) confirmed that TACE improves survival; but a meta-analysis of TACE versus TAE alone (3 RCTs, 412 patients) demonstrated no survival difference. CONCLUSIONS: No chemotherapeutic agent appears better than any other. There is no evidence for benefit with lipiodol. Gelatin sponge is the most used embolic agent, but PVA particles may be better. TAE appears as effective as TACE. New strategies to reduce the risk of post-TACE complications are required.

http://www.carcinoid.org/medpro/docs/Soulen_HaceVSBland2007.pdf

Chemoembolization and Bland Embolization of Neuroendocrine Tumor Metastases to the Liver.

Citation
Journal of Vascular and Interventional Radiology, 2007, 18(7):847-855.

Authors
Ruutiainen, A.T., Soulen, M.C., Tuite, C.m., Clark, T.W.I., Mondschein, J. I., Stavropoulos, S., & Trerotola, S.O.

Abstract
PURPOSE: To assess the toxicity and efficacy of chemoembolization and bland embolization in patients with neuroendocrine tumor metastases to the liver.
MATERIALS AND METHODS: A total of 67 patients underwent 219 embolization procedures: 23 patients received primarily bland embolization with PVA with or without iodized oil and 44 primarily received chemoembolization with cisplatin, doxorubicin, mitomycin-C, iodized oil, and polyvinyl alcohol. Clinical, laboratory, and imaging follow-up was performed 1 month after completion of therapy and every 3 months thereafter. Patients with disease relapse were treated again when feasible. Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0. Efficacy was assessed by clinical and morphologic response. Time to progression (TTP), time to treatment failure, and survival were estimated by Kaplan–Meier analysis.
RESULTS: Ten of 67 patients (15%) were lost to follow-up. The mortality rate at 30 days was 1.4%. Toxicities of grade 3 or worse in severity occurred after 25% of chemoembolization procedures and 22% of bland embolization procedures (odds ratio, 1.2; 95% CI, 0.4–4.0). Mean length of stay was 1.5 day in both groups. Rates of freedom from progression at 1, 2, and 3 years were 49%, 49%, and 35% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, *P* .16). Among the subgroup with carcinoid tumors, the proportions without progression were 65%, 65%, and 52% after chemoembolization and 0%, 0%, and 0% after bland embolization (log-rank test, *P* .08). Patients treated with chemoembolization and bland embolization experienced symptomatic relief for means of 15 and 7.5 months, respectively (*P* .14). Survival rates at 1, 3, and 5 years after therapy were 86%, 67%, and 50%, respectively, after chemoembolization and 68%, 46%, and 33%, respectively, after bland embolization (log-rank test, *P* .18).
CONCLUSIONS: Chemoembolization was not associated with a higher degree of toxicity than bland embolization. Chemoembolization demonstrated trends toward improvement in TTP, symptom control, and survival. Based on these results, a multicenter prospective randomized trial is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/17449759

Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors.

Citation
American Journal of Roentgenology, 2007, 188(5): 1201-1207.
Authors
Ho, A. S., Picus, J., Darcy, M.D., Tan, B., Gould, J. E., Pilgram, T.K., & Brown, D. B.
Abstract
OBJECTIVE: Hepatic artery chemoembolization and hepatic artery embolization (HAE) are accepted treatments of patients with hepatic metastasis from neuroendocrine tumors. Long-term outcome data are limited. We present our experience in the use of hepatic artery chemoembolization in the treatment of patients with hepatic metastasis from neuroendocrine tumors. MATERIALS AND METHODS: Forty-six patients with carcinoid (n = 31) or islet cell (n = 15) tumors were treated. Overall and progression-free survival times starting with the first treatment were calculated. Potential factors affecting survival, including presence of extrahepatic disease and resection of the primary lesion, were analyzed. Relief of symptoms was subjectively determined for tumors with hormonal secretion. RESULTS: The 46 patients underwent 93 hepatic artery chemoembolization or HAE sessions. The mean overall survival time for the entire group was 1,273 +/- 185 days. The mean overall survival times for the carcinoid (1,255 +/- 163 days) and islet cell tumor (1,311 +/- 403 days) subgroups were similar (p = 0.66). The progression-free survival times for the carcinoid (602 +/- 144 days) and islet cell (501 +/- 107 days) tumor subgroups also were similar (p = 0.72). The survival time of patients without known extrahepatic metastasis (n = 18; 1,571 +/- 291 days) trended toward significance compared with that of patients with known extrahepatic disease (n = 26; 770 +/- 112 days; p = 0.08). Resection of the primary tumor in 19 of 46 patients did not affect survival (resection survival, 1,558 +/- 400 days; nonresection survival, 1,000 +/- 179 days; p = 0.44). Twenty of 25 patients with hormonally active tumors had relief of symptoms after one cycle of treatment. The 30-day mortality was 4.3%. CONCLUSION: The overall survival time after hepatic artery chemoembolization or HAE among patients with neuroendocrine tumors is approximately 3.5 years. The progression-free survival time approaches 1.5 years. The presence of extrahepatic metastasis or an unresected primary tumor should not limit the use of hepatic artery chemoembolization or HAE.

http://www.ncbi.nlm.nih.gov/pubmed/17458596
Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned.
Citation
Journal of Gastrointestinal Surgery, 2007, 11(3): 264-271.
Authors
Blomston, M., Al-Saif, O., Klemanski, D., Pinzone, J.J., Martin, E.W., Palmer, B., Guy, G., Khabri, H., Ellison, E.C., & Shah, M.H.
Abstract
BACKGROUND: Hepatic artery chemoembolization (HACE) is a treatment option in the management of metastatic carcinoid. We reviewed our experience to identify potential factors that influence survival. METHODS: The records of 122 patients with metastatic carcinoid tumor undergoing HACE were reviewed. Log-rank analysis and Cox proportional hazards were applied to identify factors predictive of decreased survival. RESULTS: Median follow-up after HACE was 21.5 months. Complications occurred in 23% with periprocedural mortality of 5%. Radiographic tumor regression was seen in 82%, with stabilization of disease in 12%. Median duration of CT response was 19 months. Improvement in symptoms occurred in 92% for median duration of 13 months. HACE resulted in complete normalization of serum

pancreastatin in 14%, with greater than 20% reduction in another 66%. Median overall survival was 33.3 months after HACE. Only pancreastatin level > or =5,000 pg/ml was associated with decreased survival by multivariate analysis. CONCLUSION: HACE offers symptom palliation and long-term survival in patients with incurable carcinoid metastases. Although safe, it should be approached cautiously in patients with significant tumor burden as evidenced by pancreastatin levels > or =5,000 pg/ml. We do not recommend whole-liver embolization in these patients but prefer a staged approach to each lobe of the liver.

http://www.ncbi.nlm.nih.gov/pubmed/17899303

Repeat transarterial chemoembolization (TACE) for progressive hepatic carcinoid metastases provides results similar to first TACE.

Citation
Journal of Gastrointestinal Surgery, 2007, 11(12): 1680-1685.

Authors
Varker, K.A., Martin, E.W., Klemanski, D., Palmer, B., Shah, M.H., & Bloomston, M.

Abstract
BACKGROUND: Transarterial chemoembolization (TACE) is commonly used to treat metastatic carcinoid tumors; however, the management of progressive disease is less clear. We sought to determine if patients with disease progression after TACE would benefit from repeat TACE. METHODS: The records of 27 patients undergoing repeat TACE for radiologic or symptomatic progression after TACE for metastatic carcinoid were reviewed and compared to 122 undergoing first TACE. Overall and progression-free survivals were estimated by the Kaplan-Meier method. RESULTS: Mean disease-free interval after first TACE was 11.8 months. Radiologic response was observed in 61% compared to 82% after first TACE (p=0.058); hormone response in 64% compared to 80% (p=0.159); and symptomatic response in 77% compared to 92% (p=0.053). The complication rate after repeat TACE was lower than after first TACE (p=0.03). Median overall survival was similar after repeat (28.1 months) and first TACE (33.3 months) (p=0.53). Progression-free survival was shorter after repeat TACE but not significantly so. No factor examined could predict survival after repeat TACE. CONCLUSION: Repeat TACE for patients with hepatic carcinoid metastases failing first TACE or having evidence of disease progression is safe and offers a viable treatment option.

http://www.ncbi.nlm.nih.gov/pubmed/16508629

Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors.

Citation
Cancer Control, 2006, 13(1): 72-78.

Authors
Strosberg, J.R., Choi, J., Cantor, A.B., & Kvols, L.K.

Abstract
BACKGROUND: Prognosis in patients with carcinoid and pancreatic endocrine tumors with diffuse, unresectable liver metastases is poor. Palliation is often difficult despite the use of somatostatin analogs, interferon alpha, or systemic chemotherapy. Several reviews have

suggested that hepatic artery embolization, with or without intraarterial chemotherapy, can be used for control of symptoms and for cytoreduction in patients with liver dominant metastases. METHODS: Between 2000 and 2002, 161 embolizations using polyvinyl alcohol or microspheres were performed on 84 patients with carcinoid or pancreatic endocrine tumors metastatic to the liver. A retrospective review was performed to evaluate symptomatic response, biochemical response, adverse effects, and duration of survival. Baseline and follow-up computed tomography scans were also assessed to determine radiographic response rates. Further analysis of survival was performed to assess the possible impact of various postembolization therapies. RESULTS: Eighty-four patients underwent bland hepatic artery embolizations during the study period. Among 55 symptomatic patients, 44 patients had fewer symptoms, and among 35 patients whose tumor markers were followed, 28 had a major biochemical response. Objective radiographic responses were observed in 11 of 23 patients. No deaths occurred during therapy, and major toxicities were rare. Median overall survival was 36 months from time of initial embolization. CONCLUSIONS: Hepatic artery embolization frequently results in clinical and radiographic responses in patients with unresectable liver metastases from carcinoid or pancreatic endocrine tumors. Morbidity is low when appropriate supportive care is provided. Hepatic artery embolization often results in regressions in patients with unresectable liver metastases from carcinoid or pancreatic endocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/16134179

Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival.

Citation

Cancer, 2005, 104(8): 1590-1602.

Authors

Gupta, S., Johnson, M.M. Murhty, R., Ahrar, K., Wallace, M.J., Madoff, D.C., McRae, S.E., Hicks, M.E., Rao, S., Vauthery, J.N., Ajani, J.A., & Yao, J.C.

Abstract

BACKGROUND: The objective of this study was to determine the prognostic variables that influence response and survival in patients with metastatic neuroendocrine tumors who are treated with hepatic arterial embolization (HAE) or chemoembolization (HACE). METHODS: Patients with metastatic neuroendocrine tumors who underwent HAE or HACE were included in this retrospective study. Follow-up imaging studies were compared with baseline imaging to determine the radiologic response. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed to assess the prognostic variables that affected response and survival. RESULTS: The study included 69 patients with carcinoid tumors and 54 patients with pancreatic islet cell carcinomas. Patients who had carcinoid tumors had a higher response rate (66.7% vs. 35.2%; P = 0.0001) and had longer PFS (22.7 mos vs. 16.1 mos; P = 0.046) and OS (33.8 mos vs. 23.2 mos; P = 0.012) compared with patients who had islet cell carcinomas. For patients with carcinoid tumors, multivariate analysis identified male gender as the only independent risk factor for poor survival (P = 0.05). Octreotide was predictive marginally for PFS (P = 0.06). Patients who were treated with HAE had a higher response rate than patients who were treated with HACE (P = 0.004). For patients with islet cell carcinoma, an intact primary tumor, > or = 75% liver involvement, and extrahepatic metastases were associated with reduced OS in the univariate analysis; the presence of bone metastases was the only risk

factor (P = 0.031) in the multivariate analysis. Patients who were treated with HACE had a prolonged OS (31.5 mos vs. 18.2 mos) and improved response (50% vs. 25%) compared with patients who were treated with HAE, although the differences did not reach statistical significance. CONCLUSIONS: Patients with carcinoid tumors had better outcomes than patients with islet cell carcinomas. The addition of intraarterial chemotherapy to HAE did not improve the outcome of patients with carcinoid tumors, but it seemed to benefit patients with islet cell carcinomas. In patients who had carcinoid tumors, male gender predicted a poor outcome, and a trend toward prolonged PFS was observed in patients who received concomitant octreotide. An intact primary tumor, extensive liver disease, and bone metastases were associated with reduced survival in patients with islet cell carcinomas.

http://www.ncbi.nlm.nih.gov/pubmed/16371533

Hepatic arterial chemoembolization for hepatocellular carcinoma: comparison of survival rates with different embolic agents.

Citation
Journal of Vascular and Interventional Radiology, 2005, 16(12): 1661-1666.

Authors
Brown, D.B., Pilgram. T.K., Darcy, M.D., Fundakowski, C.E., Liker-Melman, M., Chapman, W.C., & Crippen, J.S.

Abstract
PURPOSE: The optimal embolic agent for transhepatic arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) has not been identified. This study reports outcomes of TACE for HCC with Gelfoam powder and polyvinyl alcohol (PVA). MATERIALS AND METHODS: Eighty-one patients underwent 152 TACE sessions with Gelfoam powder (n = 41) or polyvinyl alcohol (PVA) and Ethiodol (n = 40) as the embolic agent. Chemotherapeutic drugs were the same for all patients (50 mg cisplatin, 20 mg doxorubicin, 10 mg mitomycin-c). The groups were compared based on number of TACE sessions, maximum tumor size, bilirubin level, aspartate and alanine aminotransferase levels, Child-Pugh score, Model for End-stage Liver Disease score, and hepatitis B or C virus positivity. The number of cases of each Child class in each group was also evaluated. Survival starting from the first TACE session was calculated according to Kaplan-Meier analysis. Forty-eight patients died during the study period, 19 received transplants, and 14 were alive at the end of the study period. RESULTS: The groups were statistically similar in all categories regarding liver function, Child-Pugh score, tumor size, hepatitis status, and percentage of patients with Child class A, B, and C disease. The number of TACE sessions was significantly greater for the Gelfoam powder group (mean, 2.2) versus the PVA group (mean, 1.6; P = .01). Overall survival was similar between groups whether patients who received transplants were included in the analysis (mean, 659 days +/- 83 with Gelfoam powder vs 565 days +/- 71 with PVA; P = .42) or were excluded (mean, 519 days +/- 80 with Gelfoam powder vs 511 days +/- 75 with PVA; P = .93). CONCLUSION: In similar patient groups, survival after treatment of HCC with TACE with Gelfoam powder or PVA and Ethiodol was similar.

http://www.ncbi.nlm.nih.gov/pubmed/15532819

Prognostic factors for chemoembolization in liver metastasis from endocrine tumors.

Citation
Hepatogastroenterology, 2004, 51(60): 1751-1756.

Authors
Roche, A., Girish, B.V., de Baere, T., Ducreux, M., Elias, D., Laplance, A., Boige, V., Schlumberger, M., Ruffle, P., & Baudin, E.

Abstract
BACKGROUND/AIMS: The aims of this study were to assess response rates, evaluate side effects and determine prognostic factors for both response and toxicity in patients with liver metastasis from endocrine tumors treated with chemoembolization. METHODOLOGY: Data concerning 64 patients who underwent a total of 186 sessions of chemoembolization were retrospectively evaluated and correlated with response and toxicity after chemoembolization. RESULTS: Overall clinical, morphological and biological response rates were 93%, 74% and 52% respectively. Complete control of hormone-related symptoms was obtained in 59% of patients with a mean duration of response of 15 months. Transient major complications occurred after 5.9% of sessions and 3 patients died. In the univariate and multivariate analyses, a non-pancreatic primary and chemoembolization as first-line non-surgical treatment were prognostic factors for clinical response, and <30% of liver involvement for morphological response. A significant increase in morbidity was noted in patients with more than 70% of liver involvement. CONCLUSIONS: Hormone-related symptoms were controlled in the majority of patients with a non-pancreatic primary and in those treated with chemoembolization as first-line therapy. Morphological response and toxicity were respectively correlated with liver involvement of less than 30% and greater than 70%.

http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=DIG20030682_3094

Transarterial Chemoembolization of Advanced Liver Metastases of Neuroendocrine Tumors - A Retrospective Single-Center Analysis.

Citation
Digestion, 2003, 68(2-3): 94-101.

Authors
Kress, O., Wagner, H-J., Wied, M., Klose, K.J., Arnold, R., & Alfke, H.

Abstract
Background*:* In neuroendocrine tumors, metastases are a negative prognostic factor for survival and quality of life. Transcatheter arterial chemoembolization (TACE) is thought to be an effective symptomatic and antiproliferative treatment in patients with otherwise progressive disease. Methods*:* 62 chemoembolization procedures in 26 patients with progressive neuroendocrine tumors were reviewed. The underlying disease was carcinoid syndrome in 10, non-functional midgut tumor in 2, non-functional pancreatic tumor in 7, malignant insulinoma in 2 patients, non-functional tumor of the stomach in 1 and of unknown origin in 4 patients. Tumor burden of the liver was <25% in 3, 25-50% in 11, 50-75% in 6 and >75% in 6 patients. Results: TACE was technically successful in 57 cases. Four patients developed minor and 5 major complications. The 30-day mortality rate was 7.7%. According to WHO criteria, 14 patients had no change in tumor burden, 2 had regression and 5 progress after chemoembolization. Patients with a tumor burden >75% of the liver did not benefit from TACE due to the development of major complications, whereas patients with low (<50%) tumor burden and high (>50%) lipiodol uptake showed a trend towards longer survival. Five-year survival time after diagnosis was 48%. Patients treated with octreotide and/or -interferon

had no benefit from chemoembolization with regard to their carcinoid syndrome. Conclusions*:* In this retrospective study, patients with low (<50%) tumor burden and high (>50%) lipiodol uptake responded better to TACE than end-stage patients.

http://www.ncbi.nlm.nih.gov/pubmed/12541121

Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors.

Citation
European Radiology, 2003, 13(1): 136-140.

Authors
Roche, A., Girish, B.V., de Baère, T., Baudin, E., Boige, B., Elias, D., Lasser, P., Schlumberger, M., & Ducreux, M.

Abstract
Our objective was to report the outcome in patients with liver metastasis from endocrine tumors who underwent transarterial chemoembolization (TACE) as first-line non-surgical treatment. From January 1990 to December 2000, 14 patients with progressive unresectable liver metastases from digestive neuroendocrine tumor were treated with TACE (mean of 3.6 sessions) before any non-surgical treatment (somatostatin analogue, chemotherapy or interferon). Liver involvement was less than 50% in 11 patients. Size of the largest lesion ranged from 1.5 to 10 cm. Ten patients presented with carcinoid symptoms. The TACE was performed with Doxorubicin emulsified in Lipiodol and gelatin sponge particles. Symptomatic response upon flushes and/or diarrhea was complete in 7 of 10 cases and partial in 2 of 10 cases. An objective morphologic response was noted in 12 of 14 cases. The 5- and 10-year survival rate from diagnosis was 83 and 56%, respectively. Six patients were alive at the end of the study after 27-100 months from first TACE and 38-142 months from diagnosis. Three of them were successfully palliated for 55, 69, and 100 months with only TACE as treatment. Long-term palliation is possible in unresectable liver metastases from digestive neuroendocrine tumors with a few sessions of TACE as first-line and eventually exclusive treatment.

YTTRIUM-90 RADIOEMBOLIZATION

http://www.ncbi.nlm.nih.gov/pubmed/20395859

Factors predicting response and survival after yttrium-90 radioembolization of unresectable neuroendocrine tumor liver metastases: a critical appraisal of 48 cases.

Citation
Annals of Surgery, 2010, 251(5): 910-916.

Authors
Saxena, A., Chua, T.C., Bester, L., Kokandi, A., & Morris D. L.

Abstract
BACKGROUND: Yttrium-90 (90Y) radioembolization is a promising treatment option for unresectable neuroendocrine tumor liver metastases (NETLM). This study is the first to

evaluate the prognostic variables that influenced radiologic response and survival in patients with unresectable NETLM who were treated with 90Y radioembolization. As a secondary outcome, the impact of this treatment on serologic toxicity was assessed. METHODS: Forty-eight patients underwent resin-based 90Y radioembolization for unresectable NETLM at a single institution between December 2003 and May 2009. Patients were assessed radiologically and serologically at 1 month and then at 3 month intervals after treatment. Prognostic variables that affected response and survival were determined. The impact of this treatment on serologic toxicity over a 6-month period was assessed. DISCUSSION: No patient was lost to follow-up. The median follow-up for the patients who were alive was 41 months. The median survival was 35 months (range: 5-63). On imaging follow-up, 7 patients (15%) had a complete response and 19 patients (40%) had a partial response to treatment. Eleven patients (23%) had stable disease and 11 patients (23%) had progressive disease. Five prognostic factors were associated with an improved survival: complete/partial response (P=0.003), low hepatic tumor burden (P=0.022), female gender (P=0.022), well-differentiated tumor (P=0.001), and absence of extra-hepatic metastasis (P<0.001). Three factors were associated with a complete/partial response: female gender (P=0.040), well-differentiated tumor (P<0.001) and low hepatic tumor burden (P=0.041). There was a significant increase in the level of alkaline phosphatase over the 6-month period (P<0.001). CONCLUSIONS: 90Y radioembolization is a promising treatment option for unresectable NETLM. Patients with low hepatic tumor burden, well-differentiated tumor, female gender, and no extrahepatic disease benefit most from treatment.

http://www.ncbi.nlm.nih.gov/pubmed/19521310

Yttrium-90 radioembolization using TheraSphere in the management of primary and secondary liver tumors.

Citation
Quarterly Journal of Nuclear Medicine and Molecular Imaging, 2009, 53(3): 311-316.

Authors
Riaz, A., Lewandowski, R.J., Kulik, L., & Salem, R.

Abstract

Locoregional therapies, such as transarterial chemoembolization, radioembolization and thermal ablation (e.g., radiofrequency ablation) are establishing their roles in the management of liver malignancies. With yYttrium-90 radioembolization therapy (90Y) radionuclide labeled microspheres are injected into the tumor feeding artery. This allows the delivery of a high radioactive dose to the tumor with minimal toxicity to normal tissues. 90Y has demonstrated to be safe and effective in the management of liver tumors. Authors present a review of the literature available for the use of TheraSphere for radioembolization in the management of liver tumors.

http://www.ncbi.nlm.nih.gov/pubmed/19307736

Selective internal radiotherapy with Yttrium-90 microspheres for hepatic metastatic neuroendocrine tumors: a prospective single center study.

Citation
Digestion, 2009, 79(3): 137-142.

Authors
Kalinowski, M., Dressler, M., König, A., El-Sheik, M., Rinke, A., Höffken, H., Gress, T.M., Arnold, R., Klose, K.J., & Wagner, H.J.

Abstract
BACKGROUND: To assess prospectively the safety and efficacy of Yttrium-90 microspheres in patients with unresectable liver metastases from neuroendocrine tumors. MATERIALS AND METHODS: Microspheres were administered via a temporarily placed hepatic catheter. Patients were monitored prospectively. All patients were followed with laboratory and imaging studies at regular intervals to determine response rates. Toxicity and quality of life scores were measured. RESULTS: Nine patients (7 female) with a mean age of 58.8 years were enrolled in this prospective trial. The mean tumor load was 58.8%. The estimated percentage shunting to the lungs on MAA scans was 5.04 +/- 2.4%. Visceral artery embolization of extrahepatic arteries before treatment was performed in 6 patients. The median dose of microspheres was 2.1 +/- 0.4 GBq. A total of 12 therapy sessions was performed. The mean follow-up was 21.7 months. Technical success was 100%. No major complications occurred. Survival rates were 100, 57 and 57% for 1, 2 and 3 years, respectively. Three months after SIRT therapy partial response (PR) was seen in 6 patients (66%). Calculated reduction of liver metastasis volume was 49%. In 3 patients (33%) stable disease was seen with a calculated tumor reduction of 13%. The estimated time to progression was 11.1 months. CONCLUSION: Radioembolization with (90)Y microspheres is safe and produces high response rates even with extensive tumor replacement for up to 1 year. Acute and late toxicity was very low. Further investigations compared with other local ablative techniques is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/18525307

Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients.

Citation
American Journal of Clinical Oncology, 2008 Jun, 31(3): 271-279.

Authors
Kennedy, A. A., Dezarn, W.A., McNellie, P., Coldwell, D., Nutting, C., Carter, D., Murthy, R., Rose, S., Warner, R.R., Liu, D., Palmedo, H., Overton, C., Jones, B., & Salem, R.

Abstract
PURPOSE: The use of 90Y-microspheres to treat unresectable liver metastases originating from a variety of neuroendocrine tumors was reviewed. MATERIALS AND METHODS: This is a retrospective review from 10 institutions of patients given 90Y-microsphere therapy for neuroendocrine hepatic metastases. Physical, radiographic, biochemical, and clinical factors associated with treatment and response were examined. All patients were followed with laboratory and imaging studies at regular intervals until death, or censured whether other therapy was given after brachytherapy. Toxicities (acute and late) were recorded, and survival of the group determined. RESULTS: A total of 148 patients were treated with 185 separate procedures. The median age was 58 years (26-95 years) at treatment with median performance status of Eastern Cooperative Oncology Group (0). The median activity delivered was 1.14 GBq (0.33-3.30 GBq) with a median of 99% of the planned activity able to be given (38.1%-147.4%). There were no acute or delayed toxicity of Common Terminology Criteria for Adverse Events v3.0 grade 3 in 67% of patients, with fatigue (6.5%) the most common side effect. Imaging response was stable in 22.7%, partial response in 60.5%, complete in 2.7% and progressive disease in 4.9%. No radiation liver failure occurred. The median survival is 70 months. CONCLUSION: Radioembolization with 90Y-microspheres to the whole liver, or lobe

with single or multiple fractions are safe and produce high response rates, even with extensive tumor replacement of normal liver and/or heavy pretreatment. The acute and delayed toxicity was very low without a treatment related grade 4 acute event or radiation induced liver disease in this modest-sized cohort. The significant objective response suggests that further investigation of this approach is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/18192482

Yttrium-90 microsphere radioembolotherapy of hepatic metastatic neuroendocrine carcinomas after hepatic arterial embolization.

Citation
Journal of Vascular and Interventional Radiology, 2008, 19(1): 145-151.

Authors
Murthy, R., Kamat, P., Nunez, R., Madoff, D.C., Gupta, S., Salem, R., & Yao, J.C.

Abstract
Hepatic artery radioembolization was performed in a cohort of patients with unresectable neuroendocrine hepatic metastases who exhibited hepatic progression or toxicity despite technically adequate embolization procedures without other reasonable therapeutic options. Eight patients (five men) with a median age of 55.5 years met the study criteria. Infusions of yttrium-90 resin microspheres were performed in a lobar fashion. Standard clinical, laboratory, and imaging follow-up was performed. Median hepatic parenchyma replacement by tumor was 55% (range, 25%-60%). Twelve (90)Y resin microsphere infusions were performed, and the median delivered activity was 33.25 mCi (range, 23-55 mCi). One partial response, four cases of disease stabilization, and three cases of progressive disease were noted. No cases of radiation-induced liver disease occurred. Median survival times were 14 months (range, 3-15 months) from the time of (90)Y microsphere treatment and 36.5 months (range, 16-105 months) from the time of diagnosis of hepatic metastases. In this cohort, (90)Y microsphere radioembolization of neuroendocrine hepatic metastases was not precluded by previous nonradioactive embolization procedures, but the effectiveness in this population requires further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/18618495

Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases.

Citation
Cancer, 2008, 113(5): 921-929.

Authors
King, J., Quinn, R., Glenn, D.M., Janssen, J., Tong, D., Liaw, W., & Morris, D.L.

Abstract
BACKGROUND: There are limited effective treatment options available and a poor 5-year survival for patients with inoperable neuroendocrine liver metastases (NETLMs). In this study, the authors prospectively assessed the safety and efficacy of treatment with yttrium 90 ((90)Y) radioactive microspheres for patients with unresectable NETLMs. METHODS: Radioactive (90)Y resin microspheres (selective internal radiation [SIR-Spheres]) were

administered through a temporarily placed percutaneous hepatic artery catheter concomitantly with a 7-day systemic infusion of 5-fluorouracil to patients with progressive, unresectable NETLMs. Patients were monitored prospectively, and the response to treatment was measured by using cancer markers and tumor size on computed tomography imaging studies. RESULTS: Thirty-four patients (22 men) with a mean age 61 years (range, 32-79 years) who had unresectable NETLMs were treated between December 2003 and December 2005. The mean (+/-standard error) follow-up was 35.2 +/- 3.2 months. The site of the primary neuroendocrine tumor was the bronchus in 1 patient, the medullary thyroid in 2 patients, gastrointestinal in 15 patients, the pancreas in 8 patients, and of unknown origin in 8 patients. The tumors were classified as vipoma (1 tumor), somatostatinoma (1 tumor), glucagonoma (2 tumors), large cell (3 tumors), carcinoid (25 tumors), and of unknown origin (2 tumors). Complications after (90)Y radioembolization included abdominal pain, which was mild to severe; nausea and fever; and lethargy that lasted from 1 week to 1 month. Two patients developed biopsy-proven radiation gastritis, 1 patient developed a duodenal ulcer, and there was 1 early death from liver dysfunction and pneumonia. Subjective changes from recorded baseline hormone symptoms were reported every 3 months. Symptomatic responses were observed in 18 of 33 patients (55%) at 3 months and in 16 of 32 patients (50%) at 6 months. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses, and the mean overall survival was 29.4 +/- 3.4 months). In patients who had evaluable chromogranin A (CgA) marker levels, there was a fall in CgA marker levels after (90)Y radioembolization in 19 patients (26%) at 1 month, in 19 patients (41%) at 3 months, in 15 patients (43%) at 6 months, in 11 patients (42%) at 12 months, in 8 patients (38%) at 24 months, and in 3 patients (46%) at 30 months. CONCLUSIONS: In this open study of 34 patients, the results demonstrated that radioembolization with (90)Y resin microspheres can achieve relatively long-term responses in some patients with nonresectable NETLMs

http://www.ncbi.nlm.nih.gov/pubmed/17448867

Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium.

Citation

International Journal of Radiation Oncology, Biology, Physics, 2007, 68(1): 13-23.

Authors

Kennedy, A., Nag, S., Salem, R., Murthy, R., McEwan, A.J., Nutting, C., Benson, A 3rd, Espat, J., Bilbao, J.I., Sharma, R.A., Thomas, J.P., & Coldwell, D.

Abstract

PURPOSE: To standardize the indications, techniques, multimodality treatment approaches, and dosimetry to be used for yttrium-90 (Y90) microsphere hepatic brachytherapy. METHODS AND MATERIALS: Members of the Radioembolization Brachytherapy Oncology Consortium met as an independent group of experts in interventional radiology, radiation oncology, nuclear medicine, medical oncology, and surgical oncology to identify areas of consensus and controversy and to issue clinical guidelines for Y90 microsphere brachytherapy. RESULTS: A total of 14 recommendations are made with category 2A consensus. Key findings include the following. Sufficient evidence exists to support the safety and effectiveness of Y90 microsphere therapy. A meticulous angiographic technique is required to prevent complications. Resin microsphere prescribed activity is best estimated by the body surface area method. By virtue of their training, certification, and contribution to Y90 microsphere treatment programs, the disciplines of radiation oncology, nuclear medicine, and

interventional radiology are all qualified to use Y90 microspheres. The panel strongly advocates the creation of a treatment registry with uniform reporting criteria. Initiation of clinical trials is essential to further define the safety and role of Y90 microspheres in the context of currently available therapies. CONCLUSIONS: Yttrium-90 microsphere therapy is a complex procedure that requires multidisciplinary management for safety and success. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose-reporting policies.

http://www.ncbi.nlm.nih.gov/pubmed/17369573

Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy.

Citation

Journal of Clinical Oncology, 2007, 25(9): 1099-1106.

Authors

Sharma, R.A., Van Hazel, G.A., Morgan, B., Berry, D.P., Blanshard, K., Price, D., Bower, G., Shannon, J.A., Gibbs, P., & Steward, W.P.

Abstract

PURPOSE: Liver metastases represent the principal cause of death in patients with advanced colorectal cancer (CRC). Injection of resin microspheres (SIR Spheres)--containing the beta-emitter, yttrium-90--into the arterial supply of the liver can cause radioembolization of metastases. This treatment has not been tested with the radiosensitizing chemotherapy, oxaliplatin, which appears synergistic in the treatment of CRC when combined with fluorouracil and leucovorin (FOLFOX). PATIENTS AND METHODS: A phase I study of SIR-Spheres therapy with modified FOLFOX4 systemic chemotherapy was conducted in patients with inoperable liver metastases from CRC who had not previously received chemotherapy for metastatic disease. Oxaliplatin (30 to 85 mg/m2) was administered for the first three cycles with full FOLFOX4 doses from cycle 4 until cycle 12. The primary end point was toxicity. RESULTS: Twenty patients were enrolled onto the study. Five patients experienced National Cancer Institute (NCI; Bethesda, MD) grade 3 abdominal pain, two of whom had microsphere-induced gastric ulcers. The dose-limiting toxicity was grade 3 or 4 neutropenia, which was recorded in 12 patients. One episode of transient grade 3 hepatotoxicity was recorded. Mean splenic volume increased by 92% following 6 months of protocol therapy. Partial responses were demonstrated in 18 patients and stable disease in two patients. Two patients underwent partial hepatic resection following protocol therapy. Median progression-free survival was 9.3 months, and median time to progression in the liver was 12.3 months. CONCLUSION: The maximum-tolerated dose was 60 mg/m2 of oxaliplatin for the first three cycles, with full FOLFOX4 doses thereafter. This chemoradiation regime merits evaluation in phase II-III trials.

http://www.ncbi.nlm.nih.gov/pubmed/15869456

Selective internal radiation therapy with SIR-Spheres in patients with nonresectable liver tumors.

Citation

Cancer Biotherapy & Radiopharmaceuticals, 2005, 20(2): 200-208.

Authors

Pöpperl, G., Helmberger, T., Münzing, W., Schmid, R., Jacobs, T.F., & Tatsch, K.

Abstract

AIM: Transarterial embolization of branches of the hepatic artery with biocompatible 90Y-labeled microspheres (SIR-Spheres) is a local treatment modality for patients with liver tumors, which, most recently, has become available in Europe. The aim of this study was to evaluate the feasibility and efficacy of this selective internal radiation therapy (SIRT). METHODS: Twenty-three patients with nonresectable hepatic metastases or hepatocellular carcinoma nonresponding to polychemotherapy and/or other local treatment were treated with SIRT. SIR-Spheres (mean activity, 2270 MBq) were administered by gentle intra-arterial infusion in the hepatic artery. A follow-up was documented by fluorodeoxyglucose-positron emission tomography (FDG-PET), course of tumor markers, and computed tomography (CT). RESULTS: Common minor side-effects were abdominal pain, nausea, and fever. Mild pancreatitis and peptic ulceration were observed once each. Currently, all patients are still alive, with survival times ranging from 11 to 518 days from SIRT up to the present. Three-month follow-up investigations are available in 13 of 23 patients, which, so far, are showing a marked decrease of FDG uptake, a drop of tumor markers, and unchanged or slightly decreasing lesion size (CT) in 10 of 13 patients. Two patients showed stable findings, while another patient showed progressive disease. Long-term follow-up investigations are available in 2 of 23 patients, showing hepatic and extrahepatic progression 6 and 9 months after SIRT. CONCLUSIONS: Our initial experience confirms that SIRT is a promising local therapeutic approach in patients with nonresectable liver tumors which is feasible and has an acceptable toxicity profile. Prospective data on comparing this treatment alone or in combination with other modalities are needed to answer whether long-term survival in this unfavorable stage of disease can be markedly improved.

MEDICAL THERAPY

OVERVIEW

http://erc.endocrinology-journals.org/cgi/reprint/17/1/R75
Systemic therapy for neuroendocrine tumours of gastroenteropancreatic origin.
Citation
Endocrine-Related Cancer, 2010, 17(1): R75–R90.
Authors
Basu, B., Sirohi, B., & Corrie, P.
Abstract
Systemic therapy is one of a number of treatment options routinely used in the management of advanced, unresectable neuroendocrine tumours (NETs). In contrast to many of the other NET treatment modalities, there is at least some evidence base to justify its use. Even so, well designed clinical trials are limited, since conducting clinical research in this complex group of rare cancers is challenging. The remit of this review article is to summarise the oncology literature and explain the role of systemic therapy in treating NETs of gastroenteropancreatic origin, identifying benefits and limitations. The molecular biology of NETs is now being unravelled, which affords new opportunities for development of mechanism-driven therapies. The rationale for some of the newer systemic targeted therapies that are showing promise in the clinic is discussed.

BIOTHERAPY

SOMATOSTATIN ANALOGS

http://www.ncbi.nlm.nih.gov/pubmed/19845567

Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours.

Citation
Alimentary Pharmacology & Therapeutics, 2010, 31(2): 169-188.

Authors
Modlin, I.M., Pavel, M., Kidd, M., & Gustafsson, B.I.

Abstract
BACKGROUND: The discovery of somatostatin (SST) and the synthesis of a variety of analogues constituted a major therapeutic advance in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours (GEP-NETs). They currently provide the most efficient treatment to achieve symptomatic relief and have recently been demonstrated to inhibit tumour growth. AIM: To review 35 years of experience regarding the clinical application and efficacy of SST analogues. METHODS: The PubMed database (1972-2009) was searched using somatostatin as a search term with combinations of terms including 'treatment'; 'neuroendocrine'; 'carcinoid'; 'tumor'; 'octreotide'; 'lanreotide' and 'pasireotide'. RESULTS: In a review of 15 studies including 481 patients, the slow-release formulations Sandostatin LAR and Somatuline SR/Autogel achieved symptomatic relief in 74.2% (61.9-92.8%) and 67.5% (40.0-100%), biochemical response in 51.4% (31.5-100%) and 39.0% (17.9-58%), and tumour response in 69.8% (47.0-87.5%) and 64.4% (48.0-87.0%) respectively. Novel SST analogues like SOM230 (pasireotide) that exhibit pan SST receptor activity and analogues with high affinity to specific somatostatin receptor (sstr) subtypes may further advance the field, but efficacy studies are lacking. CONCLUSION: As more precise understanding of NET cell biology evolves and molecular biological tools advance, more accurate identification of individual tumours sstr profile will probably facilitate a more precise delineation of SST analogue treatment.

http://www.ncbi.nlm.nih.gov/pubmed/20196864

Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumours, current aspects and new perspectives.

Citation
Journal of Experimental and Clinical Cancer Research, 2010, 29:19.

Authors
Appetecchia, M., & Baldelli, R.

Abstract
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are rare tumours that present many clinical features. They secrete peptides and neuroamines that cause distinct clinical syndromes, including carcinoid syndrome. However, many are clinically silent until late presentation with mass effects. In 2000 the WHO developed a new classification which gives a better description of the characteristics and biological behaviour of the tumour. Surgical resection is the treatment of first choice for a patient with a GEP NET. In metastatic disease multiple therapeutic approaches are possible. In these cases the goal is to improve quality of

life and to extent survival. GEP NETs express somatostatin receptors (SSTRs), which are bound by somatostatin (SST) or its synthetic analogues, although the subtypes and number of SSTRs expressed is very variable. Somatostatin analogues are used frequently to control hormone-related symptoms while their anti-neoplastic activity, even if it has not been widely studied and the regarding data are discordant, seems to result prevalently in tumour stabilisation. A few patients who fail to respond or cease to respond to standard SST analogues treatment seem to have a response to higher doses of these drugs.The use of higher doses of somatostatin analogues or the development of new subtype selective agonists and chimaeric somatostatin analogues, or pan-somatostatin will probably improve the clinical management of these patients. This review provides an update on the use of somatostatin analogues in the management of GEP NETs and discusses novel clinical strategies based on SSTR 2 gene transfer therapy.

http://www.ncbi.nlm.nih.gov/pubmed/20194865

90Y-edotreotide for metastatic carcinoid refractory to octreotide.

Citation
Journal of Clinical Oncology, 2010, 28(10):1652-1659.

Authors
Bushnell, D.L., Jr, O'Dorisio, T.M., O'Dorisio, M.S., Menda, Y., Hicks, R.J., Van Cutsem, E., Baulieu, J.L., Borston-Chazot, F., Anthony, L., Benson, A.B., Oberg, K., Grossman, A.B., Connolly, M., Bouterfa, H., Li, Y., Kacena, K.A., LaFrance, N., & Pauwels, S.A.

Abstract

PURPOSE: Metastatic carcinoid is an incurable malignancy whose symptoms, such as diarrhea and flushing, can be debilitating and occasionally life-threatening. Although symptom relief is available with octreotide, the disease eventually becomes refractory to octreotide, leaving no proven treatment options. The goal of this study was to evaluate the clinical effect of using (90)Y-edotreotide to treat symptomatic patients with carcinoid tumors. PATIENTS AND METHODS: Patients enrolled had metastatic carcinoid, at least one sign/symptom refractory to octreotide, and at least one measurable lesion. Study treatment consisted of three cycles of 4.4 GBq (120 mCi) (90)Y-edotreotide each, once every 6 weeks. RESULTS: Ninety patients were enrolled in the study. Using Southwest Oncology Group tumor response criteria, 67 (74.%) of 90 patients (95% CI, 65.4% to 83.4%) were objectively stable or responded. A statistically significant linear trend toward improvement was demonstrated across all 12 symptoms assessed. Median progression-free survival was significantly greater (P = .03) for the 38 patients who had durable diarrhea improvement than the 18 patients who did not (18.2 v 7.9 months, respectively). Adverse events (AEs) were reported in 96.7% (87 of 90) of patients. These AEs consisted primarily of reversible GI events (76 of 90), which could be caused in part by concomitant administration of amino acid solution given to reduce radiation exposure to the kidneys. There was one case each of grade 3 oliguria and grade 4 renal failure, each lasting 6 days. CONCLUSION: (90)Y-edotreotide treatment improved symptoms associated with malignant carcinoid among subjects with no treatment alternatives. Treatment was well-tolerated and had an acceptable expected AE profile. Objectives: Octreotide long acting repeatable (LAR) is widely used for the control of symptoms of functional neuroendocrine tumors. At doses of 30 mg/mo, up to 40% of patients require subcutaneous octreotide "rescue" and up to 40% of patients are given more than 30 mg of LAR/mo. Octreotide acetate binds to the sst2 receptor with an affinity (Kd) of

approximately 1 x 10-9 mol/L ([approximately equal to]1000 pg/mL), but higher ([approximately equal to]10,000 pg/mL) concentrations of octreotide are required to completely saturate this receptor. Octreotide blood level measurement may be useful to guide LAR therapy in symptomatic patients or in patients who have tumor growth on traditional LAR doses. We hypothesize that LAR doses of 60 mg/mo will produce blood levels of 10,000 pg/mL or greater. At identical monthly LAR doses, patients with higher weights will require more medication to achieve similar plasma octreotide levels than individuals with lower body weights.Methods: Trough plasma, serum, urine, and saliva octreotide levels were obtained from 52 patients with carcinoid syndrome receiving 20 (n = 8), 30 (n = 19), or 60 mg LAR/mo (n = 10). Octreotide levels were determined by radioimmunoassay. Results: The mean +/- SD plasma octreotide levels for patients receiving 20, 30, or 60 mg LAR/mo were 2518 +/- 1020, 5241 +/- 3004, and 10,925 +/- 5330 pg/mL, respectively. Patient weight (kilograms) was inversely related to plasma octreotide levels. There was a significant correlation between plasma octreotide levels and octreotide levels measured in urine, saliva, and serum. Conclusions: Frequent measurement of octreotide levels may be useful to guide octreotide therapy in patients with poorly controlled symptoms or those patients experiencing tumor growth.

http://www.ncbi.nlm.nih.gov/pubmed/19573169

Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR.

Citation
Alimentary Pharmacology and Therapeutics, 2009, 30(7): 733-740.

Authors
Toumpanakis, C., Garland, J., Marelli, L., Srirajaskanthan, R., Soh, J., Davies, P., Buscombe, J., & Caplin, M.E.

Abstract
BACKGROUND: Octreotide LAR is an established treatment for malignant carcinoid syndrome. However, studies with large number of patients and long follow-up are lacking. AIM: To present long-terms results with octreotide LAR, assessing duration of clinical and objective response and treatment tolerance, in a large, homogeneous cohort of patients with malignant carcinoid syndrome. METHODS: A total of 108 patients with metastatic midgut neuroendocrine tumours were included in this 8-year study. Clinical evaluation was based on a symptom score. Radiological assessment was based on RECIST (Response Evaluation Criteria In Solid Tumours) criteria. RESULTS: Of the 108 patients, 24% had a sustained symptomatic response. In the remaining patients, loss of symptomatic response with the initial dose was noted within 3-60 months. In 17% of them, symptoms were controlled by just an increase of octreotide LAR dose, whilst the other patients required additional treatment. Overall, in 45.3% of patients, symptoms were well controlled during the study period with only octreotide LAR, and no additional treatment was required. No significant adverse effects were noted. CONCLUSIONS: Octreotide LAR treatment provides a sustained symptomatic response in about half of the patients with malignant carcinoid syndrome and contributes to disease stabilization for a longer period than previously described.

http://www.ncbi.nlm.nih.gov/pubmed/19704057

Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group.

Citation
Journal of Clinical Oncology, 2009, 27(28): 4656-4663.

Authors
Rinke, A., Müller, H.H., Schade-Brittinger, C., Klose, K.J., Barth, P., Wied, M., Mayer, C., Aminossadati, B., Pape, U-F., Bläker, M., Harder, J., Arnold, C., Gress, T., Arnold, R.; PROMID study Group.

Abstract
PURPOSE: Somatostatin analogs are indicated for symptom control in patients with gastroenteropancreatic neuroendocrine tumors (NETs). The ability of somatostatin analogs to control the growth of well-differentiated metastatic NETs is a matter of debate. We performed a placebo-controlled, double-blind, phase IIIB study in patients with well-differentiated metastatic midgut NETs. The hypothesis was that octreotide LAR prolongs time to tumor progression and survival. PATIENTS AND METHODS: Treatment-naive patients were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly in monthly intervals until tumor progression or death. The primary efficacy end point was time to tumor progression. Secondary end points were survival time and tumor response. This report is based on 67 tumor progressions and 16 observed deaths in 85 patients at the time of the planned interim analysis. RESULTS: Median time to tumor progression in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (hazard ratio [HR] = 0.34; 95% CI, 0.20 to 0.59; P = .000072). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group. Functionally active and inactive tumors responded similarly. The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor. Seven and nine deaths were observed in the octreotide LAR and placebo groups, respectively. The HR for overall survival was 0.81 (95% CI, 0.30 to 2.18). CONCLUSION: Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs. Because of the low number of observed deaths, survival analysis was not confirmatory.

http://www.carcinoid.org/medpro/docs/Woltering_OctreotideLAR_July2008.pdf

Clinical Value of Monitoring Plasma Octreotide Levels During Chronic Octreotide Long-Acting Repeatable Therapy in Carcinoid Patients.

Citation
Pancreas, 2008, 37(1): 94-100.

Authors
Woltering, E.A., Salvo, V.A., O'Dorisio, T.M., Lyons, J.3rd., Li, G., Zhou, Y., Seard, J.R., Go, V.L., Vinik, A.I., Mamikunian, P. & Mamikunian, G.

Abstract
OBJECTIVE: Octreotide is used to treat patients with neuroendocrine tumors. Previous reports show that octreotide long-acting repeatable (LAR) dose and patient body weight affect nadir plasma octreotide levels (approximately 1250, 2500, 5000, and 11,000 pg/mL for LAR doses of 10, 20, 30 and 60 mg/mo). However, plasma octreotide levels have decreased over time in patients receiving these doses of LAR. METHODS: From November 2004 until July 2007, trough plasma octreotide levels were determined in 86 patients on long-term octreotide

LAR therapy at doses of 30, 60, and 120 mg/mo. Changes in plasma drug levels were analyzed over time using random effects models. RESULTS: Current plasma octreotide levels for octreotide LAR doses of 30, 60, and 120 mg/mo are approximately 2200, 5200, and 6500 pg/mL, respectively, representing a decrease of approximately 50% to 70% compared with previously reported plasma octreotide levels. The decreases in octreotide levels over time with the 30- and 60-mg/mo LAR doses are highly statistically significant (P = 0.0067, 0.0149, respectively). CONCLUSIONS: Current plasma octreotide values are significantly lower than previously reported for 30-, 60-, and 120-mg/mo LAR doses. Serial plasma octreotide value measurements should be used to determine if increasing symptoms or tumor growth are associated with suboptimal octreotide levels.

http://www.ncbi.nlm.nih.gov/pubmed/18662970

Long-acting somatostatin analogues are an effective treatment for type 1 gastric carcinoid tumours.

Citation

European Journal of Endocrinology, 2008, 159(4): 475-482.

Authors

Grozinsky-Glasberg, S., Kaltsas, G., Gur, C., Gal, E., Thomas, D., Fichman, S., Alexandraki, K., Barak, D., Glaser, B., Shimon, I., & Gross, D.J.

Abstract

BACKGROUND: Gastric carcinoid tumours type 1 (GCA1) originate from hyperplastic enterochromaffin-like (ECL) cells secondary to hypergastrinaemia. Treatment with somatostatin analogues (SSA) might impede ECL-cell hyperplasia by suppressing gastrin secretion and/or by a direct anti-proliferative effect on ECL cells. We conducted a multicentre prospective study to assess the effects of long-acting SSA on hypergastrinaemia and ECL-cell proliferation in patients with GCA1. METHODS: We studied 15 patients with GCA1 treated with monthly long-acting release octreotide (LAR) (20-30 mg; n=14) or Lanreotide 90 mg (n=1) for at least 6 months. Patients had serum gastrin and chromogranin A measurements performed and biopsies taken from both tumours and surrounding mucosa before, and every 6-12 months following treatment. Sections were immunostained for neuroendocrine markers. The cell proliferation index Ki-67, intensity of staining before and after treatment and the degree of gastric wall invasion were also assessed. RESULTS: All patients tolerated treatment well (mean follow-up of 18 months). In 11 patients (73%), a complete disappearance of the tumours at 1 year of treatment was observed on endoscopy, while in three patients (20%), the tumours decreased significantly in number and size. Gastrin levels normalized in 25% of patients, and were reduced by more than 80% in the remaining 75%. CONCLUSIONS: Treatment with SSAs in GCA1 leads to a substantial tumour load reduction, with a concomitant decrease of serum gastrin levels. Our data indicate an important anti-proliferative effect of SSA on ECL cells, providing clinical benefit and obviating, at least temporarily, the need for invasive therapies for GCA1.

http://www.ncbi.nlm.nih.gov/pubmed/16364959

Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma.

Citation

Annals of Oncology, 2006, 17(3): 461-466.

Authors
Panzuto, F., Di Fonzo, M., Iannicelli, E., Sciuto, R., Maini, C.L., Capurso, G., Milione, M., Cattaruzza, M.S., Falconi, M., David, V., Ziparo, V., Pederzoli, P., Bordi, C., & Delle Fave, G.

Abstract
BACKGROUND: Knowledge of factors able to predict the clinical outcome of homogenous series of entero-pancreatic endocrine tumours treated with somatostatin analogues is poor. This study was aimed at identifying predictors for efficacy of somatostatin analogues at inhibiting tumour growth and modifying patients' survival during long-term follow-up. PATIENTS AND METHODS: 31 patients with entero-pancreatic well-differentiated endocrine carcinoma received long-acting somatostatin analogues. All had progressive, metastatic disease (87% liver metastases, 38.7% distant extra-hepatic metastases). RESULTS: Response rate after 6 months of treatment was 45.2% (all disease stabilisation: 27.8% of pancreatic vs. 81.8% of intestinal tumours, P = 0.007). The predictors for non-response were: pancreatic tumour (OR 5.8), no previous surgery (OR 6.7), and the presence of distant extra-hepatic metastases, the latter being also confirmed by multivariate analysis (OR 10.0). Responders maintained stabilisation for 26.5 months, and none died during follow-up. Different survival curves were observed for patients, responding at 6 months compared to non-responders (P = 0.004), 3-year survival rate being 100% and 52.3%, respectively. CONCLUSIONS: Distant extra-hepatic metastases are the major predictor of poor efficacy of somatostatin analogues in progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinomas. Patients achieving response after 6 months of treatment, maintain it throughout a long-term follow-up. Non-responders after 6 months of treatment, have a worse survival, and should be considered for alternative treatments.

http://www.ncbi.nlm.nih.gov/pubmed/16625843

Pre-clinical and clinical experiences with novel somatostatin ligands: advantages, disadvantages and new prospects.

Citation
Journal of Endocrinological Investigation, 2005, 28(11 Suppl International): 36-42.
Authors
Hofland, L.J., van der Hoek, J., Feelders, R., van der Lely, A.J., de Herder, W., & Lamberts, S.W.

Abstract
Since the cloning and characterization of the five human somatostatin receptor (SSTR) subtypes, our understanding of the expression and functional role of the five SSTR subtypes in human (neuro-)endocrine tumors has increased significantly. The majority of human (neuro-)endocrine tumors express multiple SSTR. GH-secreting pituitary adenomas preferentially express SSTR2 and SSTR5, prolactinomas SSTR1 and SSTR5, and corticotroph adenomas express SSTR2 (low number) and predominantly SSTR5s. In addition, gastroenteropancreatic (GEP) neuroendocrine tumors frequently express multiple SSTR as well, with SSTR2 being expressed at the highest level. Treatment with the current generation of octapeptide somatostatin-analogs, e.g. octreotide and lanreotide, normalizes circulating GH- and IGF-I levels in approximately 60-70% of acromegalic patients, thereby remaining about one-third of patients uncontrolled. In patients with GEP neuroendocrine tumors, both somatostatin-analogs effectively suppress the production of bioactive peptides and hormones by the tumor cells, resulting in an important improvement of the related clinical symptomatology. However, a considerable proportion of patients experience an escape from treatment within months to

several years. Altogether, the current generation of somatostatin analogs are effective medical tools in the treatment of acromegalic patients and of patients with neuroendocrine GEP tumors, but there is certainly a need for novel somatostatin analogs. In recent years, a significant number of novel somatostatin-ligands has been developed. These ligands include SSTR selective-, bi-specific, universal, as well as chimeric dopamine (DA)-somatostatin ligands. In vitro studies using human pituitary adenoma cells demonstrate a more profound inhibition of GH, PRL and ACTH secretion by somatostatin-analogs targeting both SSTR2s and SSTR5s, compared with SSTR2-preferential somatostatin-analogs. This likely reflects the SSTR subtype expression pattern in the adenoma cells. A first proof-of-concept trial with the more universal somatostatin-ligand SOM230 in 12 acromegalic patients shows that a single dose of SOM230 is effective in suppressing circulating GH concentrations in a significant larger number of patients compared with octreotide. In animal models, SOM230 has a better effect on GH and IGF-I level with less signs of tachyphylaxis compared with octreotide. Depending on the SSTR expression pattern on neuroendocrine GEP tumors, somatostatin-analogs targeting multiple SSTRs may play a future role in the more long-term control of patients with neuroendocrine GEP tumors. The first clinical trial comparing octreotide and SOM230 is ongoing. However, every advantage has its disadvantage. Targeting multiple SSTR potentially induces more adverse effects as well. Especially, glucose homeostasis might induce new problems in the long-term use of universal ligands.

http://www.ncbi.nlm.nih.gov/pubmed/15627802

Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide.

Citation
Neuroendocrinology, 2004, 80(4): 244-251.

Authors
Ruszniewski, P., Ish-Shalom, S., Wymenga, M., O'Toole, D., Arnold, R., Tomassetti, P., Bax, N., Caplin, M., Eriksson, B., Glaser, B., Ducreux, M., Lombard-Bohas, C., de herder, W.W., Delle Fave, G., Reed, N., Seitz, J.F., Van Cutsem, E., Grossman, A., Rougier, P., Schmidlt, W., & Wiedenmann, B.

Abstract
This 6-month, open, non-controlled, multicenter, dose-titration study evaluated the efficacy and safety of 28-day prolonged-release (PR) lanreotide in the treatment of carcinoid syndrome. Eligible patients had a carcinoid tumor with > or =3 stools/day and/or > or =1 moderate/severe flushing episodes/day. Six treatments of 28-day PR lanreotide were administered by deep subcutaneous injection. The dose for the first two injections was 90 mg. Subsequent doses could be titrated (60, 90, 120 mg) according to symptom response. Seventy-one patients were treated. Flushing decreased from a mean of 3.0 at baseline to 2.3 on day 1, and 2.0 on day 2, with a daily mean of 2.1 for the first week post-treatment ($p < 0.05$). Diarrhea decreased from a mean of 5.0 at baseline to 4.3 on day 1 ($p < 0.05$), and 4.5 on day 2, with a daily mean of 4.4 for the first week post-treatment ($p < 0.001$). Symptom frequency decreased further after the second and third injections, and reached a plateau after the fourth injection. By month 6, flushing and diarrhea had significantly decreased from baseline by a mean of 1.3 and 1.1 episodes/day, respectively (both p < or = 0.001); 65% of patients with flushing as the target symptom and 18% of diarrhea-target patients achieved > or =50% reduction from baseline. Median urinary 5-hydroxyindoleacetic acid and

chromogranin A levels decreased by 24 and 38%, respectively. Treatment was well tolerated. 28-day PR lanreotide was effective in reducing the symptoms and biochemical markers associated with carcinoid syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/15151956

Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system.

Citation
Annals of Oncology, 2004, 15(6): 966-973.

Authors
Oberg, K., Kvols, L., Caplin, M., Delle Fave, G,, de Herder, W., Rindi, G., Ruszniewski, P., Woltering, E.A., & Wiedenmann, B.

Abstract
This consensus report gives a detailed description of the use of somatostatin analogs in the management of neuroendocrine tumors of the gastroenteropancreatic system. As background information we have outlined critical aspects of the pathology, the use of tumor markers, a definition of functional and non-functional digestive neuroendocrine tumors, different imaging modalities, surgical considerations, liver embolization and the use of cytotoxic drugs as well as interferon. Included in the report is an overview of somatostatin, somatostatin analogs and its receptor expression in different neuroendocrine tumors. It will also define the binding affinities of different somatostatin analogs to the five different subtypes of somatostatin receptor. We compare the efficacy of octreotide and lanreotide in reducing diarrhea and flushing. Side-effects are described and we provide practical information on somatostatin analog treatment.

http://www.ncbi.nlm.nih.gov/pubmed/15248829

High-dose treatment with a long-acting somatostatin analogue in patients with advanced midgut carcinoid tumours.

Citation
European Journal of Endocrinology, 2004, 151(1): 107-112.

Authors
Welin, S.V., Janson, E.T., Sundin, A., Stridsberg, M., Lavenius, E., Granberg, D., Skogseid, B., Oberg, K.E., & Eriksson, B.K.

Abstract
OBJECTIVE: High-dose somatostatin analogue treatment has shown an antiproliferative effect in one study including patients with neuroendocrine tumours. To explore this therapeutic strategy further, we have studied the effect of a high-dose formula of octreotide, octreotide pamoate, in midgut carcinoid patients. DESIGN AND METHODS: Twelve patients with advanced midgut carcinoid tumours with a median duration of disease of more than 5 years were included. All were in a progressive state despite several previous treatment modalities. Octreotide pamoate (160 mg) was given as an intramuscular injection every 2 weeks for 2 months and then monthly. Radiological and biochemical responses were monitored. RESULTS: Tumour size and biochemical markers were stabilised for a median of 12 months in 75% of the patients. Ten patients had symptomatic improvement of flush and

diarrhoea. CONCLUSION: In this group of patients with advanced midgut carcinoid tumours and progressive disease, octreotide pamoate managed to improve symptoms, and stabilise hormone production and tumour growth in 75% of the patients. We believe that high-dose treatment with somatostatin analogues can be an important addition to the therapeutic arsenal for patients with advanced progressive midgut carcinoid tumours.

http://www.ncbi.nlm.nih.gov/pubmed/11900219

Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma.

Citation
Cancer, 2002, 94(2): 331-343.

Authors
Shojamanesh, H., Gibril, F., Louie, A., Ojeaburu, J.V., Bashir, S., Abou-Saif, A., & Jensen, R.T.

Abstract
BACKGROUND: Malignant pancreatic endocrine tumors (PETs) have a poor prognosis and existing antitumor treatments are unsatisfactory. Recent studies have shown somatostatin analogues to have antitumor growth effects in patients with malignant PETs; however, to the authors' knowledge, little information exists regarding their efficacy or effect on survival in patients with progressive malignant gastrinoma, the most common symptomatic malignant PET. The purpose of the current study was to study prospectively the efficacy, safety, and effect on survival of long-term treatment with octreotide in consecutive patients with progressive malignant gastrinoma. METHODS: Fifteen consecutive patients with malignant gastrinoma with progressive hepatic metastases were studied. All patients underwent conventional imaging studies (computed tomography scan, magnetic resonance imaging, ultrasound, and, if needed, selective angiography) and somatostatin receptor scintigraphy prior to treatment and at 3-6-month intervals while receiving treatment. The patients all were treated initially with octreotide, 200 microg every 12 hours, and at last follow-up were being maintained on long-acting release octreotide, 20-30 mg every month. Tumor size and/or number were used to classify patient responses as either no tumor response or tumor response (stabilization or decrease in size). Treatment response was correlated with tumor and clinical characteristics. RESULTS: Tumors in 8 of the 15 patients studied (53%) responded at 3 months, with 47% (7 of 15 patients) demonstrating tumor stabilization and 6% (1 of 15 patients) demonstrating a decrease in tumor size. The mean duration of response was 25.0+/-6.1 months (range, 5.5-54.1 months). Six of the eight responders were continuing to respond at the time of last follow-up. Tumor response did not correlate with any clinical parameter (e.g., tumor extent, fasting gastrin, or acid secretory rates). However, slow-growing tumors were more likely to respond prior to treatment (86% vs. 0%) ($P < 0.0014$). During follow-up (range, 4-8 years), 25% of the responders died compared with 71% of the nonresponders, a difference that approached statistical significance ($P = 0.10$). Two patients (13%) developed serious side effects that required the withdrawal of octreotide. CONCLUSIONS: Octreotide is an effective antitumor treatment in patients with progressive malignant gastrinoma. In approximately 50% of these patients octreotide has an antigrowth effect; treatment is associated with a low incidence of serious side effects compared with other antitumor treatments commonly used and, in contrast to many studies, the growth response is long-lasting. The results of the current study suggest that octreotide treatment should replace chemotherapy as the standard treatment for these patients, especially those patients with slow-growing tumors. Additional studies involving larger numbers of patients will be

needed to determine a convincing effect on survival.

http://www.ncbi.nlm.nih.gov/pubmed/12213862

Long-term safety and efficacy of depot long-acting somatostatin analogs for the treatment of acromegaly.

Citation
Journal of Clinical Endocrinology & Metabolism, 2002, 87(9): 4142-4146.

Authors
Ayuk, J., Stewart, S.E., Stewart, P.M., & Sheppard, M.C.

Abstract
Depot somatostatin analogs are now increasingly being prescribed as adjuvant and primary therapy for the treatment of acromegaly. Previous studies have shown them to be both effective and safe, suppressing GH levels to less than 2 micro g/liter in 50-65% of cases and normalizing serum IGF-I levels in 65%. However, published data on their long-term efficacy and safety is scanty. We analyzed data from 22 patients (16 female and 6 male) treated with Sandostatin LAR or Lanreotide for an average of 41 months (range 12-89). Three patients had previously been treated with surgery, two with radiotherapy, and seven with both. Ten patients had received primary medical therapy. Mean pretreatment GH levels were 13.1 +/- 3.4 micro g/liter, and IGF-I levels were 592.9 +/- 53.9 micro g/liter. Results after 12 months of therapy indicated reduction in GH (3.2 +/- 0.7 micro g/liter; P < 0.0001) and IGF-I (321.9 +/- 33.9 micro g/liter; P < 0.001) concentrations, and this was sustained at latest follow-up. Using GH criteria (serum GH < 2 micro g/liter), 46% of subjects achieved a cure at 12 months, and 36% achieved a cure long-term. Fifty-two percent achieved normal IGF-I values at 12 months, and 67% long-term. Mean fasting and 2-h plasma glucose concentrations were similar at latest follow-up and at 12 months to baseline values. Three patients developed impaired glucose tolerance within 12 months of treatment, one going on to develop frank diabetes mellitus. However, glucose tolerance improved in five patients. Five patients developed gallstones while on treatment. In summary, this study reports the long-term efficacy of the depot somatostatin analogs as either adjuvant or primary therapy. Although overall glucose tolerance did not change, the development of impaired glucose tolerance in three patients at a time when GH levels were not changing highlights the ongoing need to monitor the long-term safety of these preparations.

http://www.ncbi.nlm.nih.gov/pubmed/12269913

Use of octreotide and lanreotide in the treatment of symptomatic non-resectable carcinoid tumours.

Citation
ANZ Journal of Surgery, 2002, 72(9):635-638.

Authors
Rohaizak, M., & Farndon, J.R.

Abstract
BACKGROUND: Carcinoid tumours are rare neoplasms that secrete hormones and biogenic amines, most commonly serotonin. Octreotide and long acting lanreotide are found to be useful in the management of carcinoid syndrome by its interaction with somatostatin receptor,

found on the carcinoid tumour. The aim of this study is to look at the efficacy of octreotide and long acting lanreotide in the treatment of symptomatic non-resectable carcinoid tumours. METHOD: The effects of octreotide and long-acting lanreotide were studied in 10 patients with symptomatic non-resectable carcinoid tumours. RESULTS: Symptom improvement occurred in nine of 10 patients. Three patients responded only to octreotide, three patients responded to both octreotide and long-acting lanreotide and three patients only responded to long-acting lanreotide. Slight reductions in 24-h urine 5-hydroxyindoleacetic acid levels occurred in three of six patients but no patients were found to have objective tumour regression on computed tomography scan. CONCLUSIONS: Octreotide and long-acting lanreotide are useful palliative treatments for the control of symptoms in patients with non-resectable carcinoid tumours but there is no evidence of tumour stasis.

http://www.ncbi.nlm.nih.gov/pubmed/11790981

Somatostatin and somatostatin analogues: diagnostic and therapeutic uses.

Citation
Current Opinions in Oncology, 2002, 14(1): 53-57.

Authors
de Herder, W.W., & Lamberts, S.W.

Abstract
Somatostatin and its octapeptide analogues exert their effects through interaction with somatostatin receptor (sst) subtypes 1 through 5 (sst 1-5). Somatostatin binds with high affinity to all sst subtypes, whereas the currently commercially available octapeptide analogues bind only with a high affinity to sst 2 and sst 5. Pituitary tumors, endocrine pancreatic tumors, and carcinoid tumors express multiple sst subtypes, but sst 2 predominance is found in 90% of carcinoids and 80% of endocrine pancreatic tumors. Sst 2 and sst 5 predominance is found in growth hormone-secreting pituitary tumors. In patients harboring sst 2 - or sst 5 -positive neuroendocrine tumors, clinical symptomatology can be controlled by the chronic administration of one of the currently commercially available octapeptide somatostatin analogues. Tumors and metastases that bear sst 2 or sst 5 can be visualized in vivo after injection of radiolabeled octapeptide analogues. Radiolabeled octapeptide analogues can also be used for radiotherapy of sst 2 - and sst 5 -positive advanced or metastatic neuroendocrine tumors

http://www.ncbi.nlm.nih.gov/pubmed/11334727

Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours.

Citation
European Journal of Cancer, 2001, 37(8): 1014-1019.

Authors
Aparicio, T., Ducreux, M., Baudin, E., Sabourin, J.C., De Baere, T., Mitry, E., Schlumberger, M., & Rougier, P.

Abstract
A few studies have suggested an antitumour activity of somatostatin analogues in neuroendocrine tumours (NET). The aim of this study was to evaluate the antitumour efficacy

of somatostatin analogues in patients with documented progressive tumours. 35 consecutive patients with documented tumour progression were treated with somatostatin analogues. Patients were classified into two groups. In Group 1, tumours were progressing rapidly (an increase of 50% or more in the lesion surface area in 3 months) and in Group 2, tumours were progressing more slowly (an increase of less than 50% in the lesion surface area in 3 months but greater than 25% in 6 months). Treatment consisted of subcutaneous (s.c.) octreotide, 100 microg thrice daily for 17 patients, intramuscular lanreotide, 30 mg/every 14 days for 11 patients and for 7 patients both somatostatin analogues were used successively during the follow-up. Primary tumour sites were the small intestine (n=12), pancreas (n=13), lungs (n=5), and other sites (n=5). 18 patients had the carcinoid syndrome with flushing and/or diarrhoea. The median duration of treatment was 7 months. Treatment was discontinued in 3 patients due to side-effects. One patient (3%) achieved a partial response and the disease was stabilised in 20 patients (57%) for a median duration of 11 months (6-48 months). Stabilisation of patients in Group 1 was significantly less frequent at 6 months than that of patients in Group 2 (4/12 and 13/17 respectively, P<0.02). Somatostatin analogue treatment resulted in one partial response (3%) and 20 cases of stabilisation (57%) in 35 patients with progressive NET. A slow tumour growth rate before treatment is predictive of a good response to somatostatin analogues which could be considered an option for first-line treatment.

http://www.ncbi.nlm.nih.gov/pubmed/11762334

The clinical management of neuroendocrine tumors with long-acting repeatable (LAR) octreotide: comparison with standard subcutaneous octreotide therapy.

Citation
Annals of Oncology, 2001, 12 (Suppl 2): S105-S109.

Authors
Dogliotti, L., Tampellini, M., Stivanello, M., Gorzegno, G., & Fabiani, L.

Abstract
Neuroendocrine tumors are rare, occurring in less than 1% of the population. They are divided clinically into functionally active or non-active tumors. Functionally active tumors produce a variety of substances (mainly peptides or serotonin) that are responsible for symptoms and sometimes can lead to the death of the patient independently from tumor proliferation. The most important compounds that can control symptoms in these patients are somatostatin analogs. Native somatostatin is not suitable for long-term clinical application due to its short half-life. Therefore, synthetic drugs were developed with improved pharmacokinetic characteristics. The best-characterized analog, octreotide, has been successfully applied to patients with functioning tumors. Octreotide can ameliorate symptoms in 30%-70% of the patients, mainly through a direct inhibitory effect on hormone production from the tumors. There is little or no effect on tumor growth during octreotide therapy; clinical responses were recorded in only 10%-30% of the patients. Recently, significant improvement in the management of the disease has been demonstrated with long-acting repeatable (LAR) octreotide. This new formulation requires only one monthly intramuscolar injection, and shows better acceptability and patient compliance to therapy. Data available to date show superimposable results of both standard octreotide and LAR octreotide in controlling symptoms, lowering hormone and tumor marker levels, and in reducing tumor growth. The availability of long-acting molecules have permitted the exploration of high-dose therapy in increasing tumor shrinkage and prolonging survival. Although there is a clear dose-response trend, the published data are not conclusive and further investigations are needed. The

possible lack of cross-resistance between LAR octreotide and a different analog, Lanreotide, is a very stimulating finding and this might lead to the development of new therapeutical strategies in the management of neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/11762808

Experience in treatment of metastatic pulmonary carcinoid tumors.

Citation
Annals of Oncology, 2001, 12(10): 1383-1391.

Authors
Granberg, D., Eriksson, B., Wilander, E., Grimfjärd, P., Fjällskog, M.L, Oberg, K., & Skogseid, B.

Abstract
BACKGROUND: The only cure for patients with pulmonary carcinoids is surgery. In the present paper, we report the results of medical treatment of patients with metastatic tumors, their circulating hormone markers, and immunohistochemical profile of the tumors. PATIENTS AND METHODS/RESULTS: The response to systemic antitumoral treatment was studied in 31 patients with metastatic pulmonary carcinoids. Median survival from treatment start was 25 months. Alpha-interferon treatment has resulted in stable disease in 4 of 27 patients (median duration 15 months), while 23 patients showed progressive disease. Somatostatin analogues given as single drug treatment resulted in progressive disease. Streptozotocin and 5-fluorouracil resulted in progressive disease in seven of seven patients. Stable disease was obtained for 8 and 10 months respectively in two of two patients treated with streptozotocin + doxorubicin. Two of eight patients treated with cisplatinum + etoposide showed a significant decrease in tumor size lasting six and eight months respectively, and one displayed stable disease for seven months. Elevation of plasma chromogranin A was seen in 93%. CONCLUSIONS: The results of systemic antitumoral treatment of pulmonary carcinoids with distant metastases are generally discouraging. Chemotherapy with cisplatinum + etoposide, or doxorubicin combined with streptozotocin or paclitaxel may be of value. Alpha-interferon and octreotide offer efficient symptomatic relief, but stabilizes tumor growth in merely 15% of the cases. Plasma chromogranin A is the most frequently elevated tumor marker.

http://www.ncbi.nlm.nih.gov/pubmed/10679645

Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance.

Citation
Cancer, 2000, 88(4): 770-776.

Authors
O'Toole, D., Ducreux, M., Bommelaer, G., Wemeau, J.L., Bouché, O., Catus, F., Blumberg, J., & Ruszniewski, P.

Abstract
BACKGROUND: The somatostatin analogues lanreotide and octreotide have previously been shown to be effective in controlling flushing and diarrhea in patients with carcinoid syndrome.

As lanreotide requires injection only every 10 days, compared with twice-daily injections of octreotide, a direct comparison between these two treatments in terms of patient acceptability, patient preference, and efficacy in controlling symptoms was performed in patients with carcinoid syndrome. METHODS: Thirty-three patients with carcinoid syndrome were included in an open, multicenter, crossover study. Half of the patients received octreotide 200 microg subcutaneously twice or thrice daily for 1 month followed by lanreotide 30 mg intramuscularly every 10 days for 1 month, while the other half commenced with lanreotide followed by octreotide in a similar fashion. Quality-of-life assessments were performed at each visit and patient preference for one of the two treatments evaluated. The number and intensity of flushing episodes and bowel movements, urinary 5-hydroxyindoleacetic acid (5HIAA) levels, and plasma serotonin levels were recorded. RESULTS: No significant differences were found between lanreotide and octreotide in terms of quality of life. The majority of patients (68%) preferred lanreotide (P = 0.03), largely due to its simplified mode of administration. Disappearance or improvement in flushes occurred in 53.8% of patients (14 of 26) while on lanreotide and in 68% (17 of 25) on octreotide. A disappearance or improvement of diarrhea in 45.4% (10 of 22) on lanreotide, compared with 50% (11 of 22) on octreotide, was also observed. Lanreotide and octreotide were equally effective in reducing urinary 5HIAA levels and plasma serotonin levels. Both treatments were well tolerated, with mild symptoms of abdominal pain and nausea observed in 29% and 14% receiving octreotide and lanreotide, respectively. CONCLUSIONS: Lanreotide and octreotide are equally efficacious in terms of symptom control and reduction in tumor cell markers for patients with carcinoid syndrome. Due to its simplified mode of administration, most patients prefer treatment with lanreotide.

http://www.ncbi.nlm.nih.gov/pubmed/11061606

Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide.

Citation
Annals of Oncology, 2000, 11(9): 1127-1130.

Authors
Ricci, S., Antonuzzo, A., Galli, L., Ferdeghini, M., Bodei, L., Orlandini, C., & Conte, P.F.

Abstract

BACKGROUND: In the present study we investigated the efficacy and tolerability of i.m. octreotide acetate (octreotide LAR) in patients with metastatic neuroendocrine tumors (NETs) previously treated and failed on i.m. lanreotide. PATIENTS AND METHODS: Fifteen patients (8 females, 7 males, median age 67 years, range 28-81 years) with metastatic NETs (8 endocrine pancreatic tumors, 7 midgut carcinoids) were enrolled in the study. All patients were in progressive disease (objective: 11 patients, symptomatic: 10 patients, biochemical: 11 patients) after treatment with slow release lanreotide, 30 mg every 14 days for a median time of 8 months (range 3-19 months). All patients had measurable disease; 12 patients had elevated serum and/or urine markers and 11 were symptomatic. Octreotide scintigraphy was positive in 13 of 15 patients. Octreotide LAR was administered as i.m. injection at the dose of 20 mg every four weeks until disease progression. RESULTS: An objective partial response (PR) was documented in one patient (7%), no change (NC) in six (40%), and progressive disease (PD) in eight patients (53%). The PR was observed in one patient with non-functioning endocrine pancreatic tumor with progressive liver and lymph node metastases after 16 months of i.m. lanreotide therapy. The median duration of disease stabilization was

7.5 months (range 6-12+ months). The overall biochemical response rate was 41%, including CRs (33%) and PRs (8%); biochemical responses were observed in carcinoids as well as in endocrine pancreatic tumors; the median duration of response was 5 months for CRs and 7.5 months for PRs. The overall symptomatic response rate was 82%. The median duration of response for diarrhoea, abdominal pain, or both was 6.5 months (range 3-12+ months). Improvement in performance status (PS) was obtained in 5 of 11 patients with PS of 1 at study entry. Median duration of octreotide LAR treatment was seven months (range 3-12+ months). No serious adverse events were reported; mild side effects were reported in 26% of patients. CONCLUSIONS: Octreotide LAR 20 mg shows significant efficacy in terms of objective response rate (PR + SD), biochemical and symptomatic control in patients with metastatic NETs of the GEP system pretreated and progressing on slow release lanreotide.

http://www.ncbi.nlm.nih.gov/pubmed/9024721

Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors.

Citation
Cancer, 1997, 79(4): 830-834.

Authors
Trendle, M.C., Moertel, C.G., & Kvols, L.K.

Abstract

BACKGROUND: Octreotide, a long-acting somatostatin analogue, has demonstrated clinical utility in patients with carcinoid syndrome and malignant islet cell tumors of the pancreas. Prior studies have reported a greater than expected incidence of cholelithiasis in patients treated with octreotide for acromegaly. This study attempted to determine the incidence and morbidity of cholelithiasis in a group of patients with metastatic carcinoid or malignant pancreatic islet cell tumors who were receiving chronic therapy with octreotide. METHODS: Forty-four of 55 patients on investigational protocols with octreotide were eligible for chart review; 10 patients were excluded due to prior cholecystectomy and 1 patient due to asymptomatic cholelithiasis at presentation. Patients fell into three treatment groups. The low dose (LD) group was comprised of 17 patients receiving 150 microg of subcutaneous octreotide 3 times a day. Twenty-one patients received high dose (HD) therapy comprised of 500 microg given 3 times a day. The low dose-high dose (LD-HD) group was comprised of 6 patients who had their dose escalated from 150 microg to 225-500 microg of octreotide 3 times a day. RESULTS: The overall incidence of cholelithiasis and/or gallbladder sludge was found to be 52.3% in all 3 treatment groups. Three of the 44 patients (6.8%) had symptomatic disease requiring emergency cholecystectomy. Five other patients underwent elective or incidental gallbladder surgery. The incidence of cholelithiasis in the LD, LD-HD, and HD groups was 35.3%, 66.6%, and 61.9%, respectively. The incidence of acute cholecystitis in the three groups was 11.8%, 0%, and 4.8%, respectively. CONCLUSIONS: Although greater than 50% of patients receiving octreotide developed cholelithiasis, a much smaller percentage of patients had symptomatic gallbladder disease. Patients receiving chronic octreotide treatment require monitoring for the development of gallstones. However, prophylactic cholecystectomy is not indicated, unless it is performed in conjunction with bowel resection or cytoreductive hepatic surgery.

CHEMOTHERAPY

http://www.ncbi.nlm.nih.gov/pubmed/20234360

Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours.

Citation

British Journal of Cancer, 2010, 102(7): 1106-1112.

Authors

Turner, N.C., Strauss, S.J., Sarker, D., Gillmore, R., Kirkwood, A., Hackshaw, A., Papasopoulou, A., Bell, J., Kayani, I., Toumpanakis, C., Grillo, F., Mayer, A., Hochhauser, D., Begent, R.H., Caplin, M.E., & Meyer, T.

Abstract

BACKGROUND: The role of chemotherapy for neuroendocrine tumours remains controversial and there is no standard regimen. METHOD: We report the outcome for a consecutive series of chemonaive patients with metastatic or locally advanced neuroendocrine tumours treated with a combination of 5-fluorouracil (500 mg m(-2)), cisplatin (70 mg m(-2)) and streptozocin (1000 mg m(-2)) (FCiSt) administered three weekly for up to six cycles. Patients were assessed for radiological response, toxicity and survival. RESULTS: In the 79 patients assessable for response, treatment with FCiSt was associated with an overall response rate of 33% (38% for pancreatic primary sites and 25% for non-pancreatic primary sites). Stable disease occurred in a further 51%, with progression in 16%. The median time to progression was 9.1 months and median overall survival was 31.5 months. The most common grade 3-4 toxicity was neutropaenia (28% patients) but grade 3-4 infection was rare (7%). The most frequent non-haematological grade 3-4 toxicity was nausea and vomiting (17%). Prognostic factors included Ki-67, mitotic index, grade and chromogranin A, whereas response to chemotherapy was predicted by mitotic index, grade and alpha-fetoprotein. CONCLUSIONS: FCiSt is an effective regimen for neuroendocrine tumours with an acceptable toxicity profile. Grade and mitotic index are the best predictors of response.

http://www.ncbi.nlm.nih.gov/pubmed/19726540.

Phase III trial of chemotherapy using 5-fluorouracil and streptozotocin compared with interferon alpha for advanced carcinoid tumors: FNCLCC-FFCD 9710.

Citation

Endocrine-Related Cancer, 2009, 16(4): 1351-1361.

Authors

Dahan, L., Bonnetain, F., Rougier, P., Raoul, J.L., Gamelin, E., Etienne, P.L., Cadiot, G., Mitry, E., Smith, D., Cvitkovic, F., Coudert, B., & Richard, F.

Abstract

The aim of this randomized multicenter phase III trial was to compare chemotherapy and interferon (IFN) in patients with metastatic carcinoid tumors. Patients with documented progressive, unresectable, metastatic carcinoid tumors were randomized between 5-fluorouracil plus streptozotocin (day 1-5) and recombinant IFN-alpha-2a (3 MU x 3 per week). Primary endpoint was progression-free survival (PFS). From February 1998 to June 2004, 64 patients were included. The two arms were well matched for median age, sex ratio, PS 0-1, previous chemotherapy, surgery, or radiotherapy. The median PFS for chemotherapy was 5.5

months versus 14.1 for IFN (hazard ratio=0.75 (0.41-1.36)). Overall survival (OS), tolerance, and effects on carcinoid symptoms were not significantly different. Despite a trend in favor of IFN, there was no difference in PFS and OS in advanced metastatic carcinoid tumors and therapeutic effect of both treatments was mild.

http://www.ncbi.nlm.nih.gov/pubmed/19886987

Continuous 5-fluorouracil infusion plus long acting octreotide in advanced well-differentiated neuroendocrine carcinomas. A phase II trial of the Piemonte oncology network.

Citation

BMC Cancer, 2009, 9: 388.

Authors

Brizzi, M.P., Berruti, A., Ferraro, A., Milanesi, E., Volante, M., Casiglione, F., Birocco, N., Bombaci, S., Perroni, B., Albasio, O., Ciuffreda, L., Bertetto, O., Papotti, M., & Dogliotti, L.

Abstract

BACKGROUND: Well-differentiated neuroendocrine carcinomas are highly vascularized and may be sensitive to drugs administered on a metronomic schedule that has shown antiangiogenic properties. A phase II study was designed to test the activity of protracted 5-fluorouracil (5FU) infusion plus long-acting release (LAR) octreotide in patients with neuroendocrine carcinoma. METHODS: Twenty-nine patients with metastatic or locally advanced well-differentiated neuroendocrine carcinoma were treated with protracted 5FU intravenous infusion (200 mg/m2 daily) plus LAR octreotide (20 mg monthly). Patients were followed for toxicity, objective response, symptomatic and biochemical response, time to progression and survival. RESULTS: Assessment by Response Evaluation Criteria in Solid Tumors (RECIST) criteria showed partial response in 7 (24.1%), stable disease in 20 (69.0%), and disease progression in 2 patients. Response did not significantly differ when patients were stratified by primary tumor site and proliferative activity. A biochemical (chromogranin A) response was observed in 12/25 assessable patients (48.0%); symptom relief was obtained in 9/15 symptomatic patients (60.0%). There was non significant decrease in circulating vascular epithelial growth factor (VEGF) over time. Median time to progression was 22.6 months (range, 2.7-68.5); median overall survival was not reached yet. Toxicity was mild and manageable. CONCLUSION: Continuous/metronomic 5FU infusion plus LAR octreotide is well tolerated and shows activity in patients with well-differentiated neuroendocrine carcinoma. The potential synergism between metronomic chemotherapy and antiangiogenic drugs provides a rationale for exploring this association in the future.

http://www.ncbi.nlm.nih.gov/pubmed/19472402

Gemcitabine and oxaliplatin combination chemotherapy for metastatic well-differentiated neuroendocrine carcinomas: a single-center experience.

Citation

Cancer, 2009, 115(15): 3392-3399.

Authors

Cassier, P. A., Walter, T., Eymard, B., Ardisson, P., Perol, M., Paillet, C., Chayvialle, J.A., Scoazec, J.Y., Hervieu, V., & Bohas, C.L.

Abstract

BACKGROUND: Beyond the usual regimens based on streptozocin and doxorubicin or 5-fluorouracil, no second-line therapy of metastatic neuroendocrine tumor has gained wide acceptance. Gemcitabine and oxaliplatin are generally well tolerated and have shown activity

against a wide range of malignancies. The authors assessed the efficacy of gemcitabine-oxaliplatin combination (GEMOX) in the treatment of patients with metastatic neuroendocrine tumors. METHODS: Twenty consecutive patients with progressive disease were treated with GEMOX, in most cases after failure of other chemotherapy regimens (median=2). Patients were followed for evidence of toxicity, response, and survival. Two patients were chemotherapy-naive at treatment initiation and were excluded from the efficacy analysis. RESULTS: Toxicity was manageable overall; however, 6 (30%) patients had to discontinue treatment because of oxaliplatin-induced neurotoxicity (grade 2). Three (17%) of 18 patients had a partial response, median progression-free survival was 7.0 months, and median overall survival was 23.4 months. CONCLUSIONS: Gemcitabine-oxaliplatin combination shows interesting activity and is well tolerated in pretreated patients with neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/19521065

Temozolomide: a safe and effective treatment for malignant digestive endocrine tumors.

Citation

Neuroendocrinology, 2009, 90(1): 67-72.

Authors

Maire, F., Hammel, P., Faivre, S., Hentic, O., Yapur, L., Larroque, B., Couvelard, A., Zappa, M., Raymond, E., Lévy, P., & Ruszniewski, P.

Abstract

BACKGROUND: Systemic chemotherapies are associated with limited response rates and significant toxicity in patients with malignant digestive endocrine tumors (DET). Preliminary studies have reported interesting results with temozolomide in patients with DET. AIM: It was the aim of this study to assess the efficacy and safety of temozolomide in patients with malignant DET. PATIENTS AND METHODS: Twenty-one patients, median age 61 years (range 56-77), with metastatic well-differentiated DET were retrospectively studied. All patients except 1 had received prior treatment (hepatic resection, chemotherapy). All patients had progressive disease in the 3 months prior to entry into the study. Temozolomide was administered at doses of 200 mg/m(2) daily for 5 days, every 28 days. Treatment was assessed for safety, progression-free and overall survival. RESULTS: The median number of temozolomide cycles was 5 (range 2-15). Grade 3 hematological toxicity occurred in 5 patients. There were no toxic deaths. According to the Response Evaluation Criteria in Solid Tumors criteria, partial response and stabilization were obtained in 1 (5%) and 17 patients (81%), respectively. The median time to progression was 9 months (range 3-26). The 1-year progression-free survival and overall survival were 42 and 77%, respectively. CONCLUSION: Temozolomide is a well-tolerated oral chemotherapy in patients with malignant DET, including those who have already received treatment. In patients with progressive disease, temozolomide controls tumor progression in 86% of cases.

http://www.ncbi.nlm.nih.gov/pubmed/19118063

O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors.

Citation

Clinical Cancer Research, 2009, 15(1): 338-345.

Authors

Kulke, M.H., Hornick, J.L., Frauenhoffer, C., Hooshmand, S., Ryan, D.P., Enzinger, P.C., Meyerhardt, J.A., Clark, J.W., Stuart, K., Fuchs, C.S., & Redston, M.S.

Abstract
PURPOSE: Recent studies suggest that temozolomide has activity in neuroendocrine tumors. Low levels of the DNA repair enzyme, O(6)-methylguanine DNA methyltransferase (MGMT), are associated with sensitivity to temozolomide in other tumor types. We evaluated the prevalence of MGMT deficiency in neuroendocrine tumors and correlated MGMT deficiency with treatment response to temozolomide-based regimens. EXPERIMENTAL DESIGN: The prevalence of MGMT deficiency, measured by immunohistochemistry, was assessed in 97 archival neuroendocrine tumor specimens. Rates of treatment response and survival were next evaluated in a cohort of 101 consecutive neuroendocrine tumor patients who had received treatment with a temozolomide-based regimen at one of three institutions. MGMT expression was directly correlated with treatment response in 21 patients who had available tumor tissue and response data. RESULTS: In archival specimens, MGMT deficiency was observed in 19 of 37 (51%) pancreatic neuroendocrine tumors and 0 of 60 (0%) carcinoid tumors ($P < 0.0001$). In the clinical cohort, 18 of 53 (34%) patients with pancreatic neuroendocrine tumors but only 1 of 44 (2%) patients with carcinoid tumors ($P < 0.001$) experienced a partial or complete response to temozolomide-based therapy. Among 21 patients with evaluable tumor tissue who had also received treatment with temozolomide, 4 of 5 patients with MGMT-deficient tumors (all pancreatic neuroendocrine tumors) and 0 of 16 patients with tumors showing intact MGMT expression responded to treatment ($P = 0.001$). CONCLUSIONS: MGMT deficiency, measured by immunohistochemistry, is more common in pancreatic neuroendocrine tumors than in carcinoid tumors as is treatment response to temozolomide-based therapy. Absence of MGMT may explain the sensitivity of some pancreatic neuroendocrine tumors to treatment.

http://www.ncbi.nlm.nih.gov/pubmed/17639039

Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors.

Citation
Endocrine-Related Cancer , 2007, 14 (2): 221 -232.

Authors
Vilar, E., Salazar, R., Pérez-Garcia, J., Cortes, J., Öberg, K., & Tabernero, J.

Abstract
Neuroendocrine tumors (NETs) of the digestive tract are a heterogeneous group of rare malignancies. Three major subgroups can be defined: pancreatic endocrine tumors, carcinoid tumors, and poorly differentiated gastroenteropancreatic NETs. Classically, digestive NETS have been considered to have an indolent course characterized for prolonged stabilizations or slow progressions, but there are clear differences in terms of aggressiveness, clinical course, and response to treatment among them. Retrospective studies have identified several clinicopathological and immunohistochemical factors as angioinvasion and proliferative index assessed by Ki-67 expression, which predict biological behavior and correlate with survival. Chemotherapy regimens based on the combination of several active drugs such as streptozocin, doxorubicin, 5-fluorouracil, dacarbazine, and temozolomide show low response rates, which sets the need to improve the results of the medical treatment of these malignancies. This review will analyze the role of Ki-67 in digestive NETs under a clinical

perspective and will suggest future fields for development of this approach that enable a better patient selection for chemotherapy. Also a comprehensive review of the literature about chemotherapy in NETs is presented.

http://www.ncbi.nlm.nih.gov/pubmed/16937105

Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours?

Citation
Cancer Chemotherapy and Pharmacology, 2007, 59(5): 637-642.

Authors
Bajetta, E., Catena, L., Procopio, G., De Dosso, S., Bichisao, E., Ferrari, L., Matinetti, A., Platania, M., Verzoni, E., Formisano, B., & Bajetta, R.

Abstract
PURPOSE: The aim of this trial was to evaluate the safety and efficacy of oxaliplatin and capecitabine (XELOX) in neuroendocrine tumours' (NETs) treatment. METHODS: Forty patients (pts) with advanced NETs were treated. Of these, 13 had untreated poorly differentiated NETs, 27 had well-differentiated NETs in progression after somatostatin analogues. Patients received oxaliplatin e.v. 130 mg/mq i.v. and capecitabine 2,000 mg/mq/die. The primary sites of the disease were: lung (10 pts), pancreas (15 pts), small bowel (8 pts), unknown (1 pt), others (6 pts). RESULTS: In 13 pts with poorly differentiated NETs objective responses (OR) were: 3 PR (23%), 1 SD (7%), 9 PD (70%). Biochemical responses were 11%. In 27 patients with well-differentiated NETs the OR were: 8 PR (30%), 13 SD (48%) and 6 PD (22%). Biochemical and symptomatic responses were 20 and 50%, respectively. CONCLUSIONS: The XELOX regimen is effective and tolerated in well-differentiated NETs after progression following somatostatin analogues.

http://www.ncbi.nlm.nih.gov/pubmed/17505000

Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors.

Citation
Clinical Cancer Research, 2007, 13(10): 2986-2991.

Authors
Ekeblad, S., sundin, A., Janson, E.T., Welin, S., Granberg, D., Kindmark, H., Dunder, K., Kozlovacki, G., Orlefors, H., Sigurd, M., Oberg, K., Eriksson, B., & Skogseid, B.

Abstract
PURPOSE: A retrospective analysis of the toxicity and efficacy of temozolomide in advanced neuroendocrine tumors. EXPERIMENTAL DESIGN: Thirty-six patients with advanced stages of neuroendocrine tumor (1 gastric, 7 thymic and 13 bronchial carcinoids, 12 pancreatic endocrine tumors, 1 paraganglioma, 1 neuroendocrine foregut, and 1 neuroendocrine cecal cancer) were treated with temozolomide (200 mg/m(2)) for 5 days every 4 weeks. Patients had previously received a mean of 2.4 antitumoral medical regimens. Tumor response was evaluated radiologically according to the Response Evaluation Criteria in Solid Tumors every 3 months on an intent-to-treat basis. The circulating tumor marker plasma chromogranin A was also assessed. The expression of O(6)-methylguanine DNA methyltransferase, an enzyme

implicated in chemotherapy resistance, was studied by immunohistochemistry (n=23) and compared with response to temozolomide. RESULTS: Median overall time to progression was 7 months (95% confidence interval, 3-10). Radiologic response was seen in 14% of patients and stable disease in 53%. Side effects were mainly hematologic; 14% experienced grade 3 or 4 thrombocytopenia (National Cancer Institute toxicity criteria). Ten patients had tumors with O(6)-methylguanine DNA methyltransferase immunoreactivity in <10% of nuclei, whereas four patients showed radiologic responses. CONCLUSIONS: Temozolomide as monotherapy had acceptable toxicity and antitumoral effects in a small series of patients with advanced malignant neuroendocrine tumors and four of these showed radiologic responses.

http://www.online.karger.com/ProduktеDB/produkte.asp?Doi=93004

A Phase II Study of Irinotecan with 5-Fluorouracil and Leucovorin in Patients with Pretreated Gastroenteropancreatic Well-Differentiated Endocrine Carcinomas.

Citation

Oncology, 2006, 70(2): 134-140.

Authors

Ducreux, M.P., Boige, V., Leboulleux, S., Malka, D., Kergoat, P., Dromain, C., elias, D., de Baere, T., Sabourin, J.C., Duvillard, P., Lasser, P., Schlumberger, M., & Baudin, E.

Abstract

Only a few drugs are active in the treatment of well-differentiated endocrine carcinomas (WDEC). We evaluated the combination of the so-called 'de Gramont schedule' and irinotecan in these tumors in a phase II study. Methods*:* 20 patients were enrolled in the study. The combination regimen included irinotecan, 180 mg/m^2 on day 1, followed by 200 mg/m^2 folinic acid in a 2-hour infusion, an intravenous 10-min bolus of 400 mg/m^2 5-fluorouracil (5FU) and finally 600 mg/m^2 5FU in a 22-hour infusion. Folinic acid and 5FU were repeated on day 2. Clinical, biological and morphological parameters were assessed by CT every 8 weeks. The site of the primary tumor was the pancreas in 10 cases, the lung in 3 cases and other sites in 7 cases. Sixteen patients had previously received chemotherapy, and 6 of them had had two lines of treatment. Six patients had previously been treated with chemoembolization. Results*:* The median number of cycles administered was 8. Grade 3-4 neutropenia was observed in 8 patients, and 1 patient experienced febrile neutropenia. There was no toxicity-related death. No complete symptomatic response was observed in 7 evaluable patients; 4 patients had an objective biological response. One patient achieved a morphological objective response, stabilization was observed in 15, but progression occurred in 3 patients. Median survival was 15 months. Conclusion*:* The above-mentioned combination of LV5FU2 + irinotecan does not yield major activity in heavily pretreated unresectable metastatic gastroenteropancreatic WDEC, and significant toxicity was observed.

http://www.ncbi.nlm.nih.gov/pubmed/16865563

A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors.

Citation

Digestive Diseases and Sciences, 2006, 51(6): 1033-1038.

Authors

Kulke, M.H., Wu, B., Ryan, D.P., Enzinger, P.C., Zhu, A. X., Clark, J.W., Earle, C.C., Michelini, A., & Fuchs, C.S.

Abstract
The role of systemic chemotherapy in the treatment of patients with metastatic neuroendocrine tumors is controversial. While combination regimens containing cisplatin and etoposide have activity against more aggressive neuroendocrine tumor variants, such regimens appear to have little efficacy in patients with well-differentiated neuroendocrine tumor subtypes. The combination of irinotecan and cisplatin is active both against small cell lung cancer and in upper gastrointestinal malignancies but has not been prospectively evaluated in patients with metastatic neuroendocrine tumors. We therefore assessed the efficacy of an irinotecan/cisplatin combination in patients with this disease. Eighteen patients with metastatic neuroendocrine tumors (excluding small cell carcinoma) were treated with irinotecan, 65 mg/m2, and cisplatin, 30 mg/m2, administered weekly for 2 of every 3 weeks. Patients were followed for evidence of toxicity, response, and survival. The toxicities associated with this regimen were mild and included myelosuppression, nausea, and diarrhea. Only one radiologic response was observed among four patients with poorly differentiated neuroendocrine tumors. No radiologic responses were observed in 14 patients with well-differentiated tumors. The median overall survival duration of patients treated with this regimen was 11.4 months. We conclude that while the combination of irinotecan and cisplatin may have activity in aggressive neuroendocrine tumor subtypes, this combination is inactive in patients with well-differentiated neuroendocrine tumors.

http://jco.ascopubs.org/cgi/content/abstract/23/22/4897

Phase II/III Study of Doxorubicin With Fluorouracil Compared With Streptozocin With Fluorouracil or Dacarbazine in the Treatment of Advanced Carcinoid Tumors: Eastern Cooperative Oncology Group Study E1281.

Citation
Journal of Clinical Oncology, 2005, 23(22): 4897-4904.

Authors
Sun, W., Lipsitz, S., Catalano, P., Mailliard, J.A., & Haller, D.G.

Abstract
PURPOSE: Optimal treatments for metastatic carcinoid tumor remain undefined, and the role of chemotherapy for symptomatic patients with progressive disease is uncertain. PATIENTS AND METHODS: Two hundred forty-nine patients with advanced carcinoid tumors were randomized to either doxorubicin with fluorouracil (FU/DOX) or streptozocin with fluorouracil (FU/STZ). Patients crossed over to the dacarbazine (DTIC) treatment after disease progression following first-line treatment (either FU/DOX or FU/STZ), and 73 patients were assigned to one of these three treatments based on their previous treatment or on abnormal baseline cardiac or renal function. RESULTS: In the randomized group, there was no difference between FU/DOX and FU/STZ in response rates (15.9% v 16%) and progression-free survival (4.5 v 5.3 months). FU/STZ (24.3 months) was superior to FU/DOX (15.7 months; P = .0267) in median survival. The response rate of crossover DTIC treatment was 8.2%, with a median survival of 11.9 months. Hematologic toxicities were the major treatment-related toxicities for both FU/DOX and FU/STZ, and mild to moderate renal toxicity was reported in 40 (34.8%) of 115 patients in the FU/STZ arm. CONCLUSION: Response to all three treatment regimens were modest. FU/STZ improved survival compared with the doxorubicin-based regimen, suggesting that the combination should be considered to be an active regimen of therapy when chemotherapy is judged to be an option for selected patients with carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/16183533
Endocrine tumours of the gastrointestinal tract: Chemotherapy.
Citation
Best Practice & Research in Clinical Gastroenterology.. 2005, 19(4): 649-656.

Authors
Arnold, R., Rinke, A., Schmidt, C., & Hofbauer, L.

Abstract
Malignant neuroendocrine tumours are less sensitive to chemotherapy than other epithelial malignancies. If chemotherapy is considered, tumours of pancreatic origin have a higher sensitivity than tumours from the gastrointestinal tract ('carcinoids'). Chemotherapy with streptozocin combinations and with dacarbazine should be considered in patients with progressive malignant neuroendocrine tumours of the pancreas. A favourable response to chemotherapy can be expected in up to 60% of patients receiving a combination of streptozocin plus doxorubicin, and in up to 40% of patients receiving dacarbazine. A survival benefit has been shown for streptozocin combinations. Treatment regimens are effective in functioning and non-functioning tumours. The response to treatment cannot be predicted. Poorly differentiated neuroendocrine tumours, independent of their origin, respond to a combination of etoposide plus cisplatin. Chemotherapy is, however, almost ineffective in patients with well-differentiated neuroendocrine tumours originating in the gastrointestinal tract ('carcinoids').

http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/4216

Effective treatment of neuroendocrine tumors with temozolomide and capecitabine.

Citation
Journal of Clinical Oncology, 2005, 23,9(16S): 4216.

Authors
Fine, R.L., Fogelman, D.R., & Schreibman, S.M.

Abstract
Background: Low grade neuroendocrine tumors (NET), which are differentiated and metastatic, have a poor response to chemotherapy (<10%). This group (7000 cases per year in the U.S.) includes carcinoid tumors, pancreatic endocrine tumors (PETs), catecholamine-secreting tumors (*e.g.* pheochromocytomas), medullary carcinoma of the thyroid and excludes small cell cancers of the lung and GI tract. In our lab, we have found that capecitabine (5-FDUR), an oral pro-drug for 5-FU, and temozolomide are synergistic for induction of apoptosis in 2 human NET cell lines when given in a specific sequence and schedule. Our hypothesis is that the DNA damage induced by capecitabine, by incorporation of 5-FdUTP into DNA and reducing thymidine pools by inhibition of thymidylate synthase via 5-FdUMP, synergistically potentiates the effect of temozolomide on O6-alkylguanyl alkyl-transferase (. Methods: We have treated ten patients with progressive metastatic NET who had failed chemotherapy and/or octreotide. Treatment consisted of capecitabine (1500 mg/m^2 total per day x 14 days) and temozolamide (150–200 mg/m^2 days 10–14). A two week rest period concluded each cycle. Responses were assessed by CT and PET. Results: Six patients were evaluable for response. Of these, there was one complete response, two partial responses, one

minor response, and two patients with stable disease. The complete response duration without chemotherapy is now 18 months. Responses were seen after 2 or 3 cycles. All patients improved symptomatically, with weight gain and/or performance status improvements. The only grade 3 toxicity was one case of hand-foot syndrome. Conclusion: The combination of capecitabine and temozolamide, given in a specific sequence and schedule, appears to be an effective regimen for metastatic NET which failed previous treatment. O6-AGAT)

http://www.ncbi.nlm.nih.gov/pubmed/15084386

Outcome of patients with pulmonary carcinoid tumors receiving chemotherapy or chemoradiotherapy.

Citation
Lung Cancer, 2004, 44(2): 213-220.

Authors
Wirth, L.J., Carter, M.R., Jänee, P.A., & Johnston, BE.

Abstract
STUDY OBJECTIVES: To determine the outcome of patients with pulmonary typical and atypical carcinoid tumors treated with chemotherapy with or without radiotherapy. METHODS: Patients with pulmonary neuroendocrine tumors treated at our institution from 1990 to 2001 were identified. The medical records of patients with diagnoses of typical or atypical pulmonary carcinoids were reviewed for the presence of evaluable disease, treatment with chemotherapy with or without radiotherapy, response to these treatments, survival and cause of death. RESULTS: Eighteen patients with typical (n = 8) or atypical (n = 10) pulmonary carcinoid tumors who were treated with chemotherapy with or without radiotherapy were identified. Of these, four received chemotherapy plus chest radiotherapy. Three of these had stable disease and one had a partial response. One of the patients with stable disease to chemoradiotherapy subsequently received chemotherapy alone, to which he had a complete response. Fourteen additional patients were treated with 18 chemotherapy regimens. There were two partial responses, eight stable disease, seven progressive disease and one allergic reaction precluding further treatment. The overall response rate to any chemotherapy was 3/15 (20%, 95% CI 0.07-0.45), and the best overall response rate to chemotherapy with or without chest radiotherapy was 4/18 (22%, 95% CI 0.09-0.45). Median overall survival was 20 months (95% CI 0-51 months). CONCLUSIONS: Patients with typical and atypical pulmonary carcinoid tumors can respond to chemotherapy with or without chest radiotherapy, though with response rates that appear less than those of small cell lung cancers. Further characterization of pulmonary carcinoid tumors and study of treatment alternatives for unresectable disease is warranted.

http://annonc.oxfordjournals.org/content/13/4/614.abstract

Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumours.

Citation
Annals of Oncology, 2002, 13(4): 614-621.

Authors
Bajetta, E., Ferrari, L., Procopio, G., Catena, L., Ferrario, E., Matinetti, A., Di Bartolomeo, M.,

Buzzoni, R., Celio, L., Vitali, M., Beretta, E., Seregni, E., & Bombardieri, E.

Abstract
OBJECTIVES: Neuroendocrine tumours (NETs) are heterogeneous neoplasms for which there is no standard treatment. We have previously proposed an effective polychemotherapy (5-fluorouracil, dacarbazine and epirubicin), which only produced objective responses of brief duration. The present study aimed to assess in a multidisciplinary manner the efficacy of the same regimen at intensified doses in patients with advanced NETs. PATIENTS AND METHODS: Eighty-two consecutive patients entered the study, of whom 21 had inoperable, locally advanced disease and 61 had metastatic disease. Seventy-two patients were evaluated for objective, biochemical and subjective responses. Response rate, time to progression (TTP) and overall survival (OS) were evaluated based on histotype. RESULTS: An objective response was observed in 20 patients (intention-to-treat and standard analysis 24.4% and 27.8%, respectively). Complete biochemical and subjective responses were obtained in 25.1% and 38.9% of the cases. The median duration of treatment was 4 months and the objective responses had a median duration of 38 months. After a 60-month follow-up the median TTP and OS were 21 and 38 months, respectively. CONCLUSIONS: Our polychemotherapy regimen is effective, with long duration, and is well tolerated both for gastroenteropancreatic and lung NETs, as well as for tumours with a more aggressive clinical behaviour. The new WHO endocrine tumour histotyping, examining also the tumour biology, may give additional information for selecting patients to chemotherapy.

http://www.ncbi.nlm.nih.gov/pubmed/11571721

Treatment with cisplatin and etoposide in patients with neuroendocrine tumors.

Citation
Cancer, 2001, 92(5): 1101-1107.

Authors
Fjällskog, M.L., Granberg, D.P., Welin, S.L., Eriksson, C., Oberg, K.E., Janson, E.T., & Eriksson, B.K.

Abstract
BACKGROUND: Patients with malignant endocrine pancreatic tumors (EPTs) are responsive to combinations of chemotherapy with streptozotocin and 5-fluorouracil/doxorubicin, whereas patients with malignant carcinoids are not. For both categories of patients, alpha-interferon and/or somatostatin analogs can produce long-lasting responses. Cisplatin in combination with etoposide has been suggested to be effective in patients with malignant neuroendocrine carcinomas. The authors used this therapy as second-line or third-line treatment in patients with poorly differentiated and/or rapidly progressing disease. METHODS: Thirty-six patients with histopathologically verified malignant neuroendocrine tumors were included: Eighteen tumors were of foregut origin, of which 5 were atypical, and 15 tumors were EPTs, of which 4 were poorly differentiated endocrine carcinomas. Three tumors were of midgut origin. The median patient age was 47.5 years. The median duration of disease from the time of diagnosis was 12 months. All patients had metastatic disease. Thirty of 36 patients had received previous treatment. Etoposide was given at a dose of 100 mg/m(2) per day for 3 days, and cisplatin was given at a dose of 45 mg/m(2) on Days 2 and 3 as a continuous intravenous infusion that was repeated every 4 weeks. RESULTS: Ten of 18 patients with foregut carcinoids (56%) responded radiologically and/or biochemically, with a median duration of 9 months; and 7 of 14 patients with EPTs (50%) responded radiologically

and/or biochemically, with a median duration of 9 months. No difference in response was seen between patients with atypical or typical foregut carcinoids or between patients with well differentiated or poorly differentiated endocrine pancreatic carcinoma. Nineteen of 36 patients (53%) experienced World Health Organization (WHO) Grade 1-2 nephrotoxicity, and 23 patients (64%) suffered from WHO Grade 3-4 neutropenia. CONCLUSIONS: The combination of cisplatin and etoposide can produce significant responses in patients with heavily pretreated and poorly differentiated/rapidly progressing neuroendocrine tumors. The toxicity is considerable, and nephrotoxicity is the dose limiting factor.

http://www.ncbi.nlm.nih.gov/pubmed/9669822

5-Fluorouracil, dacarbazine, and epirubicin in the treatment of patients with neuroendocrine tumors.

Citation
Cancer, 1998, 83(2): 372-378.

Authors
Bajetta, E., Rimassa, L., Carnaghi, C., Seregni, E., Ferrari, L., Di Bartolomeo, M., Regalia, E., Cassata, A., Procopio, G., & Mariani, L.

Abstract

BACKGROUND: For patients with surgically untreatable neuroendocrine tumors (NETs), the optimal therapeutic approach remains undefined. Somatostatin analogs and interferons have failed to control neoplastic growth, and chemotherapy has been only moderately more effective. The authors' previous study of the combination of 5-fluorouracil (FU), dacarbazine (DTIC), and epirubicin (EPI) (the FDE regimen) documented good tolerability, but the results for tumor growth control were disappointing. In an attempt to improve these results, the authors conducted a preliminary trial of an intensified FDE regimen (FU 500 mg/m2 administered intravenously [i.v.], DTIC 200 mg/m2 i.v., and EPI 30 mg/m2 i.v. on Days 1, 2, and 3 every 3 weeks). METHODS: Thirty NET patients (15 male, 15 female; median age, 55 years; age range, 19-72 years) were enrolled, none of whom had previously been given chemotherapy. The histologic types of disease were gastroenteropancreatic (GEP) tumors (n = 21, 6 carcinoid tumors and 15 pancreatic NETs), other carcinoid tumors (n = 3), other NETs (n = 4), medullary thyroid carcinoma (MTC) (n = 1), and Merkel cell carcinoma (n = 1). Six patients had a syndrome related to endocrine hypersecretion. One hundred fifty-four therapy cycles were delivered (median, six per patient), and all patients could be evaluated for response on the basis of intent-to-treat analysis. RESULTS: There were 9 objective responses: 2 complete responses (in 1 patient with Merkel cell carcinoma and 1 with pancreatic NET) and 7 partial responses (in 3 patients with pancreatic NETs, 2 with other NETs, 1 with GEP carcinoid tumor, and 1 with MTC). The median duration of response was 10 months (range, 5+ to 24+ months). No reduction in symptoms was achieved among the six patients with endocrine hypersecretion syndrome. Levels of urinary 5-hydroxyindoleacetic acid and serum chromogranin A were decreased in 50% and 14% of patients, respectively, who presented with abnormal baseline values. Treatment toxicity was acceptable and included nausea and vomiting, alopecia, leukopenia, and mucositis. CONCLUSIONS: This trial demonstrated that the FDE regimen may be at least as effective as other systemic regimens. Comparison of this experience with the authors' previous trial revealed a noteworthy increase in the activity of the intensified regimen, especially in GEP NETs (the most chemoresistant tumors). Continued clinical research to improve these results is highly justified.

http://www.ncbi.nlm.nih.gov/pubmed/8111718

Phase II trial of dimethyltriazenoimidazole carboxamide in patients with metastatic carcinoid. A Southwest Oncology Group study.

Citation
Cancer, 1994, 73(5):1505-1508.

Authors
Bukowski, R.M., Tangen, C.M., Peterson, R.F., Taylor, S.A., Rinehart, J.J., Eyre, H.J., Rivkin, S.E., Fleming, T.R., & Macdonald, J.S.

Abstract
BACKGROUND: The use of chemotherapy in patients with metastatic carcinoid tumors has been of limited value, and investigation of new agents is necessary. Previous reports have suggested that dimethyltriazenoimidazole carboxamide (DTIC) may have antitumor activity. METHODS: A Phase II trial to investigate the clinical response rate to DTIC in patients with metastatic carcinoid tumors was performed. DTIC was administered at low (650 mg/m2) or high (850 mg/m2) doses every 28 days. RESULTS: Sixty-three patients were entered into the study, and 56 were evaluable for toxicity and response. Toxicity was moderate, with the most common side effect being nausea and vomiting (88%). Nine patients (16%; 95% confidence interval, 8-28%) had partial responses, 5 of 25 receiving 850 mg/m2 and 4 of 31 receiving 650 mg/m2 of DTIC. Median survival time of all patients was 20 months. CONCLUSIONS: DTIC has minimal activity in patients with metastatic carcinoid tumors.

INTERFERON

http://www.ncbi.nlm.nih.gov/pubmed/16798833

Interferon-alpha and somatostatin analog in patients with gastroenteropancreatic neuroendocrine carcinoma: single agent or combination?

Citation
Annals of Oncology, 2007, 18(1): 13-19.

Authors
Fazio, N., de Braud, F., Delle Fave, G., & Oberg, K.

Abstract
In most cases gastro-enteropancreatic neuroendocrine tumors grow slowly. Interferon-alpha and somatostatin analogs have shown symptomatic, biochemical, and, in a minority of cases, antiproliferative activity. Generally, they are proposed as single-agent therapy. However, based on in vitro and in vivo evidence, the combined use of these drugs was proposed in several non-randomized trials, indicating that there is an additive effect of the combination. Nevertheless, the three randomized trials published so far did not show a statistically significant survival benefit for the combination compared to the same agents alone, even though an advantage for the combination came out in all three studies. On the other hand, data from non-randomized trials would justify the sequential use of the two drugs or the combination after progression on single agent therapy. Therefore, at present the up-front combined use of interferon-alpha and somatostatin analog is not justified, whereas it could be

indicated after progression to single-agent therapy. Further larger, international, prospective, randomized, multicentric clinical trials studying homogeneous populations would be necessary to give a final answer, but the rarity and heterogeneity of this malignancy does not assure that it will be possible.

http://www.ncbi.nlm.nih.gov/pubmed/16426143

Efficacy and tolerability of pegylated IFN-alpha in patients with neuroendocrine gastroenteropancreatic carcinomas.

Citation
Journal of Interferon & Cytokine Research, 2006, 26(1): 8-13.

Authors

Pavel, M.E., Baum, U., Hahn, E.G., Schuppan, D., & Lohmann, T.

Abstract
Interferon-alpha (IFN-alpha) is well established in the treatment of neuroendocrine carcinomas (NEC). Treatment is accompanied by fatigue and flu-like symptoms. In patients with chronic hepatitis C, pegylated IFN (PEGIFN) leads to improved antiviral efficacy and good tolerability. Our aim was to assess the efficacy and tolerability of PEG-IFN on the management of patients with well-differentiated NEC of the gastroenteropancreatic system. In 17 patients, the effect of PEG-IFN-alpha2b was studied. After first-line octreotide treatment, IFN-alpha was added at the time of tumor progression. Six patients were switched from conventional IFN-alpha, and 11 patients were IFN naive. Inhibition of tumor growth, including stabilization of disease, occurred in 13 of 17 patients, and biochemical and symptomatic responses were seen in 7 of 10 patients with functionally active tumors. Tolerability of PEG-IFN-alpha2b was much better than that of IFN-alpha. Fatigue occurred in 59% of all patients but was mild in severity. Eleven of thirteen patients who had a benefit remained on therapy for a median time of 20 months (range 6-30 months). PEG-IFN-alpha2b provides symptomatic and antiproliferative efficacy in patients with NEC. Better tolerability of PEG-IFN-alpha2b improved patients' compliance, justifying its use in patients who do not tolerate conventional IFN-alpha treatment.

http://www.ncbi.nlm.nih.gov/pubmed/16397272

IFN-beta is a highly potent inhibitor of gastroenteropancreatic neuroendocrine tumor cell growth in vitro.

Citation
Cancer Research, 2006, 66(1): 554-562.

Authors
Vitale, G., de Herder, W.W., van Koetsveld, P.M., Waaijers, M., Schoordijk, W., Croze, E., Colao, A., Lamberts, S.W., & Hofland, L.J.

Abstract
IFN-alpha controls hormone secretion and symptoms in human gastroenteropancreatic neuroendocrine tumors (GEP-NET) but it rarely induces a measurable tumor size reduction. The effect of other type I IFNs, e.g., IFN-beta, has not been evaluated. We compared the antitumor effects of IFN-alpha and IFN-beta in BON cells, a functioning human GEP-NET cell line. As determined by quantitative reverse transcription-PCR analysis and

immunocytochemistry, BON cells expressed the active type I IFN receptor mRNA and protein (IFNAR-1 and IFNAR-2c subunits). After 3 and 6 days of treatment, IFN-beta significantly inhibited BON cell growth in a time- and dose-dependent manner. IC50 and maximal inhibitory effect on day 6 were 8 IU/mL and 98%, respectively. In contrast, the effect of IFN-alpha resulted significantly in a less potent effect (IC50: 44 IU/mL, maximal inhibition: 26%). IFN-alpha induced only cell cycle arrest, with an accumulation of the cells in S phase. IFN-beta, apart from a more potent delay in S-G2-M phase transit of the cell cycle, also induced a strong stimulation of apoptosis, evaluated by flow cytometry (Annexin V and 7-AAD) and measurement of the DNA fragmentation. Besides, only IFN-beta severely suppressed chromogranin A levels in the medium from BON cells after 6 days of treatment. In conclusion, IFN-beta is much more potent, compared with IFN-alpha, in its inhibitory effect on GEP-NET cell proliferation in vitro through the induction of apoptosis and cell cycle arrest. Further studies are required to establish whether IFN-beta has comparable potent tumor growth inhibitory effects in vivo.

http://www.ncbi.nlm.nih.gov/pubmed/16234004

Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial.

Citation
Clinical Gastroenterology & Hepatology, 2005, 3: 761-771.

Authors
Arnold, R., Rinke, A., Klose, K.J., Müller, H.H., Wied, M., Zamzow, K., Schmidt, C., Schade-Brittinger, C., Barth, P., Moll, R., Koller, M., Unterhalt, M., Hiddemann, W., Schmidt-Lauber, M., Pavel, M., & Arnold, C.M.

Abstract
BACKGROUND & AIMS: The effect of octreotide plus interferon-alpha versus octreotide monotherapy on the primary study end points of time to treatment failure (progression, death, stop of study treatment) and long-term survival was investigated in patients with progressive metastatic neuroendocrine foregut (mainly pancreatic) and midgut tumors. METHODS: One hundred nine of 125 registered patients were randomized starting in January 1995, and 105 patients (51 monotherapy, 54 combination treatment) were finally analyzed in March 2000. Tumor growth was assessed at 3-month intervals by computed tomography or magnetic resonance imaging. Long-term survival was studied up to April 2004 in all analyzed patients and in 9 patients not randomized because of stable disease. RESULTS: Partial tumor regression occurred in 2.9%, 1.9%, and 5.7% and stabilization of tumor growth in 44.8%, 27.6%, and 15.2% at 3, 6, and 12 months, respectively, with no significant differences between both treatment arms. In March 2000, 9.5% of patients were in treatment. Time to treatment failure and long-term survival did not differ significantly between the 2 groups, with a median survival of 32 and 54 months for the octreotide and the combination groups, respectively. Survival was longer in patients not randomized because of stable disease (median, 68 months) and in those with low nuclear Ki-67. A trend toward longer survival was shown for patients with slow spontaneous tumor growth before randomization. Patients responding to treatment lived longer than unresponsive patients. CONCLUSIONS: Combination treatment was not superior to monotherapy concerning progression-free and long-term survival. Patients responding to treatment and those with slow spontaneous tumor growth had a survival advantage.

http://www.carcinoid.org/medpro/docs/WiedenmIInterferonAlfaStudyGroup.pdf

Prospective, Randomized, Multicenter Trial on the Antiproliferative Effect of Lanreotide, Interferon Alfa, and Their Combination for Therapy of Metastatic Neuroendocrine Gastroenteropancreatic Tumors—The International Lanreotide and Interferon Alfa Study Group.

Citation
Journal of Clinical Oncology, 2003, 21(14): 2689-2696.

Authors
Siegbert F., Pape, U-F., Boehmig, M., Doerffel, Y., Mansmann, U., Golder, W., Riecken, E.O., & Wiedenmann, B.

Abstract
Purpose: Somatostatin analogs and interferon alfa control hormone-active/functional neuroendocrine gastroenteropancreatic tumors. In addition to hormonal control, variable degrees of antiproliferative effects for both agents have been reported. Until now, however, no prospective, randomized studies in therapy-naive patients have compared somatostatin analogs or interferon alfa alone with a combination of the two.
Methods*:* Eighty therapy-naive patients with histologically verified neuroendocrine tumor disease (primary localization: foregut, n 36; midgut, n 30; hindgut, n 3; unknown, n 11; functional, n 29; nonfunctional, n 51) were randomly treated either with lanreotide (1 mg three times a day administered subcutaneously [SC]) or interferon alfa (5 106 U three times a week SC) or both. All patients had disease progression in the 3 months before study entry, verified with imaging procedures.
Results*:* Twenty-five patients were treated with lanreotide, 27 patients were treated with interferon alfa, and 28 patients were treated with the combination. Partial tumor remission was seen in four patients (one patient who received lanreotide, one patient who received interferon alfa, and two patients who received the combination). During the 12 months of therapy, stable disease was observed in 19 patients (seven patients who received lanreotide, seven patients who received interferon alfa, and five patients who received the combination), whereas tumor progression occurred in 14 of 25 patients (lanreotide), 15 of 27 patients (interferon alfa), and 14 of 28 patients (combination). Side effects leading to an interruption of therapy were more frequent in the combination group than in the monotherapy arms.
Conclusion: This prospective, randomized, multicenter study shows for the first time that somatostatin analogs, interferon alfa, or the combination of the two had comparable antiproliferative effects in the treatment of metastatic neuroendocrine gastroenteropancreatic tumors. Response rates were lower compared with those published in previous, nonrandomized studies. The antiproliferative effect of the tested substances was similar for functional and nonfunctional neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/12808615.

Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours.

Citation
British Journal of Surgery, 2003, 90(6): 687-693.

Authors
Kölby, L., Persson, G., Franzén, A. & Ahrén, B.

Abstract
BACKGROUND: Midgut carcinoid tumours often present with widespread disease making curative surgery impossible. Medical treatment therefore plays a major role in the treatment

of these patients. METHODS: In this prospective randomized study, the effect of interferon (IFN) alpha on survival and risk of tumour progression was evaluated in 68 patients with midgut carcinoid tumours metastatic to the liver. All patients had undergone primary surgical treatment and hepatic arterial embolization of liver metastases before randomization. Patients were randomized to treatment with either octreotide alone (n = 35) or octreotide in combination with IFN-alpha (n = 33). RESULTS: Forty-one of the 68 patients died during a follow-up period of 33-120 months, equivalent to a 5-year survival rate of 46.5 per cent. There was no significant difference in survival between patients treated with octreotide alone (5-year survival rate 36.6 per cent) and those given octreotide in combination with IFN-alpha (56.8 per cent). However, patients treated with IFN-alpha had a significantly reduced risk of tumour progression during follow-up (P = 0.008). CONCLUSION: Addition of IFN-alpha to octreotide may retard tumour growth in patients with midgut carcinoid tumours.

http://www.ncbi.nlm.nih.gov/pubmed/1353693

The action of interferon alpha on human carcinoid tumours.

Citation
Seminars in Cancer Biology, 1992, 3(1): 35-41.

Authors
Oberg, K.

Abstract
The action of IFN-alpha has been studied in patients with carcinoid tumours. More than 300 patients have been treated with IFN-alpha for long periods of time (median 2.5 years). IFN-alpha exerts many pleiotrophic effects in carcinoid tumours. Antiproliferative effects are manifest mainly by a cell cycle block in GO-G1 phase and prolongation of the S-phase. Hormone synthesis is impaired with reduced circulating hormone levels after IFN-alpha therapy and the mechanism includes reduction of mRNA expression for various hormones. Induction in vitro of the nuclear enzyme 2'-5-A synthetase in tumour cells correlates with biochemical response and might account for reduced mRNA expression. IFN-alpha induces significantly increased intratumoral fibrosis in carcinoid metastases without significant changes in tumour size. Finally IFN-alpha causes alteration of the major histocompatibility complex (MHC) with increased expression of class I antigens on the tumour cells. The net result of all these effects of IFN-alpha is an antitumour effect in 70-80% of carcinoid tumour patients with biochemical control and abrogated tumour growth for extended periods of time. However, when IFN-alpha therapy is withdrawn tumour progression occurs within 3-9 months, indicating a controlling but not curing effect.

NOVEL TARGETED THERAPIES

OVERVIEW

http://annonc.oxfordjournals.org/content/18/8/1307.short
New drug development in digestive neuroendocrine tumors.

Citation
Annals of Oncology, 2007, 18(8): 1307-1313.
Authors

Duran, I., Salazar, R., Casanovas, O., Arrazubi, V., Vilar, E., Siu, L.L., Yao, J., & Taberno, J.

Abstract
The traditional cytotoxic agents are of limited efficacy in the treatment of neuroendocrine tumors of the gastrointestinal tract (NETs). Recent investigations have brought up a number of biological features in this family of neoplasms that could represent targets for anticancer treatment. NETs seem to have an extraordinary tumor vascularization with high expression of proangiogenic molecules such as the vascular endothelial growth factor along with overexpression of certain tyrosine kinase receptors such as the epidermal growth factor receptor (EGFR), the insulin growth factor receptor (IGFR) and their downstream signaling pathway components (PI3K-AKT-mTOR). The rationale of an antiangiogenic approach in the treatment of NETs and the use of other pharmacological strategies such as EGFR, IGFR and mammalian target of rapamycin inhibitors are discussed. Additionally, the emerging results of recent clinical trials with these targeted drugs are presented.

STUDIES

http://journals.lww.com/pancreasjournal/Citation/2010/03000/An_Open_Label,_Phase_II_Study_Evaluating_the.34.aspx

An Open-Label, Phase II Study Evaluating the Safety and Efficacy of PTK787/ZK222584 in Patients With Metastatic Neuroendocrine Tumors That Have Evidence of Progressive Disease or an Increase in Disease Related Syndrome Symptoms.

Citation
Pancreas, 2010, 39(2): 271

Authors
Anthony, L.B., , Chester, M.M., Brown, B.J., Michael, S.L., Seward, J., O'Dorisio, M.S., & O'Dorisio, T.M.

Abstract
Background: Vatalanib inhibits endothelial growth factor receptor (VEGFR) by binding to the intracellular kinase domain of all 3 VEGFRs. Neuroendocrine tumors (NETs) express VEGF receptors. Inhibiting VEGF with bevacizumab, sorafenib, and sunitinib reduced time to progression or tumor size in some NET patients (pts). To determine vatalanib's tolerability and efficacy in NET pts, a trial was performed. Methods: Eligibility criteria included NET pts with biopsy-proven metastatic disease and rising biomarkers on somatostatin analog therapy. Eligible pts had measurable lesions, a KPS 9 60%, and normal hematologic, renal, and hepatic functions. A stable octreotide LAR dose, not exceeding 30 mg monthly, was required. Initial total daily dosing of vatalanib was 1,250 mg. Biochemical responses within a 90 day interval were the primary response criteria. Secondary endpoints included radiographic/scintigraphic scan changes and safety. Results: Twenty-four pts (12 males)were enrolled between 5/20/05 to 5/28/09. The median age (range) was 60.4 (25Y74). Eighteen pts were evaluable for efficacy and safety. Four pts continue on therapy. One pt withdrew consent; 2 pts died of disease prior to first cycle initiation; 1 pt was allergic to vatalanib. Six pts required a 10Y28 day discontinuation for rising SGOT/SGPT, alkaline phosphatase, G2 proteinuria, G2 headache, and G3 nausea/vomiting. Resumption of vatalanib at 1,000 mg daily was well tolerated in 2 pts and 750 mg in another. One pt developed carcinoid crisis with fever,

flushing, and rising 5HIAA. Grade 1 nausea occurred in 15 pts with antiemetics required for 4 pts. A partial (9 50% decrease) biochemical response occurred in 4 pts. The observed radiographic and scintigraphic responses in 16 pts have shown progressive disease in 6 and stable/minimal response in 10 pts. Accrual continues. Conclusions: Vatalanib is well tolerated in most pts and results in a 24% biochemical partial response rate in NET pts with rising biochemical markers on somatostatin analog therapy.

http://jco.ascopubs.org/cgi/content/abstract/28/1/69

Daily Oral Everolimus Activity in Patients With Metastatic Pancreatic Neuroendocrine Tumors After Failure of Cytotoxic Chemotherapy: A Phase II Trial.

Citation

Journal of Clinical Oncology, 2010, 28(1): 69-76.

Authors

Yao, J.C., Lombard-Bohas, C., Baudin, E., Kvols, L.K., Rougier, P., Ruszniewski, P., Hoosen, S., St. Peter, J., Haas, T., Lebwohl, D., Van Cutsem, E., Kulke, M.H., Hobday, T.J., O'Dorisio, T.M., Shah, M.H., Cadiot, G., Luppi, G., Posey, J.A., & Wiedenmann, B.

Abstract

PURPOSE No established treatment exists for pancreatic neuroendocrine tumor (NET) progression after failure of chemotherapy. Everolimus (RAD001), an oral inhibitor of mammalian target of rapamycin, in combination with octreotide has demonstrated encouraging antitumor activity in patients with NETs. PATIENTS AND METHODS This open-label, phase II study assessed the clinical activity of everolimus in patients with metastatic pancreatic NETs who experienced progression on or after chemotherapy. Patients were stratified by prior octreotide therapy (stratum 1: everolimus 10 mg/d, n = 115; stratum 2: everolimus 10 mg/d plus octreotide long-acting release [LAR], n = 45). Tumor assessments (using Response Evaluation Criteria in Solid Tumors) were performed every 3 months. Chromogranin A (CgA) and neuron-specific enolase (NSE) were assessed monthly if elevated at baseline. Trough concentrations of everolimus and octreotide were assessed. Results By central radiology review, in stratum 1, there were 11 partial responses (9.6%), 78 patients (67.8%) with stable disease (SD), and 16 patients (13.9%) with progressive disease; median progression-free survival (PFS) was 9.7 months. In stratum 2, there were two partial responses (4.4%), 36 patients (80%) with SD, and no patients with progressive disease; median PFS was 16.7 months. Patients with an early CgA or NSE response had a longer PFS compared with patients without an early response. Coadministration of octreotide LAR and everolimus did not impact exposure to either drug. Most adverse events were mild to moderate and were consistent with those previously seen with everolimus. CONCLUSION Daily everolimus, with or without concomitant octreotide LAR, demonstrates antitumor activity as measured by objective response rate and PFS and is well tolerated in patients with advanced pancreatic NETs after failure of prior systemic chemotherapy.

http://www.ncbi.nlm.nih.gov/pubmed/20150630

The cytotoxic agents NSC-95397, brefeldin A, bortezomib and sanguinarine induce apoptosis in neuroendocrine tumors in vitro.

Citation

Anticancer Research, 2010, 30(1): 149-156.

Authors

Larsson, D.E., Wickström, M., Oberg, K., & Granberg, D.

Abstract

The aim of this study was to investigate the apoptosis resulting from NSC 95397, brefeldin A, bortezomib and sanguinarine in neuroendocrine tumor cell lines. MATERIALS AND METHODS: A multiparametric high-content screening assay for measurement of apoptosis was used. The human pancreatic carcinoid cell line, BON-1, human typical bronchial carcinoid cell line NCI-H727 and the human atypical bronchial carcinoid cell line NCI-H720 were tested. After incubation with cytotoxic drugs, the DNA-binding dye Hoechst 33342, fluorescein-tagged probes that covalently bind active caspase-3 and chloromethyl-X-rosamine to detect mitochondrial membrane potential were added. Image acquisition and quantitative measurement of fluorescence was performed using automated image capture and analysis instrument ArrayScan. In addition, nuclear morphology was examined on microscopic slides stained with May-Grunewald-Giemsa. RESULTS: A time- and dose-dependent activation of caspase-3 and increase in nuclear fragmentation and condensation were observed for the drugs using a multiparametric apoptosis assay. These results were confirmed with nuclear morphological examination on microscopic slides. CONCLUSION: NSC 95397, brefeldin A, bortezomib and sanguinarine induced caspase-3 activation with modest changes in nuclear morphology.

http://www.ncbi.nlm.nih.gov/pubmed/20389030

VEGF Secretion by Neuroendocrine Tumor Cells Is Inhibited by Octreotide and by Inhibitors of the PI3K/AKT/mTOR Pathway.

Citation
Neuroendocrinology, 2010, 91(3): 268-278.

Authors
Villaume, K., Blanc, M., Gouysse, G., Walter, T., Couderc, C., Nejjari, M., Vercherat, C., Cordier-Bussat, M., Roche, C., & Scoazec, J.Y.

Abstract

Gastroenteropancreatic (GEP) endocrine tumors are hypervascular tumors able to synthesize and secrete high amounts of VEGF. We aimed to study the regulation of VEGF production in GEP endocrine tumors and to test whether some of the drugs currently used in their treatment, such as so- matostatin analogues and mTOR inhibitors, may interfere with VEGF secretion. We therefore analyzed the effects of the somatostatin analogue octreotide, the mTOR inhibitor rapamycin, the PI3K inhibitor LY294002, the MEK1 inhibitor PD98059 and the p38 inhibitor SB203850 on VEGF secretion, assessed by ELISA and Western blotting, in three murine endocrine cell lines, STC-1, INS-r3 and INS-r9. Octreotide and rapamycin induced a significant decrease in VEGF production by all three cell lines; LY294002 significantly inhibited VEGF production by STC-1 and INS-r3 only. We detected no effect of PD98059 whereas SB203850 significantly inhibited VEGF secretion in INS-r3 and INS-r9 cells only. By Western blotting analysis, we observed decreased intracellular levels of VEGF and HIF-1alpha under octreotide, rapamycin and LY294002. For rapamycin and LY294002, this effect was likely mediated by the inhibition of the mTOR/HIF-1/VEGF pathway. In addition to its well-known anti-secretory effects, octreotide may also act through the inhibition of the PI3K/Akt pathway, as suggested by the decrease in Akt phosphorylation detected in all three cell lines. In conclusion, our study points out to the complex regulation of VEGF synthesis and secretion in neoplastic GEP endocrine cells and suggests that the inhibition of VEGF production by octreotide and rapamycin may contribute to their therapeutic effects.

http://www.ncbi.nlm.nih.gov/pubmed/19923785

ZM447439, a novel promising aurora kinase inhibitor, provokes antiproliferative and proapoptotic effects alone and in combination with bio- and chemotherapeutic agents in gastroenteropancreatic neuroendocrine tumor cell lines.

Citation
Neuroendocrinology, 2010, 91(2): 121-130.

Authors
Georgieva, I., Koychev, D., Wang, Y., Holstein, J., Hopfenmüller, W., Zeitz, M., & Grabowski, P.

Abstract
Background: Therapeutic approaches to gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are still not satisfactory. A new direction in treatment options could be the novel aurora kinase inhibitor ZM447439, which was previously reported to interfere with the mitotic spindle integrity checkpoint and chromosome segregation, but does not interfere with other kinases when used up to 5 muM. Methods: We evaluated the antineoplastic effects of ZM447439 on growth and apoptosis of the GEP-NET cell lines BON, QGP-1 and MIP-101, representing the different malignant tumor types, using standard cell biological tests as crystal violet assays, caspase activation, DNA fragmentation and cell cycle analysis. Results: ZM447439 dose-dependently inhibited proliferation of all three cell lines with IC(50) values in the nanomolar to low micromolar range. Moreover, aurora kinase inhibition by ZM447439 potently induced apoptosis, which was accompanied by DNA fragmentation and caspase 3 and 7 activation. Furthermore, we observed cell cycle arrest at G(0)/G(1) phase as well as a block in G(2)/M transition. In addition, combined treatment with the chemotherapeutic agents streptozocin and cisplatin augmented significantly the antiproliferative effects of those agents. Conclusion: Aurora kinase inhibition by ZM447439 seems to be a promising new therapeutic approach in GEP-NETs, which should be evaluated in further clinical trials.

http://www.lexicon-genetics.com/pipeline/lx1032.html

LX1032 : A Novel Agent to Reduce Peripheral Serotonin as a Potential Treatment for Carcinoid Syndrome.

Citation
Pancreas, 2010, 39(2): 272

Authors
Brown,P., Frazier, K.S., Jackson, S., Turnage, A., Heydorn, W.E., Yang, Q., Lamanchili, P., & Liu, Q.

Abstract
LX1032 is a novel, orally delivered, inhibitor of tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of serotonin (5-HT). Elevated 5-HT is a hallmark finding in carcinoid tumors, and in advanced forms of the disease 5-HT is thought to contribute to symptoms associated with carcinoid syndrome (CS), including diarrhea, abdominal pain and cramping, as well as longerterm disease sequelae such as mesenteric and cardiac fibrosis. In advanced tumors, morbidity and mortality relate as much to the secretion of 5-HT and

peptide hormones, as to tumor growth and metastasis. In humans, as well as in other mammals, there are two distinct TPH genes that encode two isoforms of TPH:(1-3) TPH1, found predominantly in the enterochromaffin (EC) cells of the GI tract, and TPH2, which is expressed in neuronal cell types and is the predominant isoform in the brain. The vast majority (95%) of 5-HT is produced in the periphery, principally by EC cells. Prior experience in the 1960's with another TPH inhibitor, para-chlorophenylalanine (pCPA), illustrated that reduction in 5-HT synthesis could provide a significant improvement in symptoms of patients with CS.4 Further development of pCPA was ultimately curtailed because it crossed the blood-brain-barrier, resulting in depletion of brain 5-HT and subsequent neuro-psychiatric side effects such as depression. We therefore developed an agent capable of inhibiting 5-HT production in the periphery without affecting brain 5-HT production that could potentially exert a therapeutic effect on multiple CS symptoms without causing undesired effects in the CNS. Consistent with this approach *Tph1* knockout mice, which have almost no intestinal 5-HT but normal levels of brain 5-HT (Figure 1), displayed no abnormalities in any neurobehavioral screens. In preclinical studies, LX1032 was shown to reduce peripheral 5-HT in a dose-dependent fashion without affecting brain 5-HT, recapitulating the *Tph1* knockout mouse phenotype (Figure 2). These important preclinical observations have now translated into favorable results in Phase 1 clinical studies involving 87 normal healthy volunteers. In Phase 1 studies, LX1032 was well tolerated and produced a reduction in peripheral 5-HT levels, suggesting that LX1032 may provide a new approach for the management of many of the symptoms and morbidity experienced by patients with CS, by altering peripheral 5-HT levels without impacting brain 5-HT.

http://www.ncbi.nlm.nih.gov/pubmed/19381631

Combination analyses of anti-cancer drugs on human neuroendocrine tumor cell lines.

Citation
Cancer Chemotherapy & Pharmacology, 2009, 65(1): 5-12 .

Authors
Larsson, D.E., Hassan, S., Larsson, R., Oberg, K., & Granberg, D.

Abstract

PURPOSE: There is a large need for better pharmacological treatment of neuroendocrine tumors. The aim of this study was to investigate and quantify the cytotoxic potentiating effects resulting from a combination of five substances, NSC 95397, emetine, CGP-74514A hydrochloride, Brefeldin A and sanguinarine chloride, chosen from a previous screening of 1,280 pharmacologically active agents on neuroendocrine tumor cells, with standard cytotoxic agents currently used in the treatment of neuroendocrine tumors. METHOD: The human pancreatic carcinoid cell line BON-1, human typical bronchial carcinoid cell line NCI-H727 and the human atypical bronchial carcinoid cell line NCI-H720 were used. Combinations between doxorubicin, etoposide, oxaliplatin, docetaxel, and each one of the five agents were studied and simultaneous exposures were explored using the median-effect method. RESULTS: Most of the combinations of NSC-95397 and emetine with doxorubicin, etoposide, docetaxel, and oxaliplatin showed synergism, and their remaining combinations were additive. Almost all of the CGP-74514A hydrochloride interactions were additive, while brefeldin A and sanguinarine displayed less synergy but more additive and antagonistic interactions in combination with the standard drugs. CONCLUSION: The synergistic and additive interactions make NSC-95397, emetine, and CGP-74514A hydrochloride potential candidates for incorporation into combination chemotherapy regimens and these drugs might be the

suitable candidates for further clinical studies in patients with bronchial carcinoids and pancreatic endocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/19030935

Combination therapy with histone deacetylase inhibitors and lithium chloride: a novel treatment for carcinoid tumors.

Citation

Annals of Surgical Oncology, 2009, 16(2): 481-486.

Authors

Adler, J.T., Hottinger, D.G., Kunnimalaiyaan, M., & Chen H.

Abstract

In carcinoid cell lines, the histone deacetylase (HDAC) inhibitors valproic acid (VPA) and suberoyl bis-hydroxamic acid (SBHA) activate the Notch1 pathway, whereas lithium inhibits glycogen synthase kinase-3beta (GSK-3beta). These compounds limit growth and decrease hormonal secretion in vitro. We hypothesized that lower-dose combination therapy of HDAC inhibitors and lithium chloride could achieve similar growth inhibition to that of the drugs alone. Gastrointestinal and pulmonary carcinoid cells were treated with either VPA or SBHA and lithium chloride for up to 48 hours. Western blot analysis was used to measure the effects on the Notch1 and GSK-3beta pathways and the neuroendocrine tumor marker chromogranin A (CgA). Growth was measured by a cellular proliferation assay. With lower-dose combination therapy, a decrease in CgA was observed. The HDAC inhibitors increased the amount of active Notch1 protein, whereas treatment with lithium was associated with inhibition of GSK-3beta. Moreover, growth was inhibited with lower-dose combination therapy. Treatment of carcinoid cells with either VPA or SBHA and lithium chloride suppresses the neuroendocrine marker CgA while upregulating Notch1 and inhibiting GSK-3beta. This combination effectively reduces growth. Thus, lower-dose combination therapy may be a viable therapeutic approach for carcinoid tumors.

http://www.ncbi.nlm.nih.gov/pubmed/18612155

Activity of sunitinib in patients with advanced neuroendocrine tumors.

Citation

Journal of Clinical Oncology, 2008, 26(20): 3403-3410.

Authors

Kulke, M.H., Lenz, H.J., Meropol, N.J., Posey, J., ryan, D.P., Picus, J., Bergsland, E., Stuart, K., Tye, L., Huang, X., Li, J.Z., Baum, C.M., & Fuchs, C.S.

Abstract

PURPOSE: Standard cytotoxic chemotherapy has limited efficacy in metastatic neuroendocrine tumor patients. Neuroendocrine tumors express vascular endothelial growth factor (VEGF) and its receptor (VEGFR). Sunitinib malate, an oral tyrosine kinase inhibitor, has activity against VEGFRs as well as platelet-derived growth factor receptors, stem-cell factor receptor, glial cell line-derived neurotrophic factor, and FMS-like tyrosine kinase-3. We evaluated the efficacy of sunitinib in a two-cohort, phase II study of advanced carcinoid and pancreatic neuroendocrine tumor patients. PATIENTS AND METHODS: Patients were treated with repeated 6-week cycles of oral sunitinib (50 mg/d for 4 weeks, followed by 2 weeks off treatment). Patients were observed for response, survival, and adverse events. Patient-reported outcomes were assessed. RESULTS: Among 109 enrolled patients, 107 received sunitinib (carcinoid, n = 41; pancreatic endocrine tumor, n = 66). Overall objective response rate (ORR) in pancreatic endocrine tumor patients was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease (SD). Among carcinoid patients, ORR was

2.4% (one of 41 patients), and 83% (34 of 41 patients) had SD. Median time to tumor progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients. One-year survival rate was 81.1% in pancreatic neuroendocrine tumor patients and 83.4% in carcinoid patients. No significant differences from baseline in patient-reported quality of life or fatigue were observed during treatment. CONCLUSION: Sunitinib has antitumor activity in pancreatic neuroendocrine tumors; its activity against carcinoid tumors could not be definitively determined in this nonrandomized study. Randomized trials of sunitinib in patients with neuroendocrine tumors are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/18323556

Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b.

Citation
Journal of Clinical Oncology, 2008, 26(8): 1316-1323.

Authors
Yao, J.C., Phan, A., Hoff, P.M., Chen, H.X., Charsangavej, C., Yeung, S.C., Hess, K., Ng., C., Abbruzzese, J.L., & Ajani, J.A.

Abstract
PURPOSE: Effective systemic therapy for advanced carcinoid is lacking. The combination of bevacizumab (BEV) and pegylated (PEG) interferon alpha-2b was evaluated among patients with metastatic or unresectable carcinoid tumors. PATIENTS AND METHODS: Forty-four patients on stable doses of octreotide were randomly assigned to 18 weeks of treatment with bevacizumab or PEG interferon alpha-2b. At disease progression (PD) or at the end of 18 weeks (whichever occurred earlier), patients received bevacizumab plus PEG interferon until progression. Functional computer tomography (CT) scans were performed to measure effect on tumor blood flow. RESULTS: In the bevacizumab arm, four patients (18%) achieved confirmed partial response (PR), 17 patients (77%) had stable disease (SD), and one patient (5%) had PD. In the PEG interferon arm, 15 patients (68%) had SD and six patients (27%) had PD. Progression-free survival (PFS) rates after 18 weeks of monotherapy were 95% in bevacizumab versus 68% on the PEG interferon arm. The overall median PFS for all 44 patients is 63 weeks. Compared with paired baseline measurements on functional CT scans, we observed a 49% ($P < .01$) and 28% ($P < .01$) decrease in tumor blood flow at day 2 and week 18 among patients treated with bevacizumab. No significant changes in tumor blood flow were observed following PEG interferon. PEG interferon alpha-2b treatment was associated with decrease in plasma basic fibroblast growth factor (bFGF; $P = .04$) and increase in plasma interleukin-18 (IL-18; $P < .01$). No significant changes in bFGF or IL-18 following treatment with bevacizumab were observed. CONCLUSION: Bevacizumab therapy resulted in objective responses, reduction of tumor blood flow, and longer PFS in patients with carcinoid than PEG interferon treatment.

http://www.ncbi.nlm.nih.gov/pubmed/18310292
Antitumor activity of rapamycin and octreotide as single agents or in combination in neuroendocrine tumors.
Citation
Endocrine-Related Cancer, 2008, 15(1): 257-266.

Authors
Moreno, A., Akcakanat, A., Munsell, M.F., Soni, A., Yao, J.C., & Meric-Bernstam, F.
Abstract
The mammalian target of rapamycin (mTOR) signaling pathway has emerged as a promising target for cancer therapy. Rapamycin inhibits mTOR activity but induces upstream signaling, leading to Akt activation, potentially limiting antitumor activity. Octreotide, a somatostatin analog, decreases phosphatidylinositol-3-kinase/Akt signaling in some models, and thus theoretically may enhance rapamycin's antitumor activity. The aim of this study was to determine the antitumor activity of rapamycin and octreotide as single agents and in combination in neuroendocrine tumors. In carcinoid cell lines BON-1 and NCI-H727, cell proliferation was significantly inhibited by rapamycin in vitro, although rapamycin treatment did lead to Akt phosphorylation. Octreotide had limited antiproliferative effects alone, and did not demonstrate synergistic or additive interactions with rapamycin. Furthermore, octreotide did not overcome rapamycin-induced Akt phosphorylation. In vivo, rapamycin alone caused significant tumor suppression. Octreotide alone did not inhibit in vivo tumor growth and did not enhance rapamycin-mediated growth inhibition. In conclusion, rapamycin causes significant growth inhibition in carcinoid tumor cell lines in vitro and in vivo, thus mTOR is a promising therapeutic target for neuroendocrine tumors. Octreotide does not enhance the efficacy of rapamycin's antiproliferative effects in the models tested, and does not inhibit rapamycin-mediated feedback activation of Akt. Further study is needed in order to determine whether octreotide or other somatostatin analogs enhance the efficacy of mTOR inhibitors in other models.

http://www.ncbi.nlm.nih.gov/pubmed/18224665
Inhibition of proliferation of small intestinal and bronchopulmonary neuroendocrine cell lines by using peptide analogs targeting receptors.
Citation
Cancer , 2008, 112(6): 1404-1414 .
Authors
Kidd, M., Schally, A.V., Pfranger, R., Malfertheiner, M.V., & Modlin, I.M.
Abstract
BACKGROUND: Currently, no consistently effective therapy is available to inhibit cell proliferation or metastasis of neuroendocrine tumor (NET) disease. The effects of 4 novel peptides were analyzed: a targeted cytotoxic analog of luteinizing hormone-releasing hormone (LH-RH) analog (AN-152), a targeted cytotoxic analog of somatostatin (AN-238), and 2 antagonists of growth hormone-releasing hormone (GH-RH) on 3 NET (carcinoid) cell lines that expressed respective peptide receptors. METHODS: The effects of the compounds were evaluated on cell proliferation in vitro using MTT uptake and Ki67 expression, apoptosis (caspase 3 expression and activity), and cell cycle parameters (DNA distribution). RESULTS: Proliferation of the LH-RH receptor-expressing lung NET, NCI-H720 line, was inhibited 2-fold by AN-152 containing doxorubicin compared with the chemotherapy alone (IC50 of 9.1 nM vs 24 nM). This was associated with a reduction in Ki67 transcript and an increase in both caspase 3 mRNA levels and activity. Proliferation of the GH-RH receptor expressing lung NET, NCI-H727 line, was inhibited by both GH-RH antagonists, the effects being mediated through changes in Ki67 expression, but not in caspase 3-mediated apoptosis. The small intestinal NET, KRJ-I line, was 8x more sensitive to inhibition by AN-238 than to 2-pyrolino-doxorubicin, reflected by increased caspase 3 transcript as well as activity. AN-238-mediated growth inhibition culminated in complete G1 arrest. CONCLUSIONS: The data demonstrate GH-RH antagonists or peptide-linked antineoplastic agents such as AN-152 and AN-238 are

effective inhibitors of NET proliferation in vitro. Because peptide receptors such as those for GH-RH, LH-RH, and SST subtypes are commonly expressed by NETs, the development of antineoplastic agents targeted to specific tumor receptors may provide a more efficacious strategy than systemic chemotherapeutic agents currently in use.

http://www.ncbi.nlm.nih.gov/pubmed/18779618

Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study.

Citation

Journal of Clinical Oncology, 2008, 26(26): 4311-4318.

Authors

Yao, J.C., Phan, A.T., Chang, D.Z., Wolff, R.A., Hess, K., Gupta, S., Jacobs, C., Mares, J.E., Landgraf, A.N., Rashid, A., & Meric-Berstram, F.

Abstract

PURPOSE: Evaluate the activity of everolimus (RAD001) in combination with octreotide long-acting repeatable (LAR) in patients with advanced low- to intermediate-grade neuroendocrine tumors. METHODS: Treatment consisted of RAD001 5 mg/d (30 patients) or 10 mg/d (30 patients) and octreotide LAR 30 mg every 28 days. Thirty carcinoid and 30 islet cell patients were enrolled. RESULTS: Intent-to-treat response rate was 20%. Per protocol, there were 13 with partial responses (22%), 42 with stable disease (SD; 70%), and five patients with progressive disease (8%). Overall median progression-free survival (PFS) was 60 weeks. Median PFS for patients with known SD at entry was longer than for those who had progressive disease (74 v 50 weeks; P < .01). Median overall survival has not been reached. One-, 2-, and 3-year survival rates were 83%, 81%, and 78%, respectively. Among 37 patients with elevated chromogranin A, 26 (70%) achieved normalization or more than 50% reduction. Most common toxicity was mild aphthous ulceration. Grade 3/4 toxicities occurring in >or= 10% of patients included hypophosphatemia (11%), fatigue (11%), and diarrhea (11%). Treatment was associated with a dose-dependent rise in lactate dehydrogenase (LDH). Those with lower than 109 U/L rise in LDH at week 4 had shorter PFS (38 v 69 weeks; P = .01). Treatment was also associated with a decrease in proliferation marker Ki-67 among patients who underwent optional paired pre- and post-treatment biopsy (P = .04). CONCLUSION: RAD001 at 5 or 10 mg/d was well tolerated in combination with octreotide LAR, with promising antitumor activity. Confirmatory studies are ongoing.

http://clincancerres.aacrjournals.org/content/13/1/234.abstract

Clinical and In vitro Studies of Imatinib in Advanced Carcinoid Tumors.

Citation

Clinical Cancer Research, 2007, 13; 234

Authors

Yao, J.C., Zhang, J.X., Rashid, A., Yeung, S.J., Szklaruk, J., Hess, K., Ellis, L., Abbruzzese, J.L., & Ajani, J.A.

Abstract

PURPOSE: Effective systemic therapy options for carcinoid tumors are lacking. We conducted in vitro studies and a phase II clinical trial to explore the activity of imatinib in carcinoid tumors. EXPERIMENTAL DESIGN: Cells of the human bronchial carcinoid cell line NCI-H727 and the human pancreatic carcinoid cell line BON-1 were treated with increasing

concentrations of imatinib using standard procedures to assess in vitro growth-inhibitory activity. A clinical trial using a two-stage phase II design to assess the response rate and safety profile of imatinib at a dose of 400 mg given twice daily in patients with advanced carcinoid tumors was completed. RESULTS: In both cell lines, there was a dose- and time-dependent cytotoxic effect. The clinical trial enrolled 27 evaluable patients. Median duration on trial was 16 weeks. One patient had a partial response, 17 had stable disease, and 9 had progressive disease by the Response Evaluation Criteria in Solid Tumors criteria. Median progression-free survival time was 24 weeks. Median overall survival is 36 months. Seven patients who achieved a biochemical response had a superior progression-free survival time compared with patients without biochemical response (115 weeks compared with 24 weeks; P = 0.003). An increase in plasma basic fibroblast growth factor was associated with a shorter progression-free survival duration (P = 0.02). CONCLUSIONS: Our data suggest that imatinib is active in vitro and has a modest clinical activity in carcinoid patients. Changes in tumor markers may help select patients who are likely to benefit from therapy.

http://www.asco.org/ASCOv2/Meetings/Abstracts?

MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): a Phase II Consortium (P2C) study.

Citation

Journal of Clinical Oncology, 2007, 25 (18S): 4504.

Authors

Hobday, T. J., Rubin, J., Holen, K., Picus, J., Donehower, R., Marschke, R., Maples, W., Lloyd, R., Mahoney, M,. & Erlichman, C.

Abstract

Background: Treatment options for metastatic NET, including islet cell carcinoma (ICC) and carcinoid tumor (CT), are limited. These tumors frequently express vascular endothelial growth factor receptor-2 (VEGFR-2) and platelet derived growth factor receptor receptor-β (PDGFR-β). Sorafenib, a small-molecule inhibitor of the VEGFR-2 and PDGFR-β tyrosine kinase domains, is a rational targeted therapy to evaluate in NET. Methods: Eligibility criteria included: ECOG PS = 2, = 1 prior chemotherapy, good organ function and signed informed consent. Prior interferon and prior or concurrent octreotide at a stable dose were allowed. Pts unable to take oral medications, with uncontrolled hypertension or with symptomatic coronary artery disease were excluded. Pts received sorafenib 400 mg po BID. Primary endpoint was response by RECIST in two cohorts (ie, CT and ICC) using separate 2-stage phase II designs. Results: 93 pts were enrolled: (50 CT, 43 ICC). For pts evaluable for the primary endpoint, 4 of 41 (10%) CT pts and 4 of 41 (10%) ICC pts had a PR. There were 3 minor responses (MR = 20-29% decrease in sum of target lesion diameters) in CT pts and 9 MRs in ICC pts for PR+MR rate of 17% for CT pts and 32% for ICC pts. For pts evaluable, 6-month progression-free survival was observed in 8/20 CT and 14/23 ICC pts. Grade 3-4 toxicity occurred in 43% of pts, with skin (20%), GI (7%) and fatigue (9%) most common. Translational studies from tumor tissue will be presented. Conclusions: Sorafenib at 400 mg po BID has modest activity in metastatic neuroendocrine tumors, with frequent grade = 3 toxicity.

http://jco.ascopubs.org/cgi/content/abstract/24/3/401

Phase II Study of Temozolomide and Thalidomide in Patients With Metastatic Neuroendocrine Tumors

Citation

Journal of Clinical Oncology, 2006, 24(3): 401-406.

Authors

Kulke, M.H., Stuart, K., Enzinger, P.C., Ryan, D.P., Clark, J.W.,Muzikansky, A., Vincitore, M., Michelini, A., & Fuchs, C.S.

Abstract

PURPOSE: Standard, intravenous chemotherapy regimens for neuroendocrine tumors have been associated with limited response rates and significant toxicity. We evaluated the efficacy of an oral regimen of temozolomide and thalidomide in patients with metastatic carcinoid, pheochromocytoma, or pancreatic neuroendocrine tumors. PATIENTS AND METHODS: Twenty-nine patients were treated with a combination of temozolomide, administered at a dose of 150 mg/m2 for 7 days, every other week, and thalidomide at doses of 50 to 400 mg daily. Patients were followed for evidence of toxicity, biochemical response, radiologic response, and survival. RESULTS: Treatment with temozolomide and thalidomide was associated with an objective biochemical (chromogranin A) response rate of 40%, and a radiologic response rate of 25% (45% among pancreatic endocrine tumors, 33% among pheochromocytomas, and 7% among carcinoid tumors). The median duration of response was 13.5 months, 1-year survival was 79%, and 2-year survival was 61%. The median administered dose of temozolomide was 150 mg/m(2), and the median administered dose of thalidomide was 100 mg daily. Grade 3-4 toxicities were uncommon, with the exception of grade 3-4 lymphopenia, which developed in 69% of the patient population. Opportunistic infections occurred in three patients (10%) during the time of lymphopenia, and included single cases of Pneumocystis carinii pneumonia, disseminated varicella zoster virus, and herpes simplex virus. CONCLUSION: Orally administered temozolomide and thalidomide seems to be an active regimen for the treatment of neuroendocrine tumors. In this 29-patient study, this regimen appeared more active in pancreatic endocrine tumors than in carcinoid tumors.

http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/4044

A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors.

Citation
Journal of Clinical Oncology, 2006, 24(81S): 40-44.

Authors
Kulke, M.H., Stuart, K., Earle, C.C., Bhargava, P., Clark, J.W., Enzinger, P.C., Meyerhardt, M., Attawia, M., Lawrence, C., & Fuchs, C. S.

Abstract

Background**:** Inhibitors of the VEGF pathway have been shown to have activity in neuroendocrine tumors (NETs). Temozolomide (TMZ), an oral analog of dacarbazine is also active in this setting. We performed a prospective, phase II study to assess the safety and efficacy of TMZ, administered in combination with bevacizuamb, in patients (pts) with advanced NETs. Methods**:** Pts received TMZ, 150 mg/m^2/day po for 7 days every other week, and bevacizumab, 5 mg/kg IV every other week. Due to anticipated lymphopenia, pts received prophylaxis with trimethoprim/sulfamethoxazole (1 DS tablet q MWF) and acyclovir (400 mg po TID). Pts were followed for toxicity, response, and survival. Results: Enrolled patients (n=34) had the following characteristics: M:F = 19:15; median age 61 (range 37–75); ECOG PS 0/1/2 = 12/20/2; carcinoid/pancreatic NET = 16/18. Prior treatments included chemoembolization (n=7) chemotherapy (n=12); and octreotide (n=17); pts on octreotide

remained on octreotide at stable doses for the duration of the study. Pts had either well-differentiated tumors (n=27) or moderately/poorly-differentiated NETs (n=7); pts with small cell carcinoma were not eligible for the study. Pts have received treatment for a median of 22 weeks. Grade 3–4 toxicities included: lymphopenia (n=21, 62%), leukopenia (n=2, 6%), thrombocytopenia (n=7, 21%), neutropenia (n=2, 6%), hyponatremia (n=1, 3%), vomiting (n=3, 9%), nausea (n=2, 6%), dehydration (n=1, 3%), fatigue (n=2, 6%), constipation (n=1, 3%), and hypertension (n=1, 3%). 20 pts had elevated CGA levels (>36.4 ng/ml) at baseline; 0/9 (0%) carcinoid and 4/11 (36%) pancreatic NET experienced CGA decreases of >50% from baseline on two consecutive assessments. 29 pts are currently evaluable for radiologic response (Table). Conclusions: The combination of TMZ and bevacizumab can be safely administered and shows promising activity in pts with advanced pancreatic NETs. Additional studies with this combination are warranted.

http://jco.ascopubs.org/cgi/content/abstract/24/22/3555

Phase II Study of Recombinant Human Endostatin in Patients With Advanced Neuroendocrine Tumors.

Citation

Journal of Clinical Oncology, 2006, 24(22): 3555-3561.

Authors

Kulke, M.H., Bergsland, E.K., Ryan, D.P., Enzinger, P.C., Lynch, T.J., Zhu, A.X., Meyerhardt, J.A., Heymach, J.H., Fogler, W.E., Sidor, C., Michelini, A., Kinsella, K., Venook, A.P., & Fuchs, C.S.

Abstract

PURPOSE: Endostatin is a 20-kd proteolytic fragment of collagen XVIII that, in preclinical studies, has been shown to have antiangiogenic and antitumor activity. Both preclinical and human phase I studies of recombinant human endostatin (rhEndostatin) suggested activity in neuroendocrine tumors, which are known to be hypervascular. We therefore performed a multicenter phase II study of rhEndostatin in patients with carcinoid or pancreatic neuroendocrine tumors. PATIENTS AND METHODS: Forty-two patients with advanced pancreatic endocrine tumors or carcinoid tumors were treated with rhEndostatin administered as a bid subcutaneous injection at a starting dose of 60 mg/m2/d. Steady-state trough levels were obtained after 6 weeks of therapy; patients who did not achieve a target therapeutic level of 300 ng/mL underwent dose escalation to 90 mg/m2/d. Patients were observed for evidence of toxicity, response, and survival. RESULTS: rhEndostatin was associated with minimal toxicity. However, among 40 patients assessable for radiologic response, none experienced partial response to therapy, as defined by WHO criteria. The median steady-state trough level achieved after dose escalation was 331 ng/mL, within the postulated therapeutic range. CONCLUSION: Treatment with rhEndostatin did not result in significant tumor regression in patients with advanced neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360568/

A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas.

Citation

British Journal of Cancer, 2006, 95(9): 1148–1154.

Authors

Duran, I., Kortmansky, J., Singh, D, Hirte, H., Kocha, W., Goss, G., Le, L., Oza, A., Nicklee, T., Ho, J., Birel, D., Pond, G.R., Arboine, D., Dancey, J., Aviel-Ronen, S., Tsao, M-S., Hedley, D., & Siu, L.

Abstract
Standard cytotoxic treatments for neuroendocrine tumours have been associated with limited activity and remarkable toxicity. A phase II study was designed to evaluate the efficacy, safety and pharmacodynamics of temsirolimus in patients with advanced neuroendocrine carcinoma (NEC). Thirty-seven patients with advanced progressive NEC received intravenous weekly doses of 25 mg of temsirolimus. Patients were evaluated for tumour response, time to progression (TTP), overall survival (OS) and adverse events (AE). Twenty-two archival specimens, as well as 13 paired tumour biopsies obtained pretreatment and after 2 weeks of temsirolimus were assessed for potential predictive and correlative markers. The intent-to-treat response rate was 5.6% (95% CI 0.6–18.7%), median TTP 6 months and 1-year OS rate 71.5%. The most frequent drug-related AE of all grades as percentage of patients were: fatigue (78%), hyperglycaemia (69%) and rash/desquamation (64%). Temsirolimus effectively inhibited the phosphorylation of S6 (P=0.02). Higher baseline levels of pmTOR (phosphorylated mammalian target of rapamycin) (P=0.01) predicted for a better response. Increases in pAKT (P=0.041) and decreases in pmTOR (P=0.048) after treatment were associated with an increased TTP. Temsirolimus appears to have little activity and does not warrant further single-agent evaluation in advanced NEC. Pharmacodynamic analysis revealed effective mTOR pathway downregulation.

http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/4008

A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs).

Citation
Journal of Clinical Oncology, 2005, 23(16S): 4008.

Authors
Kulke, M., Lenz, H.J., Meropol, N.J., Posey, J., Ryan, D.P., Picus, J., Bergsland, E., Stuart, K., Baum, C.M., & Fuchs, C.S.

Abstract
Background: Standard cytotoxic chemotherapy has limited efficacy in pts with metastatic NETs. SU11248 is an oral multitargeted tyrosine kinase inhibitor with antiangiogenic and antitumor activity that specifically inhibits VEGFR, PDGFR, and c-KIT. NETs are known to be highly vascular, and both pancreatic NETs and carcinoid tumors have been shown to express high levels of both VEGF and VEGFR. In addition, evidence of clinical activity was seen in phase 1 studies. Methods: In this ongoing phase 2 study, pts with advanced, unresectable NETs were treated with repeated 6-wk cycles of SU11248, 50 mg po qd for 4 wks, followed by a 2-wk break. Treatment with prior cytotoxic chemotherapy was allowed, and pts receiving octreotide were allowed to continue treatment while on study. Pts were followed for adverse events, response, and overall survival. Pt-reported outcomes were compiled across four of the 6-week cycles using the EQ-5D and the FACIT-Fatigue subscale. Results: 106 pts were enrolled. Preliminary results are presented on 93 pts with the following characteristics: islet cell/carcinoid = 52/41; median age = 56 (range 32–81); M/F = 52/40; ECOG PS 0/1 = 50/41; prior systemic therapy: 53%; median days on treatment: 204 (range 26–543). Treatment-related toxicities were observed in 86 pts. Grade 3/4 toxicities included diarrhea (n=3, 3%), fatigue (n=23, 26%), glossodynia (n=3, 3%), nausea (n=6, 7%), neutropenia (n=12, 13%), thrombocytopenia (n=8, 9%), and vomiting (n=5, 6%). Other toxicities were infrequent. Response to therapy is shown in Table 1. There were no significant changes in quality of life

over the first four treatment cycles. Conclusions**:** SU11248 is well tolerated and is associated with modest RRs and a high level of SD when used as a single agent in pts with advanced unresectable NET. Additional studies to explore the clinical benefit of SU11248 in pts with NET are warranted.

http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=33446

Improved progression free survival (PFS), and rapid, sustained decrease in tumor perfusion among patients with advanced carcinoid treated with bevacizumab.

Citation
Journal of Clinical Oncology, 2005, 23 (16S, Part I): 4007.

Authors
Yao, J.C., Ng, C., Hoff, P.M., Phan, A.T., Hess, K., Chen, H., Wang, X., Abbruzzese, J.L. & Ajani, J.A .

Abstract
Background: Carcinoid is a vascular tumor that expresses VEGF. Effective systemic therapy for advanced disease is lacking. We are evaluating anti-angiogenic therapy in a phase II study of Bevacizumab (BVZ) and PEG Interferon alpha-2b (PEGI) in patients with metastatic or unresectable carcinoid tumors. Methods: Patients on a stable dose of octreotide were randomly assigned to therapy with BVZ or PEGI for 18 weeks. After 18 weeks, the patients receive both drugs. Functional CT was used to monitor changes in blood flow (BF), blood volume (BV), and permeability surface (PS). PFS durations, calculated by Kaplan Meier method, were compared by log rank test. Results: Planned accrual of 44 patients is complete. 41 (20 BVZ, 21 PEGI) have completed at least 9 weeks of therapy. 35 (18 BVZ, 17 PEGI) patients have completed 18 weeks of octreotide plus BVZ or PEGI. We have previously reported decreased in tumor perfusion within 48 hours of treatment with BVZ by functional CT (ASCO 2004 abstr # 3013). We now also reported sustained decrease in tumor perfusion at week 18 (21 days after the previous dose of bevacizumab). By RECIST criteria, 3 PR (3 BVZ, 0 PEGI), 31 SD (16 BVZ, 15 PEGI), 6 PD (1 BVZ, 5 PEGI) have been observed. An additional patient achieved PR on BVZ + PEGI following PD on PEGI alone. Twenty-two patients remain on study. PFS duration was superior in the BVZ arm (P=.01). PFS rates after 18 weeks of monotherapy were 95% in BVZ versus 67% in PEGI arm. During the 18 weeks of monotherapy, ≥ 50% reduction in 5HIAA was observed in 21% on BVZ and 43% on PEGI. Overall, 46% achieved ≥ 50% reduction in 5HIAA. Conclusions: BVZ therapy is associated with suppression of tumor blood flow and prolongation of PFS duration in carcinoid tumors. Addition of PEGI may help to control hormonal output in patients refractory to octreotide.

http://prod2.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=31122

Preliminary results of a phase II trial of gefitinib in progressive metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study.

Citation
Journal of Clinical Oncology, 2005, 23(16S, Part I): 4083.

Authors Hobday, T.J., Mahoney, M., Erlichman, C., Lloyd, R., Kim, G., Mulkerin, D., Picus, J., Fitch, T., & Donehower, R.

Abstract
Background: Metastatic NET (including islet cell carcinoma (ICC) and carcinoid tumors) are progressive in nature despite their indolent behavior. Systemic treatment options are limited. Immunohistochemichal (IHC) data suggest these tumors frequently express the epidermal growth factor receptor (EGFR). This suggests that EGFR mediated signaling may contribute to the growth of NET. Gefitinib is a small-molecule inhibitor of the EGFR tyrosine kinase domain. Methods: We evaluated 6 month progression-free survival (PFS) in two separate cohorts (ie, carcinoid and ICC) and using two separate Phase II trial designs. PFS rates at 6 months of 30% (carcinoid) and 10% (ICC) were considered promising. Importantly, objective radiologic progression by RECIST criteria was required for study entry. Other eligibility criteria included: ECOG PS ≤ 2, ≤ 1 prior chemotherapy, and good organ function. Prior or concurrent octreotide and prior interferon were allowed. Results: 37 patients (pts) were enrolled: (22 carcinoid, 15 ICC). There were 16, 20, and 1 patients with PS of 0, 1, and 2 respectively. Median age was 56 yrs (range 36-79). 14 of 22 (64%) pts with carcinoid tumors and 2 of 15 (13%) pts with ICC were progression-free at 6 months. No objective responses have been observed. Grade 3-4 toxicity (i.e. at least possibly related to gefinitib) was observed in 3 carcinoid pts including diarrhea (1), nausea (1), duodenal ulcer (1), anorexia (1), dehydration (1), fatigue (1), and rash (1);and 3 ICC pts including fatigue (1), hyperglycemia (1), and rash (1). IHC markers of the EGFR pathway on tumor tissue will be presented. Conclusion: Gefitinib can produce prolonged disease stabilization in pts with prior documented objective progression of carcinoid tumors and ICC. Further accrual to this multicenter P2C trial is ongoing.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

OVERVIEW

http://www.ncbi.nlm.nih.gov/pubmed/19590162

Targeted Radionuclide Therapy for Neuroendocrine Tumours: Principles and Application.

Citation
Neuroendocrinology, 2010, 91: 1-15.

Authors
Druce, M.R., Lewington, V., & Grossman, A.B.

Abstract
Neuroendocrine tumours comprise a group of neoplasms with variable clinical behaviour. Their growth and spread is often very slow and initially asymptomatic, and thus they are often metastatic at the time of diagnosis and incurable by surgery. An exciting therapeutic strategy for cytoreduction, both for stabilisation of tumour growth and inhibition of hormone production, is the use of targeted radionuclide therapy. Evidence from large-scale, randomised, placebo-controlled trials is very difficult to obtain in these rare diseases, but current data appear promising. It is timely to review the principles underlying the use of these therapies, together with the clinical outcomes to date and potential directions for future research.

STUDIES

http://www.ncbi.nlm.nih.gov/pubmed/20113677

Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors.

Citation
Seminars in Nuclear Medicine, 2010, 40(2): 78-88.

Authors
Kwekkeboom, D.J., de Herder, W.W., van Eijck, C.H., Kam, B.L., van Essen, M., Teunissen, J.J., & Krenning, E.P.

Abstract
Somatostatin receptor imaging with [(111)In-DTPA(0))octreotide has proven its role in the diagnosis and staging of gastroenteropancreatic neuroendocrine tumors. Treatment with radiolabeled somatostatin analogues is a promising new tool in the management of patients with inoperable or metastasized, well-differentiated neuroendocrine tumors. Symptomatic improvement may occur with all (111)In, (90)Y, or (177)Lu-labeled somatostatin analogues that have been used for peptide receptor radionuclide therapy. The results that were obtained with [(90)Y-DOTA(0), Tyr(3)]octreotide and [(177)Lu-DOTA(0), Tyr(3)]octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the median duration of the therapy response for these radiopharmaceuticals is 30 and 40 months, respectively. The patients' self-assessed quality of life increases significantly after treatment with [(177)Lu-DOTA(0), Tyr(3)]octreotate. Finally, compared with historical controls, there is a benefit in overall survival of several years from time of diagnosis in patients treated with [(177)Lu-DOTA(0), Tyr(3)]octreotate. These data compare favorably with the limited number of alternative treatment approaches. If more widespread use of peptide receptor radionuclide therapy can be guaranteed, such therapy may well become the therapy of first choice in patients with metastasized or inoperable gastroenteropancreatic neuroendocrine tumors.

http://www.ncbi.nlm.nih.gov/pubmed/18445841

Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival.

Citation
Journal of Clinical Oncology, 2008, 26(13): 2124-2130.

Authors
Kweekeboom, D.J., de Herder, W.W., Kam, B.L., van Eijck, Ch.H., van Hessen, M., Kooij, P.P., Feelders, R.A., van Aken, M.O., & Krenning, E.P.

Abstract
PURPOSE: Despite the fact that most gastroenteropancreatic neuroendocrine tumors (GEPNETs) are slow-growing, median overall survival (OS) in patients with liver metastases is 2 to 4 years. In metastatic disease, cytoreductive therapeutic options are limited. A relatively new therapy is peptide receptor radionuclide therapy with the radiolabeled somatostatin analog [(177)Lu-DOTA(0),Tyr(3)]octreotate. Here we report on the toxicity and efficacy of this treatment, performed in over 500 patients. PATIENTS AND METHODS: Patients were

treated up to a cumulative dose of 750 to 800 mCi (27.8-29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients, and efficacy analysis in 310 patients. RESULTS: Any hematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients, and temporary, nonfatal, liver toxicity in two patients. Complete and partial tumor remissions occurred in 2% and 28% of 310 GEPNET patients, respectively. Minor tumor response (decrease in size > 25% and < 50%) occurred in 16%. Median time to progression was 40 months. Median OS from start of treatment was 46 months, median OS from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis. CONCLUSION: Treatment with [(177)Lu-DOTA(0),Tyr(3)]octreotate has few adverse effects. Tumor response rates and progression-free survival compare favorably to the limited number of alternative treatment modalities. Compared with historical controls, there is a benefit in OS from time of diagnosis of several years.

http://www.ncbi.nlm.nih.gov/pubmed/18210106

Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate.

Citation
European Journal of Medical & Molecular Imaging, 2008, 35(4):749-755.

Authors
de Keizer, B., van Aken, M.O., Feelders, R.A., de Herder, W.W., Kam, B.L., van Essen, M., Krenning, E.P., & Kwekkeboom, D. J.

Abstract
INTRODUCTION: Receptor radionuclide therapy is a promising treatment modality for patients with neuroendocrine tumors for whom alternative treatments are limited. The aim of this study was to investigate the incidence of hormonal crises after therapy with the radiolabeled somatostatin analogue [(177)Lu-DOTA(0),Tyr(3)]octreotate ((177)Lu-octreotate). MATERIALS AND METHODS: All (177)Lu-octreotate treatments between January 2000 and January 2007 were investigated. Four hundred seventy-six patients with gastroenteropancreatic neuroendocrine tumors and three patients with metastatic pheochromocytoma were included for analysis. RESULTS: Four hundred seventy-nine patients received a total of 1,693 administrations of (177)Lu-octreotate. Six of 479 patients (1%) developed severe symptoms because of massive release of bioactive substances after the first cycle of (177)Lu-octreotate. One patient had a metastatic hormone-producing small intestinal carcinoid; two patients had metastatic, hormone-producing bronchial carcinoids; two patients had vasoactive intestinal polypeptide-producing pancreatic endocrine tumors (VIPomas); and one patient had a metastatic pheochromocytoma. With adequate treatment, all patients eventually recovered. CONCLUSION: Hormonal crises after (177)Lu-octreotate therapy occur in 1% of patients. Generally, (177)Lu-octreotate therapy is well tolerated.

http://www.ncbi.nlm.nih.gov/pubmed/17260141

Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin.

Citation

European Journal of Nuclear Medicine & Molecular Imaging, 2007, 34(8):1219-1227.

Authors
van Essen, M., Krenning, E.P., Bakker, W.H., de Herder, W.W., van Aken, M.O., & Kwekkeboom, D.J.

Abstract

PURPOSE: Foregut carcinoid tumours have a different embryological origin than other gastroenteropancreatic neuroendocrine tumours (GEP NETs). In the total group of GEP NETs (n = 131), treatment with (177)Lu-octreotate resulted in tumour remission in 47% of patients, with a median time to progression (TTP) of >36 months. As patients with foregut carcinoids may respond differently, we here present the effects of this treatment in a subgroup of patients with foregut carcinoids of bronchial, gastric or thymic origin. METHODS: Nine patients with bronchial, five with gastric and two with thymic carcinoids were treated. All patients had metastasised disease. The intended cumulative dose of (177)Lu-octreotate was 22.2-29.6 GBq. Southwest Oncology Group criteria were used for response evaluation. RESULTS: Bronchial carcinoids: Five patients had partial remission, one had minor response (MR, tumour size reduction: > or =25%, <50%), two had stable disease (SD) and one had progressive disease (PD). Median TTP was 31 months. Gastric carcinoids: One patient had complete remission, one had MR and two had SD, including one with PD at baseline. One patient developed PD. Thymic carcinoids: One patient had SD. In the other patient, disease remained progressive. All patients: Overall remission rate was 50%, including MR. CONCLUSION: (177)Lu-octreotate treatment can be effective in patients with bronchial and gastric carcinoids. Its role in thymic carcinoids cannot be determined yet because of the limited number of patients. The overall remission rate of 50% in patients with the studied foregut carcinoids is comparable to that in the total group of GEP NETs.

http://www.ncbi.nlm.nih.gov/pubmed/17653893

Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours.

Citation
Acta Oncologica., 2007, 46(6): 723-734.

Authors
Van Essen, M., Krenning, E.P., De Jong, M ., Valkema, R., & Kwekkeboom, D.J.

Abstract

Peptide Receptor Radionuclide Therapy (PRRT) with radiolabelled somatostatin analogues is a promising treatment option for patients with inoperable or metastasised neuroendocrine tumours. Symptomatic improvement may occur with all of the various (111)In, (90)Y, or (177)Lu-labelled somatostatin analogues that have been used. Since tumour size reduction was seldom achieved with (111)Indium labelled somatostatin analogues, radiolabelled somatostatin analogues with beta-emitting isotopes like (90)Y and (177)Lu were developed. Reported anti-tumour effects of [(90)Y-DOTA(0),Tyr(3)]octreotide vary considerably between various studies: Tumour regression of 50% or more was achieved in 9 to 33% (mean 22%). With [(177)Lu-DOTA(0),Tyr(3)]octreotate treatments, tumour regression of 50% or more was achieved in 28% of patients and tumour regression of 25 to 50% in 19% of patients, stable disease was demonstrated in 35% and progressive disease in 18%. Predictive factors for tumour remission were high tumour uptake on somatostatin receptor scintigraphy and

limited amount of liver metastases. The side-effects of PRRT are few and mostly mild, certainly when using renal protective agents: Serious side-effects like myelodysplastic syndrome or renal failure are rare. The median duration of the therapy response for [(90)Y-DOTA(0),Tyr(3)]octreotide and [(177)Lu-DOTA(0),Tyr(3)]octreotate is 30 months and more than 36 months respectively. Lastly, quality of life improves significantly after treatment with [(177)Lu-DOTA(0),Tyr(3)]octreotate. These data compare favourably with the limited number of alternative treatment approaches, like chemotherapy. If more widespread use of PRRT is possible, such therapy might become the therapy of first choice in patients with metastasised or inoperable gastroenteropancreatic neuroendocrine tumours. Also the role in somatostatin receptor expressing non-GEP tumours, like metastasised paraganglioma/pheochromocytoma and non-radioiodine-avid differentiated thyroid carcinoma might become more important.

http://www.ncbi.nlm.nih.gov/pubmed/1651723

Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors.

Citation
Seminars in Nuclear Medicine, 2006, 36(2): 147-156.

Authors
Valkema, R., Pauwels, S., Kvols, L.K., Barone, R., Jamar, F., Bakker, W.H., Kwekkeboom, D.J., Bouterfa, H., & Krenning E.P.

Abstract
Because the role of chemotherapy, interferon, or somatostatin analogs as antiproliferative agents is uncertain, currently few treatment options exist for patients with metastatic or inoperable gastroenteropancreatic neuroendocrine tumors (GEP-NET). Fifty-eight patients with somatostatin receptor-positive GEP-NET were treated in a phase I dose-escalating study with cumulative doses of 47 mCi to 886 mCi of the radiolabeled somatostatin analog [(90)Y-DOTA(0),Tyr(3)]-octreotide. At baseline, 47 patients had progressive disease, and 36 were symptomatic. The extent of disease was: 4 patients without liver metastases and 52 patients with liver metastases, including 16 patients with very advanced disease, qualified as "end-stage," and 2 end-stage patients without liver metastases. The objective responses were 5 partial response (PR), 7 minor response (MR), 29 stable disease (SD), and 17 PD. Overall, 33 patients (57%) experienced some improvement in their disease status, including conversion from PD into SD and improvement from SD into MR. Accordingly, 21 of 36 patients (58%) had improvement in Karnofsky performance score or symptoms. The median overall survival (OS) was 36.7 months (95% confidence interval [CI] 19.4-54.1 months). The median progression-free survival in 41 patients who had at least stable disease at the end of the treatment period was 29.3 months (95% CI 19.3-39.3 months). Patients who had SD at baseline had a significantly better OS than patients who had PD at baseline. The extent of disease at baseline also was a significant predictive factor for OS. The OS after therapy with [(90)Y-DOTA(0),Tyr(3)]-octreotide was significantly better than in a historic control group of 32 comparable patients with GEP-NET who had been treated with another radiolabeled somatostatin analog, [(111)In-DTPA(0)]-octreotide (median OS 12.0 months, 95% CI 6.2-17.8 months). The difference in OS for both therapies remained highly significant in a multivariate Cox proportional hazard model including progression status and extent of disease at baseline as covariates. Although the objective response after therapy with [(90)Y-DOTA(0),Tyr(3)]-octreotide by standard criteria seems modest, the significantly longer OS compared with

historic controls is most encouraging.

http://www.ncbi.nlm.nih.gov/pubmed/15653653

Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs.

Citation
Journal of Nuclear Medicine, 2005, 46(Suppl 1):62S-66S.

Authors
Kwekkeboom, D.J., Mueller-Brand, J., Paganelli, G., Anthony, L.B., Pauwels, S., Kvols, L.K., O'Dorisio, T.M., Valkema, R., Bodei, L., Chinol, M., Maeke, HR., & Kenning, E.P.

Abstract
A new treatment modality for inoperable or metastasized gastroenteropancreatic tumors is the use of radiolabeled somatostatin analogs. Initial studies with high doses of [(111)In-diethylenetriaminepentaacetic acid (DTPA)(0)]octreotide in patients with metastasized neuroendocrine tumors were encouraging, although partial remissions were uncommon. Another radiolabeled somatostatin analog that is used for peptide receptor radionuclide therapy (PRRT) is [(90)Y-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA)(0),Tyr(3)]octreotide. Various phase 1 and phase 2 PRRT trials have been performed with this compound. Despite differences in the protocols used, complete and partial remissions in most of the studies with [(90)Y-DOTA(0),Tyr(3)]octreotide were in the same ranges, 10%-30%; these ranges were higher than those obtained with [(111)In-DTPA(0)]octreotide. Treatment with the newest radiolabeled somatostatin analog, [(177)Lu-DOTA(0),Tyr(3)]octreotate, which has a higher affinity for the subtype 2 somatostatin receptor, resulted in complete or partial remissions in 30% of 76 patients. Tumor regression was positively correlated with a high level of uptake on OctreoScan imaging, a limited hepatic tumor mass, and a high Karnofsky performance score. Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Symptomatic improvement may occur with all (111)In-, (90)Y-, or (177)Lu-labeled somatostatin analogs that have been used for PRRT. The results obtained with [(90)Y-DOTA(0),Tyr(3)]octreotide and [(177)Lu-DOTA(0),Tyr(3)]octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the duration of the therapy response for both radiopharmaceuticals is more than 2 y. These data compare favorably with those for the limited number of alternative treatment approaches.

http://www.ncbi.nlm.nih.gov/pubmed/15653656

Long-term follow-up of renal function after peptide receptor radiation therapy with (90)Y-DOTA(0),Tyr(3)-octreotide and (177)Lu-DOTA(0), Tyr(3)-octreotate.

Citation
Journal of Nuclear Medicine, 2005, 46 (Suppl 1):83S-91S.

Authors

Valkema, R., Pauwels, S.A., Kvols, L.K., Kwekkeboom, D.J., Jamar, F., de Jong, M., Barone, R., Walrand, S., Kooij, P.P., Bakker, W.H., Lasher, J., & Krenning, E.P.

Abstract
The kidneys are critical organs in peptide receptor radiation therapy (PRRT). Renal function loss may become apparent many years after PRRT. We analyzed the time course of decline in creatinine clearance (CLR) in patients during a follow-up of at least 18 mo after the start of PRRT with (90)Y-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA),Tyr(3)-octreotide ((90)Y-DOTATOC) or (177)Lu-DOTA(0),Tyr(3)-octreotate ((177)Lu-DOTATATE). METHODS: Twenty-eight patients with metastasized neuroendocrine tumors received 1-5 cycles of (90)Y-DOTATOC, leading to renal radiation doses of 5.9-26.9 Gy per cycle and a total of 18.3-38.7 Gy. Median follow-up was 2.9 y (range, 1.5-5.4 y), with a median of 16 measurements (range, 5-53) per patient. Thirty-seven patients with metastasized neuroendocrine tumors received 3-7 cycles of (177)Lu-DOTATATE, leading to renal radiation doses of 1.8-7.8 Gy per cycle and a total of 7.3-26.7 Gy. Median follow-up was 2.4 y (range, 1.7-4.0 y), with a median of 10 (range, 6-27) measurements per patient. All renal dose estimates were calculated with the MIRDOSE3 model. All patients were infused with renoprotective amino acids during the administration of the radioactive peptides. The time trend of CLR was determined by fitting a monoexponential function through the data of individual patients, yielding the decline in CLR in terms of percentage change per year. RESULTS: The median decline in CLR was 7.3% per y in patients treated with (90)Y-DOTATOC and 3.8% per y in patients treated with (177)Lu-DOTATATE (P = 0.06). The time trend of decline in CLR was sustained during the follow-up period. Eleven patients had a >15% per y decline in CLR. Cumulative renal radiation dose, per-cycle renal radiation dose, age, hypertension, and diabetes are probable contributing factors to the rate of decline in CLR after PRRT. CONCLUSION: This study showed that the time course of CLR after PRRT was compatible with the pattern of sustained CLR loss in progressive chronic kidney disease.

http://www.ncbi.nlm.nih.gov/pubmed/15226340

Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate.

Citation
Journal of Clinical Oncology, 2004, 22(13): 2724-2729.

Authors
Teunissen, J.J., Kwekkeboom, D.J., & Krenning, E.P.

Abstract
PURPOSE: To evaluate the quality of life (QoL) in patients with metastatic somatostatin receptor positive gastroenteropancreatic tumors treated with [(177)Lu-DOTA(0),Tyr(3)]octreotate ((177)Lu-octreotate) therapy. PATIENTS AND METHODS: Fifty patients who had been treated with 600 to 800 mCi of (177)Lu-octreotate and had a follow-up of at least 3 months were studied. The patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 before therapy and at follow-up visit 6 weeks after the last cycle. Overall QoL and specific QoL domains of both the total group of patients and subgroups according to treatment outcome were analyzed. Twenty-four patients had regression, 19 had stable disease, six had progressive disease, and one had nonassessable disease status. Analysis of variance was used for statistical comparison. RESULTS: A significant improvement in the global health status/QoL scale was observed

after therapy with (177)Lu-octreotate (P <.01). The score increased significantly six weeks after therapy to a mean of 78.2, up from 69.0 (scale range, 0 to 100). Furthermore, significant improvement was observed in the role, emotional, and social function scales. The symptom scores for fatigue, insomnia, and pain were significantly decreased. Patients with proven tumor regression most frequently had an improvement of QoL domains. Unexpectedly, patients with progressive disease also indicated an improvement in their global health/QoL score. CONCLUSION: (177)Lu-octreotate therapy significantly improved the global health/QoL and several function and symptom scales in patients with metastasized gastroenteropancreatic tumors, but especially in those patients with proven tumor regression.

http://www.ncbi.nlm.nih.gov/pubmed/12902423

Crucial role for somatostatin receptor subtype 2 in determining the uptake of [111In-DTPA-D-Phe1]octreotide in somatostatin receptor-positive organs.

Citation
Journal of Nuclear Medicine, 2003, 44(8): 1315-1321.

Authors
Hofland, L.J., Lamberts, S.W., van Hagen, P.M., Reubi, J.C., Schaeffer, J., Waaijers, M., van Koetsveld, P.M., Srinivasan, A., Krenning, E.P., & Breeman, W.A.

Abstract
Human somatostatin (SS) receptor (sst)-positive tumors can be visualized by gamma camera scintigraphy after the injection of [(111)In-diethylenetriaminepentaacetic acid (DTPA)-D-Phe(1)] octreotide. Uptake of [(111)In-DTPA-D-Phe(1)]octreotide is dependent on sst-mediated internalization of the radioligand by the tumor cells. Human sst-positive tumors frequently express multiple sst subtypes. In vitro studies have demonstrated that the 5 sst subtypes (sst(1-5)) differentially internalize sst-bound ligand. The present study was performed to evaluate the role of sst(2) in vivo in determining the uptake of [(111)In-DTPA-D-Phe(1)]octreotide, as well as of the more "universal" ligand [(111)In-DTPA]SS-14, by sst-positive organs expressing multiple sst subtypes. METHODS: Wild-type and sst(2) knockout mice (n = 4 per treatment group) were injected intravenously with 1 MBq (0.1 micro g) [(111)In-DTPA-D-Phe(1)]octreotide or [(111)In-DTPA]SS-14. After 24 h, the animals were sacrificed and radioactivity in the organs under investigation was determined. In addition, the sst subtype messenger RNA (mRNA) expression pattern in these organs was determined by reverse transcriptase polymerase chain reaction (RT-PCR) analysis. RESULTS: RT-PCR analysis demonstrated the presence of all 5 sst subtype mRNAs in the adrenals and pituitary of wild-type mice but no sst(2) in the knockout mice. The thymus expressed mRNA for sst(2) and sst(4) mRNA in wild-type mice, whereas no sst(2) was detected in knockout mice. In wild-type mice, the in vivo uptake values (in percentage injected dose per gram of tissue) of [(111)In-DTPA-D-Phe(1)]octreotide for the pituitary, adrenals, pancreas, and thymus amounted to 1.2 +/- 0.2, 0.26 +/- 0.03, 0.18 +/- 0.03, and 0.30 +/- 0.05, respectively, in wild-type mice. Compared with wild-type mice, sst(2) knockout mice had dramatically lower uptake values in these organs-lower by 97%, 83%, 96%, and 94%, respectively (P < 0.01 vs. wild type). Comparable differences in the uptake of radioactivity between wild-type and knockout mice were found using [(111)In-DTPA]SS-14 as the radiotracer. Interestingly, in some organs expressing sst(2) mRNA (liver, muscle, and peripheral blood mononuclear cells), no specific binding of [(111)In-DTPA-D-Phe(1)]octreotide or [(111)In-DTPA]SS-14 to sst in vivo was found, suggesting that the sst(2) protein expression level was very low in these tissues. CONCLUSION: The uptake of [(111)In-DTPA-D-Phe(1)]octreotide and [(111)In-

DTPA]SS-14 in sst-positive organs is determined predominantly by sst(2).

http://www.ncbi.nlm.nih.gov/pubmed/12515868

Long-term efficacy of high-activity 111in-pentetreotide therapy in patients with disseminated neuroendocrine tumors.

Citation Journal of Nuclear Medicine, 2003, 44(1): 1-6.

Authors
Buscombe, J.R., Caplin, M.E., & Hilson, A.J.

Abstract
High-activity (111)In-pentetreotide has been used to treat patients with disseminated neuroendocrine tumors. There is, however, little information related to the efficacy of this agent beyond the normal 6-mo assessment period. Before we can assume that such treatment would be beneficial to patients with neuroendocrine tumors the outcome of the patients over a longer time course should be determined. METHODS: The case records of 16 patients who had received high activities of (111)In-pentetreotide (with cumulative activities as high as 36.6 GBq) over a 2.5-y period, from January 1, 1997, to June 30, 2000, were reviewed. There were 8 female and 8 male patients (age range, 32-76 y): 10 patients had carcinoid, 2 had medullary cell carcinoma of the thyroid, and 1 each had a gastrinoma, glucagonoma, fibrolamellar cancer, and malignant histiocytoma. The minimum number of treatments received was 1 in 2 patients (with activities of 3.1 and 7 GBq); the maximum was 10 treatments (total, 36.6 GBq). Treatment was given using an infusion pump and was repeated at 4- to 12-wk intervals (mean number of treatments per patient, 6). Response to therapy was determined by changes in the size of the tumor on CT using the response evaluation criteria in solid tumors. Toxicity was measured using blood and urine tests of renal, hepatic, thyroid, and bone marrow function. The mean and median time from the last treatment to progression of disease and death (if applicable) was also calculated. RESULTS: No significant or long-lasting toxicity was encountered. At 6 mo after the patient's last treatment, 5 patients (30%) had disease progression, 2 had complete responses, and 3 had partial responses. Twelve months after their last treatment, 9 patients (56%) had disease progression, and, at 18 mo, 11 patients (69%) had disease progression. The mean progression-free survival was 12.25 mo (median, 9 mo). For those who survived 6 mo after their last treatment, the mean survival was 15.75 mo (median, 16 mo). At the 6-mo assessment point, there had been 3 deaths (19%): 1 death was not related to cancer. At 12 mo, there was 1 additional cancer death. At 18 mo, there were 3 additional deaths (1 was not related to the patient's carcinoid tumor but was due to a second coexistent cancer). By the end of the 18-mo assessment period, 7 patients (44%) had died. The mean time interval between disease progression and death was 5 mo. CONCLUSION: In patients treated with high-activity (111)In-pentreotide, 70% had some benefit for at least 6 mo after the end of treatment; however, 31% of patients will have sustained benefit at 18 mo from this treatment. This was obtained without significant toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/12483404

Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine.

Citation
European Journal of Medical & Molecular Imaging, 2003. 30(1): 9-15.

Authors
Rolleman, E.J., Valkema, R., de Jong, M., Kooij, P.P., & Krenning, E.P.

Abstract
As scintigraphy with [(111)In-DTPA(0)]octreotide has become a standard technique in analysing somatostatin receptor-receptor positive lesions such as neuroendocrine tumours, a logical next step is peptide receptor radionuclide therapy (PRRT). Initial studies on PRRT were performed with high doses of [(111)In-DTPA(0)]octreotide, and recently other radionuclides coupled to other somatostatin analogues have been used for this purpose. However, the dose delivered to the kidney is a major dose-limiting factor. Amino acid solutions have previously been used to reduce renal uptake of radioactivity, but these solutions have some disadvantages, i.e. their hyperosmolarity and their propensity to cause vomiting and metabolic changes. In this study we tested various amino acid solutions in patients receiving [(111)In-DTPA(0)]octreotide PRRT in order to assess their safety and their capacity to inhibit the renal uptake of radioactivity. Patients served as their own non-infused control. Renal radioactivity at 24 h following the injection of [(111)In-DTPA(0)]octreotide was inhibited by (1) a commercially available amino acid solution (AA) (21%+/-14%, P<0.02), (2) by 25 g (17%+/-9%, P<0.04), 50 g (15%+/-13%, P<0.04) or 75 g of lysine (44%+/-11%, P<0.001) and (3) by a combination of 25 g of lysine plus 25 g of arginine (LysArg) (33%+/-23%, P<0.01). Fluid infusion alone (500, 1,000 or 2,000 ml of saline/glucose) did not change renal uptake of radioactivity. In patients studied with 75 g of lysine (Lys75) and LysArg, serum potassium levels rose significantly. Maximal potassium levels were within the toxic range (6.3, 6.7 and 6.8 mmol/l) in three out of six patients infused with Lys75, whereas with LysArg the highest concentration measured was 6.0 mmol/l. Electrocardiographic analysis did not reveal significant changes in any of the patients. Vomiting occurred in 50% of patients infused with AA, but in only 6% of patients receiving no amino acid infusion (controls) and 9% of patients receiving LysArg. We conclude that co-infusion of Lys75 or LysArg results in a significant inhibition of renal radioactivity in PRRT, allowing higher treatment doses and thus resulting in higher tumour radiation doses. Because Lys75 produced serious hyperkalaemia, it is not suitable for clinical use. LysArg, however, is effective in offering renal protection in PRRT and is safe.

http://www.seminarsinnuclearmedicine.com/article/S0001-2998%2802%2980030-7/abstract

Indium-111-pentetreotide prolongs survival in gastroenteropancreatic malignancies.

Citation
Seminars in Nuclear Medicine, 2002; 32(2): 123-132.

Authors
Anthony, L.B., Woltering E.A., Espenan, G.D., Cronin, M.D., Malone, T.J., & McCarthy, K.E.

Abstract
Somatostatin and its analogues bind to somatostatin receptors (sst) 1 through 5 that are overexpressed in neuroendocrine neoplasms such as gastroenteropancreatic (GEP) malignancies. After ligand-receptor binding, a fraction of the ligand-receptor complexes internalize. This internalization process is an effective means of delivering cytotoxic radiolabeled somatostatin analogues, especially those emitting short-range decay particles such as Auger electrons, to the neoplastic cell nucleus. Indium-111-pentetreotide, an sst 2

preferring somatostatin analogue with gamma and Auger electron decay characteristics, is commonly used for the scintigraphic evaluation and management of neuroendocrine cancer patients. This clinical trial was performed to determine the effectiveness and tolerability of therapeutic doses of 111In-pentetreotide in patients with GEP tumors. GEP tumor patients who had failed all forms of conventional therapy, with worsening of tumor-related signs and symptoms and/or radiographically documented progressive disease, an expected survival less than 6 months, and sst positivity as determined by the uptake on a 6.0 mCi 111In-pentetreotide scan (OctreoScan; Mallinckrodt Medical, Inc, St. Louis, MO), were treated with at least 2 monthly 180-mCi intravenous injections of 111In-pentetreotide. Baseline clinical assessments, serum chemistries, and plasma pancreastatin levels were measured and repeated before each 111In-pentetreotide treatment. From February 1997 to February 1998, 27 GEP (24 carcinoid neoplasms with carcinoid syndrome and 3 pancreatic islet cells) patients were accrued, with 26 patients evaluable for clinical and radiographic responses, 21 patients evaluable for biochemical assessments, and 27 patients evaluable for survival analysis and safety. Toxicity was evaluated by using standard National Cancer Institute (NCI) Common Toxicity Criteria guidelines. Clinical benefit occurred in 16 (62%) patients. Pancreastatin levels decreased by 50% or more in 81% of the patients. Objective partial radiographic responses occurred in 2 (8%) patients, and significant tumor necrosis (defined by 20 Hounsfield units or greater decrease from baseline) developed in 7 (27%) patients. The following transient Grades 3/4 NCl Common Toxicity Criteria side effects were observed, respectively: leukocyte: 1/1; platelets: 0/2; hemoglobin: 3/0; bilirubin: 1/3; creatinine: 1/0; neurologic: 1/0. Myeloproliferative disease and/or myelodysplastic syndrome have not been observed in the 6 patients followed-up for 48+ months. The median survival was 18 months (range, 3–54+ mo). Two doses (180 mCi) of 111In-pentetreotide are safe, well-tolerated, and improve symptoms in 62% of patients, decrease hormonal markers in 81% of patients, decrease Hounsfield units on computed tomography (CT) scans in 27% of patients, with 8% partial radiographic responses and increased expected survival in GEP cancer patients with somatostatin receptor-expressing tumors. The maximal tolerated dose of 111In-pentetreotide and the optimal dosing schedules remain under investigation.

http://www.ncbi.nlm.nih.gov/pubmed/11994522

Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC.

Citation

Journal of Nuclear Medicine, 2002, 43(5): 610-616.

Authors

Waldherr, C., Pless, M., Maeke, H.R., Schumacher, T., Crazzolara, A., Nitzsche, E.U., Haldemann, A., & Mueller -Brand, J.

Abstract

The aim of this prospective phase II study was to evaluate the tumor response of neuroendocrine tumors to high-dose targeted irradiation with 7.4 GBq/m(2) of the radiolabeled somatostatin analog (90)Y-1,4,7,10-tetra-azacyclododecan-4,7,10-tricarboxy-methyl-1-yl-acetyl-D-Phe-Tyr(3)-octreotide (DOTATOC). In addition, we investigated the clinical benefit of (90)Y-DOTATOC regarding the malignant carcinoid syndrome and tumor-associated pain. METHODS: Thirty-nine patients (mean age, 55 y) with progressive neuroendocrine gastroenteropancreatic and bronchial tumors were included. The treatment consisted of 4 equal intravenous injections of a total of 7.4 GBq/m(2) (90)Y-DOTATOC, administered at intervals of 6 wk. After each treatment cycle, a standardized clinical benefit

assessment using the National Cancer Institute grading criteria (NCI-CTC) was performed. RESULTS: The objective response rate according to World Health Organization (WHO) criteria was 23%. For endocrine pancreatic tumors (13 patients), the objective response rate was 38%. Complete remissions were found in 5% (2/39), partial remissions in 18% (7/39), stable disease in 69% (27/39), and progressive disease in 8% (3/39). A significant reduction of clinical symptoms could be found in 83% of patients with diarrhea, in 46% of patients with flush, in 63% of patients with wheezing, and in 75% of patients with pellagra. The overall clinical benefit was 63%. All responses (both clinical benefit and WHO response) were ongoing for the duration of follow-up (median, 6 mo; range, 2-12 mo). Side effects were grade 3 or 4 (NCI-CTC) lymphocytopenia in 23%, grade 3 anemia in 3%, and grade 2 renal insufficiency in 3%. CONCLUSION: High-dose targeted radiotherapy with 7.4 GBq/m(2) (90)Y-DOTATOC is a well-tolerated treatment for neuroendocrine tumors, with remarkable clinical benefit and objective response.

http://www.ncbi.nlm.nih.gov/pubmed/12658726

90Y-DOTA-D-Phe1-Try3-octreotide in therapy of neuroendocrine malignancies.

Citation

Biopolymers, 2002, 66(6): 393-398.

Authors

Paganelli, G., Bodei, L., Handkiewicz, J.D., Rocca, P., Papi, S., Lopera Sierra, M., Gatti, M., Chinol, M., Bartolomei, M., Fiorenza, M., & Grana, C.

Abstract

Somatostatin receptors type 2 (sst(2)) are expressed in high concentration on numerous neudoendocrine tumors. The successful use of radiolabeled somatostatin analogs in imaging promoted further studies in utilizing them in radiopeptide therapy. The somatostatin analog [(90)Y-DOTA-D-Phe(1)-Try3]octreotide (DOTATOC) (DOTA: 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) possesses favorable characteristic for its therapeutic use; shows high affinity for sst(2), moderately high affinity for sst(5), and intermediate affinity for sst(3); high hydrophilicity; stable and facile labeling with (111) In and (90) Y. In this article we report our experience with (90)Y-DOTATOC in neuroendocrine tumors. Eighty-seven patients with neuroendocrine tumors were treated with a cumulated activity ranging from 7.4 to 20.2 GBq. Most patients responded with stabilization of disease (48%); however, objective responses were observed in 28% of patients (5% complete response). No major acute reactions were observed up to the activity of 5.55 GBq per cycle. The dose limiting was bone marrow toxicity and the maximal tolerated dose was defined as 5.18 GBq

http://www.ncbi.nlm.nih.gov/pubmed/11965610

In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial.

Citation

Seminars in Nuclear Medicine, 2002, 32(2): 148-155.

Authors

Virgolini, I., Britton, K., Buscombe, J., Moncayo, R., Paganelli, G., & Riva, P.

Abstract

The high-level expression of somatostatin receptors (SSTR) on various tumor cells has provided the molecular basis for successful use of radiolabeled peptide analogues as tumor tracers in nuclear medicine. The vast majority of human tumors seem to overexpress one or the other of 5 distinct hSSTR subtype receptors. Whereas neuroendocrine tumors frequently overexpress human(h) SSTR2, intestinal adenocarcinomas frequently express hSSTR3 or hSSTR4, or both of these hSSTRs. In contrast to (111)In-diethylenetriamine pentaacetic acid

(DTPA)-(D)he(1)-octreotide (OctreoScan; Mallinckrodt, Petten, NL), which binds to hSSTR2 and 5 with high affinity (K(d)0.1-5 nmol/L), to hSSTR3 with moderate affinity (K(d)10-100 nmol/L), and does not bind to hSSTR1 and hSSTR4, (111)In /(90)Y-DOTA-lanreotide was found to bind to hSSTR2, 3, 4, and 5 with high affinity, and to hSSTR1 with lower affinity (K(d)200 nmol/L). Based on its unique hSSTR binding profile, (111)In-DOTA-lanreotide was suggested to be a potential radioligand for tumor diagnosis, and (90)Y-DOTA-lanreotide suitable for receptor-mediated radionuclide therapy. When directly compared with (111)In-DTPA-(D)he(1)-octreotide and (111)In-DOTA-(D)he(1)-Tyr(3)-octreotide, discrepancies in the scintigraphic imaging pattern are seen in about one third of tumor patients concerning both the tumor uptake as well as the detection of tumor lesions. On a molecular level, these discrepancies seem to be based on a higher high-affinity binding affinity of (111)In-DOTA-(D)he(1)-Tyr(3)-octreotide for hSSTR2 (K(d)0.1-1 nmol/L). Beneficial results of receptor-mediated experimental radionuclide therapy were first reported for high-dose treatment with (111)In-DTPA-(D)he(1)-octreotide, based on the emission of Auger electrons. Phase IIa of the Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative, a European Study (MAURITIUS), shows in progressive cancer patients (therapy entry criteria) with a calculated tumor dose > 10 Gy/GBq (90)Y-DOTA-lanreotide, the proof-of-principle for treating tumor patients with peptide receptor imaging agents. In the MAURITIUS study, cumulative treatment doses up to 232 mCi (90)Y-DOTA-lanreotide were given as short-term intravenous infusion. Preliminary treatment results in 154 patients indicate stable tumor disease in 41% (63 of 154) of patients and regressive tumor disease in 14% (22 of 154) of tumor patients with different tumor entities expressing hSSTR. No severe acute or chronic hematologic toxicity, change in renal or liver function parameters caused by (90)Y-DOTA-lanreotide treatment were reported for patients in the MAURITIUS trial. In two thirds of patients with neuroendocrine tumor lesions, (90)Y-DOTA-(D)he(1)-Tyr(3)-octreotide showed a higher tumor uptake and should therefore be considered the first choice for experimental receptor-based therapy. Potential indications for (90)Y-DOTA-lanreotide treatment are radioiodine-negative thyroid cancer, hepatocellular cancer, lung cancer, some brain tumors, and possibly melanomas. In conclusion, preclinical data and clinical studies confirm the potential usefulness of radiolabeled lanreotide for tumor diagnosis and therapy. However, careful consideration of the type of radiotracer used for receptor-mediated therapy should be made for the individual patient. Whole-body dosimetry should always be performed to predict doses for tumors and the critical organs, which are kidney and bone marrow.

RADIOIODINATED METAIODOBENZYLGUADINE (MIBG)

http://www.ncbi.nlm.nih.gov/pubmed/19877881

Radioiodinated metaiodobenzylguanidine treatment of neuroendocrine tumors in adults.

Citation

Cancer Biotherapy and Radiopharmaceuticals, 2009, 24(5):519-25.

Authors

Postema, E.J., & McEwan, A.J.

Abstract

Metaiodobenzylguanidine (MIBG), radioiodinated with (131)I, has been available for 25 years. Its role in the United States is limited to diagnostic imaging, whereas its therapeutic application in patients with neuroendocrine tumors for whom surgical treatment would not lead to a cure, has been approved in Europe. (131)I-MIBG treatments can be a valuable addition to the current gamut of treatment options for patients with metastatic

neuroendocrine tumors, especially given the limited role for other systemic treatments, such as chemotherapy. There are basically two treatment strategies: one or two high-dose treatments or continuous low-dose treatments. (131)I-MIBG could induce symptomatic relief in the vast majority of patients treated, both following high-dose treatment and low-dose maintenance treatment. Biochemical responses can be observed in about half of the patients, whereas radiographic responses are described in roughly one third of the patients. Several articles suggested a survival benefit to patients treated with (131)I-MIBG. Side-effects of the treatment mainly consist of myelotoxicity, nausea, and hypothyroidism. Future developments are focused on the use of high-specific-activity (131)I-MIBG in high doses. The role of (131)I-MIBG in relation to other treatments remains to be established, although treatment (131)I-MIBG seems to be at least as effective as other systemic treatments, with limited side-effects.

http://www.ncbi.nlm.nih.gov/pubmed/18283308

Assessment of the efficacy and toxicity of (131)I-metaiodobenzylguanidine therapy for metastatic neuroendocrine tumours.

Citation

British Journal of Cancer, 2008, 98(6): 1053-1058.

Authors

Nwosu, A.C., Jones, L., Vora, J., Poston, G.J., Vinjamuri, S., & Pritchard, D.M.

Abstract

(131)I-metaiodobenzylguanidine ((131)I-MIBG) is a licensed palliative treatment for patients with metastatic neuroendocrine tumours. We have retrospectively assessed the consequences of (131)I-MIBG therapy in 48 patients (30 gastroenteropancreatic, 6 pulmonary, 12 unknown primary site) with metastatic neuroendocrine tumours attending Royal Liverpool University Hospital between 1996 and 2006. Mean age at diagnosis was 57.6 years (range 34-81). (131)I-MIBG was administered on 88 occasions (mean 1.8 treatments, range 1-4). Twenty-nine patients had biochemical markers measured before and after (131)I-MIBG, of whom 11 (36.7%) showed >50% reduction in levels post-therapy. Forty patients had radiological investigations performed after (131)I-MIBG, of whom 11(27.5%) showed reduction in tumour size post-therapy. Twenty-seven (56.3%) patients reported improved symptoms after (131)I-MIBG therapy. Kaplan-Meier analysis showed significantly increased survival (P=0.01) from the date of first (131)I-MIBG in patients who reported symptomatic benefit from therapy. Patients with biochemical and radiological responses did not show any statistically significant alteration in survival compared to non-responders. Eleven (22.9%) patients required hospitalisation as a consequence of complications, mostly due to mild bone marrow suppression. (131)I-MIBG therefore improved symptoms in more than half of the patients with metastatic neuroendocrine tumours and survival was increased in those patients who reported a symptomatic response to therapy.

http://www.ncbi.nlm.nih.gov/pubmed/15455358

Iodine-131 metaiodobenzylguanidine treatment for metastatic carcinoid. Results in 98 patients.

Citation

Cancer, 2004, 101(9): 1987-1993.

Authors

Safford, S.D., Coleman, R.E., Gockerman, J.P., Moore, J., Feldman, J., Onaitis, M.W., Tyler, D.S., & Olson, J.A. Jr.

Abstract

BACKGROUND: Iodine-131 metaiodobenzylguanidine (131I-MIBG) is useful for imaging carcinoid tumors and recently has been applied to the palliative treatment of metastatic carcinoid in small studies. The authors now report their results on the therapeutic utility of high-dose 131I-MIBG treatment in a large group of patients with metastatic carcinoid tumors. METHODS: The authors performed a retrospective review of 98 patients with metastatic carcinoid who were treated at their institution with 131I-MIBG over a 15-year period. Endpoints examined included the World Health Organization criteria for treatment response: symptoms, hormone (5-hydroxyindoleacetic acid [5-HIAA]) production, and clinical tumor response. RESULTS: Patients received a median dose of 401 +/- 202 millicuries (mCi) 131I-MIBG. The median survival after treatment was 2.3 years. Patients who experienced a symptomatic response had improved survival (5.76 years vs. 2.09 years; P < 0.01). For the 56 patients who had 5-HIAA levels monitored, the mean urine 5-HIAA levels decreased significantly after 131I-MIBG treatment (126 +/- 122 ng/mL vs. 91 +/- 125 ng/mL; P < 0.01); however, the patients with reduced 5-HIAA levels did not experience improved survival (4.11 years vs. 3.42 years; P = 0.2). Patients who received an initial 131I-MIBG dose > 400 mCi lived longer than patients who received < 400 mCi (4.69 years vs. 1.86 years; P = 0.05). Radiographic tumor response did not predict survival. Toxicity included pancytopenia, thrombocytopenia, nausea, and emesis. CONCLUSIONS: The current data support 131I-MIBG treatment in select patients with metastatic carcinoid who progress despite optimal medical management. Improved survival was predicted best by symptomatic response to 131I-MIBG treatment, but not by hormone or radiographic response.

http://www.ncbi.nlm.nih.gov/pubmed/15657579

The palliative role of 131I-MIBG and 111In-octreotide therapy in patients with metastatic progressive neuroendocrine neoplasms.

Citation
Surgery, 2004, 136(6): 1218-1226.

Authors
Pasieka, J.L., McEwan, A.J., & Rorstad, O.

Abstract

BACKGROUND: Radiolabeled octreotide and metaiodobenzylguanidine (MIBG) have demonstrated limited antitumor effect on neuroendocrine neoplasms (NENs). The purpose of this study was to assess the palliative benefit of radionuclide therapy (RNT) in NENs. METHODS: Since April 2001, RNT for progressive, nonsurgically resectable NENs was utilized. NENs that were MIBG positive received 131 I-MIBG therapy, whereas octreotide-only-positive neoplasms received 111 In-octreotide therapy. Symptomatic, quality of life (QoL), biochemical, and radiographic responses to RNT were evaluated. RESULTS: Twenty-four patients had either MIBG or octreotide avid NENs. A mean (range) of 4 (1-7) 131 I-MIBG treatments were given to 13 patients over a duration of 18 months (6-42). The group consisted of 2 medullary thyroid cancer (MTC), and 2 foregut and 9 small-bowel carcinoids; 12 patients (92%) had symptomatic improvement. Stability of tumor size was confirmed in 6, regression in 2, and progression in 5. Biochemical responses were demonstrated in 2. Five (2-16) treatments of 111 In-octreotide was given to 11 patients over 17 months (6-40). There were 1 MTC, 1 insulinoma, 2 gastrinomas, and 3 small-bowel and 4 foregut carcinoids. Symptomatic benefit was seen in 6 (55%), biochemical response in 3. Tumor regression was seen in 1, stability in 5, and progression in 5. CONCLUSIONS: Radionuclide therapy appears to offer good palliation to patients with progressive NENs.

http://www.ncbi.nlm.nih.gov/pubmed/15490060

131I-meta-iodobenzylguanidine in the management of metastatic midgut carcinoid tumors.

Citation
World Journal of Surgery, 2004, 28(11): 1157-1162.

Authors Sywak, M.S., Pasieka, J.L., McEwan, A., Kline, G., & Rorstad, O.

Abstract
The management of metastatic neuroendocrine tumors incorporates multimodal therapy with surgery, biotherapy, and chemotherapy. Tumor-targeted therapies using radiolabeled octreotide and metaiodobenzylguanidine (mIBG) represent a novel treatment approach. The aim of this study was to evaluate the effectiveness of 131I-mIBG in the treatment of metastatic midgut carcinoid tumors. survival outcomes were assessed for patients treated at two regional cancer centers and then compared. One center used 131I-mIBG routinely in the management of metastatic carcinoid tumors (center A), and the other did not use this modality (center B). Only patients with histologically proven metastatic carcinoid tumor shown, or thought most likely, to be of midgut origin were included in the study. During the period 1980 to 2002, a series of 58 patients from center A with metastatic carcinoid tumor arising from the midgut underwent multimodality therapy with the addition of 131I-mIBG. Their median age was 64 years. The median dose of 131I-mIBG administered was 6751 MBq, and there was an average of 2.8 treatments per patient. During the same period, 58 patients with metastatic carcinoid were treated at center B with similar multimodality therapy without the use of 131I-mIBG therapy. Their median age was 65 years. Survivals at 3 and 5 years were 77% and 63%, respectively (95% CI 47-75), for group A. The 3- and 5-year survivals for group B were 56% and 47% (95% CI 34-59), respectively. The mean follow-up was 6.6 years for group A and 5.0 years for group B. Although retrospective in nature, this study suggests that the addition of 131I-mIBG therapy to the treatment protocol of patients with metastatic midgut carcinoid tumors prolongs survival.

PROGNOSIS

http://www.ncbi.nlm.nih.gov/pubmed/19569047
European disparities in malignant digestive endocrine tumours survival.
Citation
International Journal of Cancer, 2010, 126(12): 2928-2934.
Authors
LePage, C., Cicolallo, L., De Angelis, R., Bouvier, A.M., Faivre, J., & Gatta, G.: EUROCARE working group.

Abstract
The aim of this study was to report on malignant digestive endocrine tumours (MDET) prognosis in several European countries. We analysed survival data from 19 cancer registries in 12 European countries on 3,715 MDET diagnosed between 1985 and 1994. The overall 5-year survival rate was 47.5%. It was 58.1% for differentiated MDET and 8.1% for small-cell MDET ($p < 0.001$), 55.9% for patients under 65 and 37.0% for older patients. Survival rates for small intestinal and colorectal were higher than for the other sites. The 5-year relative survival rates were 60.3% in Northern Europe, 53.6% in Western Continental Europe, 42.5%

in the UK, 37.6% in Eastern Europe ($p < 0.001$). Among well-differentiated pancreatic tumours, 5-year relative survival was 55.6% for insulinoma, 48.4% for gastrinoma, 33.4% for glucagonoma, 28.8% for carcinoid tumours and 49.9% for non-functioning tumours. The relative excess risk of death was significantly lower in Western Continental Europe and Northern Europe and significantly higher in Easter European compared to the UK. MDET differentiation, site, geographic area, age and sex, were independent prognostic factors. Overall, in Europe approximately half of the patients with MDET survive 5 years after the initial diagnosis. Prognosis varies with tumour differentiation, anatomic site and histological type. There are significant differences in survival from MDET among European countries, independently of other prognostic factors.

http://www.ncbi.nlm.nih.gov/pubmed/19174605

Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut.

Citation

Neuroendocrinology, 2009, 89(4): 471-476.

Authors

Strosberg, J., Gardner, N., & Kvols, L.

Abstract

Background: Gastrointestinal neuroendocrine tumors (NETs) are heterogeneous neoplasms that vary in mortality according to location of primary tumor and stage of disease. Past analyses of survival suggest a trend towards improving longevity among patients with metastatic mid-gut NETs. Methods: We evaluated all cases of metastatic NETs of the mid-gut seen in our institution between 1999 and 2003, measuring survival from time of diagnosis of distant metastatic disease. Median and 5-year survival rates were estimated using Kaplan-Meier methodology. We assessed the impact of various prognostic factors including age, gender, hepatic cytoreductive surgery, and operative resection of the primary tumor. Results: 146 cases of metastatic mid-gut NETs were identified. The median overall survival was 103 months and the 5-year survival rate was 75%. Most patients (91%) received octreotide therapy. Other medical treatments included hepatic artery embolization, chemotherapy, and peptide receptor radiotherapy. Primary tumor resection was performed in 69% of cases, and hepatic cytoreductive surgery in 22% of cases. A median survival of 95 months was observed among patients who did not undergo cytoreductive surgery. Operative resection of the primary tumor was not associated with a significant survival advantage. Conclusions: Median overall survival is 103 months (8.5 years) in patients with metastatic mid-gut NETs. Among patients who are not candidates for hepatic cytoreductive surgery, median survival is 95 months (7.9 years). Resection of the primary tumor does not appear to be associated with a survival benefit in the metastatic setting.

http://www.ncbi.nlm.nih.gov/pubmed/19572232

Small intestinal neuroendocrine tumors: prognostic factors and survival.

Citation

Scandinavian Journal of Gastroenterology, 2009, 44(9): 1084-1091.

Authors

Bergestuen, D.S., Aabakken, L., Holm, K., Vatn, M., & Thiis-Evensen, E.

Abstract

OBJECTIVE: Small intestinal neuroendocrine tumors (SI-NETs) make up 38% of gastroenteropancreatic neuroendocrine tumors. We report our experience with SI-NETs at

the National Center for Neuroendocrine Tumors in Norway, focusing on prognostic factors and survival. MATERIAL AND METHODS: The medical records of 258 patients with SI-NETs diagnosed between 1983 and 2007 were retrospectively reviewed. Demographic, clinical and tumor characteristics were registered in a database. RESULTS: Median age at diagnosis was 62 years (range 28-84); 53% of patients were men. Median survival was 9.3 years [95% confidence interval (CI) 7.6; 10.8]. Survival did not improve for patients diagnosed between 1998 and 2007 compared with those diagnosed between 1990 and 1997 (p=0.44), median survival 8.1 [7.1;9.1] versus 6.8 [4.0; 9.5] years. Overall 5-year survival was 72%, while expected 5-year survival in the general population was 92%. The corresponding relative 5-year survival for the patient group was 78%. Distant metastases, urinary 5-hydroxyindoleacetic acid ratio > or =3.7 times the upper limit of normal, chromogranin A ratio > or =6.2 times the upper limit of normal, age > or =64, male gender, carcinoid heart disease, and Ki-67 > or =5% were associated with decreased survival. Using multivariate analysis, only distant metastases (hazard ratio (HR) 1.98 [1.04;3.76], p=0.04), chromogranin A ratio > or =6.2 (HR 1.90 [1.12; 3.20], p=0.02), and age > or =64 (3.12 [1.93; 5.04], p<0.001) remained independent predictors. CONCLUSIONS: Survival did not improve over the study period. Overall and relative 5-year survival compared favorably with that in population-based studies. Distant metastases, elevated chromogranin A levels, and advanced age were the only independent predictors of poor survival.

http://www.ncbi.nlm.nih.gov/pubmed/19240182

Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma.

Citation
Endocrine-Related Cancer, 2009, 16(2): 585-597.
Authors
Durante, C., Boukheris, H., Dromain, C., Duvillard, P., Leboulleux, S., Elias, D., de Baere, T., Malka, D., Lumbroso, J., Guigay, J., Schlumberger, M.., Ducreux, M., & Baudin, E.
Abstract
Survival of metastatic gastroenteropancreatic well-differentiated endocrine carcinoma (GEP WDEC) is not well characterized. We evaluated the long-term outcome and prognostic factors for survival in 118 patients with distant metastases from GEP WDEC. Inclusion criteria were 1) pathological review by a single pathologist according to the present WHO criteria, 2) absence of previous therapy apart from surgery, 3) complete morphological evaluation within 3 months including somatostatin receptor scintigraphy, and 4) follow-up at Gustave-Roussy Institute until death or study's end. Clinical, biological marker, and pathological parameters were analyzed in univariate and multivariate statistical models. Survival after the first complete imaging work-up of the metastatic disease was determined using Kaplan-Meier method. Overall, survival for 5 years after the diagnosis of metastatic disease was 54%. In multivariate analysis, age (hazard ratio (HR): 1.05, 95% confidence interval (CI): 1.01-1.08, P = 0.01), the number of liver metastases (HR: 3.4, 95% CI: 1.4-8.3, P = 0.01), tumor slope (HR: 1.1, 95% CI: 1.0-1.1, P = 0.001), and initial surgery (HR: 0.3, 95% CI: 0.1-0.8, P = 0.01) were predictive of survival. Five-year survival was 100%, 91% (95% CI, 51-98%), 62% (95% CI, 37-83%), and 9% (95% CI, 6-32%) when patients had 0, 1, 2, 3 or more poor prognostic features respectively. This study enables the stratification of metastatic GEP WDEC patients into distinct risk groups. These risk categories can be used to tailor therapeutic approaches and also to design and interpret clinical trials.

http://www.ncbi.nlm.nih.gov/pubmed/18603570

Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours.

Citation
Endocrine-Related Cancer, 2008, 15(4): 1083-1097.
Authors
Pape, U-F., Berndt, U., Müller-Nordhorn, J., Böhmig, M., Roll, S., Koch, M., Willich, S.N., & Wiedenmann, B.
Abstract
Neuroendocrine tumours (NET) of the gastroenteropancreatic system comprise a malignant entity with a low incidence. Only limited information is available on long-term clinical outcome and clinically applicable prognostic factors. We performed a retrospective analysis of a large, well-characterized centre-based patient cohort of 399 patients with histologically proven NET. Data were analysed according to epidemiological, clinical and histopathological characteristics. Detailed survival analyses using the Kaplan-Meier method were performed. Prognostic factors were tested by log-rank testing and independent risk factors were analysed using a Cox regression model. In the studied cohort, primary tumours originated in the fore-, mid- and hindgut in 46.1, 37.1 and 4.5% respectively. Extra-intestinal or unknown primary tumours were present in 8.4 and 10.5% respectively. Distant metastasis was present at initial diagnosis in 69.4%. Most frequent metastatic sites were liver (85%), peritoneal cavity (18%), bones (8%), other intra-abdominal sites (6%) and lungs (4%). Overall, 5- and 10-year survival rates were 78 and 63% respectively. Time to progression after initial diagnosis was significantly shorter in pancreatic as compared with ileal NET. Survival analysis revealed significantly better clinical outcome for primary tumours smaller than 25 mm, absence of metastasis, absence of any clinical symptoms, positive immunohistochemical staining for chromogranin A and a lower Ki67 index. These results were confirmed as independent by multivariate analysis. Therefore, this large retrospective analysis of a well-documented cohort of patients with NET demonstrates several prognostic factors of clinical relevance and wide availability, which should be considered for risk stratification in the management of NET.

http://www.ncbi.nlm.nih.gov/pubmed/19173835

[Clinicopathological features and prognosis of different gastric carcinoid subtypes] [Article in Chinese]

Citation
Zhonghua Zhong Liu Za Zhi, 2008, 30(11): 866-869.
Authors
Liang, J.W., Zhou, Z.X., Liu, Q., Bai, X.F., & Zhao, P.

Abstract
OBJECTIVE: To analyze the clinicopathological features and their relation to treatment and prognosis in different gastric carcinoid subtypes. METHODS: The data of surgically treated 39 patients with gastric carcinoids (9 of type I and 30 of type III) were retrospectively analyzed. Univariate and multivariate analysis were performed using Chi square test (chi(2)) and Cox model, respectively. The survival rates were analyzed by Kaplan-Meier method, and the factors affecting survival by Log rank test. RESULTS: Of the 9 patients with type I carcinoids,

5 underwent endoscopic or surgical resection, and extra antrectomy was performed in 2 patients simultaneously. 3 cases had a proximal gastrectomy, and 1 underwent total gastrectomy. Among the 30 patients with type III gastric carcinoids, 21 underwent radical resection, 6 had a palliative resection, and the remaining 3 underwent exploration and biopsy only due to invasion into adjacent organs and distant metastasis. Infiltration beyond the submucosa was found in all 30 type III gastric carcinoid patients, but in only 1 of 9 patients with type I gastric carcinoids. Regional lymph node metastases were found in 27 of 30 type III carcinoid cases, but in none of type I. Distant metastases occurred in 5 patients of type III carcinoid (4 in the liver and 1 in the ovary). There were statistically significant differences between type I and type III carcinoids in the sex, tumor number, location, size and infiltration depth of the tumors, the regional lymph node metastasis, distant metastasis and lymphatic emboli ($P < 0.05$ in all). The overall 5-year survival rate was 49.7% for the whole group, and 100.0% and 37.2% for type I and type III carcinoids, respectively. Univariate analysis revealed that the number of tumor, tumor size (> 2 cm), serosal invasion, regional lymph node metastasis and distant metastasis were all significant factors affecting the survival ($P < 0.05$ in all). However, by multivariate analysis, only distant metastasis was found to be a significant prognostic predictor. CONCLUSION: The prognosis of type III carcinoids is much poorer than that of type I. Subtyping of gastric carcinoids is helpful in guiding clinical management, and also in prediction of malignant potential and prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/18281671

Indium-111-pentetreotide scintigraphy and somatostatin receptor subtype 2 expression: new prognostic factors for malignant well-differentiated endocrine tumors.

Citation

Journal of Clinical Oncology, 2008, 26(6): 963-970.

Authors

Asnacios, A, Courbon, F., Rochaix, P., Bauvin, E., Cances-Lauwers, V., Susini, C., Schulz, S., Boneu, A., Guimbaud, R. & Buscail, L.

Abstract

PURPOSE: Well-differentiated metastatic endocrine carcinomas are difficult to manage because of variable disease outcome. New prognostic factors are required. These tumors overexpress somatostatin receptors (sst), implying the use of somatostatin analogs for tumor localization by somatostatin receptor scintigraphy using indium-111-pentetreotide ((111)In-pentetreotide) and for medical treatment. The aim of the present study was to evaluate the correlation between (111)In-pentetreotide scintigraphy, sst receptor expression, and prognosis. PATIENTS AND METHODS: Between 1994 and 2002, 48 consecutive patients with well-differentiated endocrine carcinomas and a negative (111)In-pentetreotide scintigraphy were retrospectively paired according to sex, age, and tumor localization with 50 patients with well-differentiated endocrine carcinomas and a positive tracer uptake at (111)In-pentetreotide scintigraphy. Overall survival and expression of sst1 to sst5 receptors by immunohistochemistry were assessed. RESULTS: The lack of tracer uptake at the (111)In-pentetreotide scintigraphy seemed to be a poor prognostic factor ($P = .007$) for overall survival by Kaplan-Meier test and in multivariate analysis; age and absence of clinical secretory syndrome also seemed to be poor prognostic factors. The tracer uptake (positive (111)In-pentetreotide scintigraphy) correlated with the tumor expression of somatostatin receptor sst2 ($P < .001$) but not with that of sst1, sst3, sst4, or sst5. In a bivariate analysis, lack of sst2 expression also significantly correlated with poor prognosis. CONCLUSION: We demonstrate the prognostic value of (111)In-pentetreotide scintigraphy in well-differentiated

malignant endocrine tumors. In these tumors, sst2 somatostatin receptor expression correlates with both tracer uptake and a better prognosis.

http://www.ncbi.nlm.nih.gov/pubmed/17213340

Prognosis and risk factors of metastasis in colorectal carcinoids: results of a nationwide registry over 15 years.

Citation

Gut, 2007, 56(6): 863-868.

Authors

Konishi, T., Watanabe, T., Kishimoto, J., Kotake, K., Muto, T., & Nagawa, H.

Abstract

BACKGROUND: Colorectal carcinoids are often described as low-grade malignant. However, no study has compared the survival between patients with colorectal carcinoids and those with carcinomas, in a large series. In addition, no global consensus has been established on the crucial determinants of metastasis in colorectal carcinoids. AIM: To determine the predictive factors for metastasis in colorectal carcinoids and clarify their prognosis compared with adenocarcinomas. METHODS: Data of all patients diagnosed as having colorectal carcinoids were extracted from a large nationwide database of colorectal tumours, the Multi-Institutional Registry of Large-Bowel Cancer in Japan, for the period from 1984 to 1998. Risk factors for lymph node (LN) metastases and distant metastases were analysed among those who were undergoing surgery, by univariate and multivariate analysis. Cancer-specific survival was also compared between patients with colorectal carcinoids and those with adenocarcinomas registered in the same period. RESULTS: Among the 90 057 cases of colorectal tumours that were diagnosed, a total of 345 cases of carcinoids were identified, including 247 colorectal carcinoids of those undergoing surgery. Risk factors for LN metastasis were tumour size >/=11 mm and lymphatic invasion, whereas those for distant metastasis were tumour size >/=21 mm and venous invasion. Colorectal carcinoids without these risk factors exhibited no LN metastasis or distant metastasis. Cancer-specific survival of patients with colorectal carcinoids without metastasis was better than that of those with adenocarcinomas. However, the survival was similar between carcinoids and adenocarcinomas if the tumours had LN metastasis or distant metastasis. CONCLUSIONS: The presence of metastasis in colorectal carcinoids could lead to survival that is as poor as in adenocarcinomas. Tumours </=10 mm and without lymphatic invasion could be curatively treated by local resection, but others would need radical LN dissection.

http://www.ncbi.nlm.nih.gov/pubmed/17383419

Survival from malignant digestive endocrine tumors in England and Wales: a population-based study.

Citation

Gastroenterology, 2007, 132(3): 899-904.

Authors

Lepage, C., Rachet, B., & Coleman, M.P.

Abstract

BACKGROUND AND AIMS: Little is known about the prognosis of patients with malignant digestive endocrine tumors (MDETs), primarily because of their rarity. METHODS: Survival from these tumors has been evaluated in a large, well-defined, national population. All patients diagnosed and registered in England and Wales during the 14-year period from 1986 to 1999 were followed up for vital status to the end of 2001. Relative survival was estimated

and the impact of age, sex, period, histology, and anatomic site modeled. RESULTS: Among 4104 cases of MDETs, 21.2% were small cell tumors. Relative survival for all MDETs combined was 45.9% at 5 years and 38.4% at 10 years. Five-year survival was 56.8% for well-differentiated tumors but only 5.2% for small cell tumors (P < .0001). Survival was highest for large bowel tumors and lowest for esophageal tumors. Among well-differentiated pancreatic tumors, 5-year relative survival was 49.2% for insulinomas, 39.9% for gastrinomas, 17.1% for glucagonomas, 26.3% for carcinoid tumors, and 29.3% for nonfunctioning tumors. There was no difference in survival between socioeconomic groups. Five-year survival did not improve between 1986 and 2001. Survival was higher for women and for younger patients. Gender, age at diagnosis, and anatomic site were independent prognostic factors. CONCLUSIONS: The prognosis of patients with MDETs in the general population is considerably worse than is often reported from small hospital case series. Prognosis varies with tumor differentiation, anatomic site, and histologic type. Early diagnosis is difficult; new therapeutic options appear to represent the best approach to improved prognosis

http://www.ncbi.nlm.nih.gov/pubmed/17939909

[Trends in prognostic factors for neuroendocrine lung tumors] [Article in Spanish]

Citation
Archivos Bronconeumologia, 2007, 43(10): 549-556.
Authors
Garcia-Yuste, M., Molins, L., Matilla, J.M., González-Aragoneses, F., López-Pujol, J., & de la Torre, M.: (EMETNE-SEPAR).
Abstract
OBJECTIVE: The aim of this study was to analyze trends in a variety of prognostic factors for neuroendocrine lung carcinomas through analysis of 2 groups of surgically treated patients. PATIENTS AND METHODS: Group A contained the first 361 patients, treated between 1980 and 1997. That group was analyzed retrospectively and contained 261 patients with typical carcinoid tumors, 43 with atypical carcinoid tumors, 22 with large-cell neuroendocrine carcinoma, and 35 with small-cell neuroendocrine carcinoma. Group B contained 404 patients enrolled prospectively between 1998 and 2002: 308 with typical carcinoid tumors, 49 with atypical carcinoid tumors, 18 with large-cell neuroendocrine carcinoma, and 29 with small-cell neuroendocrine carcinoma. The following clinical variables were considered: sex, mean age, tumor site, tumor size, lymph node involvement, stage, metastasis, and local recurrence. The 1997 TNM classification was used for staging of lung cancer and survival analysis was performed along with assessment of factors influencing survival. Statistical analysis of the data involved univariate and multivariate analysis. RESULTS: In both groups, significant differences were observed between patients with typical and atypical carcinoid tumors in terms of mean age, tumor size, node involvement, and recurrence. In group A, female sex, node involvement, and recurrence differed between patients with atypical carcinoid tumors and those with large-cell neuroendocrine carcinoma; the same was true for group B, with the exception of lymph node involvement. Node involvement differed between patients with small-cell versus large-cell neuroendocrine carcinoma in group A but not group B. Both groups displayed significant differences in overall survival and survival of patients with lymph node involvement between patients with typical and atypical carcinoid tumors and between patients with atypical carcinoid tumors and those with large-cell neuroendocrine carcinoma; no differences were observed between patients with large-cell versus small-cell neuroendocrine carcinoma. Histological type and lymph node involvement had the greatest influence on prognosis in the multivariate analysis. CONCLUSIONS: A well-defined trend is

observed in prognostic factors for neuroendocrine lung tumors. Histological type and lymph node involvement show the greatest influence on survival.

http://www.ncbi.nlm.nih.gov/pubmed/16556667

Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours.

Citation
Gut, 2006, 55(11): 1586-1591.
Authors
Turner, G.B., Johnston, B.T., McCance, D.R., McGinty, A., Watson, R.G., Patterson, C.C., & Ardill, J.E.
Abstract
BACKGROUND AND AIMS: Midgut carcinoid tumours are uncommon tumours with an unpredictable clinical behaviour and few useful prognostic markers. Somatostatin analogues are widely used in treatment but a survival advantage has not been proven. We analysed features associated with poor prognosis and assessed the clinical implications of the biochemical response to therapy. METHODS: Clinical and biochemical data were collected for patients with midgut carcinoid tumours attending a tertiary referral neuroendocrine clinic from 1978 to 2000. Using death as the end point, univariate and multivariate survival analyses were performed to identify prognostic indicators. The significance of altering biomarkers with therapy was also studied by including repeated measurements of the most prognostic biochemical parameter in a time dependent covariate survival analysis. RESULTS: We identified 139 patients with sufficient data for our analyses. Factors associated with a poor outcome on univariate analysis included: plasma neurokinin A (NKA), urinary 5-hydroxyindolacetic acid output, age, and >/=5 liver metastases. Plasma NKA was the strongest and only independent predictor of outcome on multivariate analysis. Patients in whom NKA continued to rise despite somatostatin analogues had a significantly worse survival than those in whom NKA stabilised or fell (one year survival rate 40% v 87%). Time dependent covariate analysis concluded that survival was better predicted by the most recent plasma NKA value rather than by the initial value. CONCLUSIONS: Plasma NKA is an accurate marker of prognosis for midgut carcinoid tumours. This is the first paper to support a survival advantage in patients in whom plasma NKA is altered by somatostatin analogues.

http://www.ncbi.nlm.nih.gov/pubmed/16322345

Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization.

Citation Endocrine-Related Cancer, 2005, 12(4): 1083-1092.

Authors
Panzuto, F., Nasoni, S., Falconi, M., Corleto, V.D., Capruso, G., Cassetta, S., Di Fonzo, M., Tornatore, V., Milione, M., Angeletti, S., Cattaruzza, M.S., Ziparo, V., Bordi, C., Pederzoli, P., & Delle Fave, G.

Abstract
Since gastro-entero-pancreatic endocrine tumors are rare and heterogeneous diseases, their prognosis and long-term survival are not well known. This study aimed at identifying prognostic factors and assessing long-term survival in gastro-entero-pancreatic endocrine

tumors. A total of 156 patients enrolled. Prognostic factors were determined by univariate/multivariate analysis; survival rates were assessed by the Kaplan-Meier method. The tumors were non-functioning in 59.6% of patients, and originated from the pancreas in 42.9%. At diagnosis, 64.3% of patients had metastases. The tumors were well differentiated in 89.6% of patients. Ki67 was >2% in 39.6% of patients. Primary tumor size was >3 cm in 49.6% of cases studied. For the univariate analysis, the negative prognostic factors were: pancreatic origin (rate ratio 4.64, P = 0.0002), poorly differentiated tumor (rate ratio 7.70, P = 0.0001), primary tumor size >3 cm (rate ratio 4.26, P = 0.0009), presence of distant metastases (liver: rate ratio 5.88, P = 0.01; distant extra-hepatic: rate ratio 13.41, P = 0.0008). The pancreatic site, the poor degree of differentiation and the distant metastases were confirmed as negative prognostic factors at multivariate analysis. Overall 5-year survival rate was 77.5%. Survival rates differed according to: primary tumor site (62% for pancreatic vs 89.9% for gastrointestinal tract, P = 0.0001) and size (65.7% for >3 cm vs 88.8% for < or = 3 cm, P = 0.0003), degree of differentiation (22% for poor vs 86.8% for good, P < 0.0001), Ki67 (53.5% for > 2% vs 90.1% for < or = 2%, P = 0.003), metastases (96.1, 77, 73.3 and 50.1% for absent, local, liver and distant extra-hepatic metastases respectively), age at diagnosis (85.3% for < or = 50 years vs 70.3% for > 50 years, P = 0.03). Although 64.3% of gastro-entero-pancreatic endocrine tumors present metastases at diagnosis, the 5-year survival rate is 77.5%. Pancreatic site, a poor degree of tumor cell differentiation and distant extra-hepatic metastases are the major negative prognostic factors.

http://www.ncbi.nlm.nih.gov/pubmed/15719376

Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract.

Citation
Journal of Surgical Oncology, 2005, 89(3): 151-160.

Authors
Rorstad, O.

Abstract
Factors that determine the clinical course and outcome of patients with gastrointestinal (GI) carcinoid tumors are complex and multifaceted. These include the site of origin within the GI tract, the size of the primary tumor, and the anatomical extent of disease, whether localized, regional, or metastatic to distant sites. The new World Health Organization (WHO) histological classification of endocrine tumors, including carcinoids, represents a significant advance in terms of providing a consistent framework for histopathological interpretation that should facilitate multicenter research on treatment outcomes. Histochemical indicators of a poorer prognosis are the degree of expression of the proliferation protein Ki-67 and the p53 tumor suppressor protein. Adverse clinical indicators are the malignant carcinoid syndrome, carcinoid heart disease, and high concentrations of the tumor markers, urinary 5-HIAA and plasma chromogranin A

http://www.ncbi.nlm.nih.gov/pubmed/15807874

Circulating levels of angiogenic cytokines can predict tumour progression and prognosis in neuroendocrine carcinomas.

Citation

Clinical Endocrinology (Oxf)., 2005, 62(4): 434-443

Authors
Pavel, M.E., Hassler, G., Baum, U., Hahn, E.G., Lohmann, T., & Schuppan, D.

Abstract
OBJECTIVE: The growth behaviour of well-differentiated neuroendocrine carcinomas of the gastro-entero-pancreatic system varies greatly and parameters predicting their prognosis are lacking. The aim of our study was to investigate whether tumour growth could be correlated with the release of proangiogenic factors into the circulation. PATIENTS AND METHODS: Circulating vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), basic fibroblast growth factor (bFGF) and angiogenin were measured in 38 patients with advanced neuroendocrine carcinomas and compared to healthy age-matched controls. In 20 patients, angiogenic cytokine levels were measured at consecutive time points and correlated to tumour progression as assessed by abdominal CT scan, MRI and chromogranin A levels. RESULTS: VEGF levels were elevated in patients compared to controls ($P < 0.002$) and clearly associated with tumour progression ($P < 0.005$). Angiogenin levels were significantly higher in patients than in controls ($P < 0.003$), while high IL-8 levels were predictive of shorter survival. Angiogenin and bFGF levels were correlated neither with tumour growth nor with patient survival. CONCLUSIONS: VEGF and IL-8 are associated with tumour progression and might qualify as markers of prognosis and therapy control in patients with neuroendocrine carcinomas. Our results support the notion that specific anti-angiogenic therapies should be evaluated in neuroendocrine carcinoma patients.

http://www3.interscience.wiley.com/journal/118765678/abstract

Survival and Clinical Outcome of Patients with Neuroendocrine Tumors of the Gastroenteropancreatic Tract in a German Referral Center.

Citation
Annals of the New York Academy of Sciences, 2004, 1014: 222-233.

Authors
Pape, U-F., Böhmig, M., Berndt, U., Tilin, N., Wiedenmann, B., & Plöckinger, U.

Abstract
Neuroendocrine tumors (NETs) are rare neoplasms. Approximately 75% of all cases manifest in the gastroenteropancreatic (GEP) system. Because of the low incidence of NETs, limited data about the clinical outcome and prognostic variables are available. In an attempt to identify prognostic parameters, we investigated the distribution of primary tumors, pattern of metastasis formation, clinical presentation, histological classification, and outcome of therapeutic interventions in a large patient cohort cared for in a German referral center. In 254 patients with GEP-NETs, the primary tumor was of foregut, midgut, or hindgut origin in 44.1% (28.7% pancreas), 43.7% (34.7% jejunoileum), and 4.3%, respectively. No primary tumor was found in 7.9%. Metastases occurred preferentially in lymph nodes and the liver. The overall 5-year survival rate was 57.1%. In the absence or presence of metastases at initial diagnosis the 5-year survival rate was 80.0% and 51.7%, respectively. The 5-year survival rate was related to the localization of the primary and was 75.0% and 42.9% for jejunoileal and pancreatic tumors, respectively. The size of the primary tumor (<2 cm) and histological grading as low-grade malignant were both associated with a significantly longer survival. Surgery with curative intent was attempted in 141 patients. However, an R_0 resection was achieved in only 66.0% of these patients. Five-year survival rate in the latter group was significantly higher (77.3%) as compared with all surgical patients (55.4%). Long-term tumor-

free survival was obtained in only 53.7% of successfully resected patients. Palliative medical treatment, either with chemotherapy (i.e., especially for foregut NETs) or biotherapy (especially for midgut NETs), was only moderately effective for both therapeutic regimens.

http://www.ncbi.nlm.nih.gov/pubmed/14994141
Gastrointestinal carcinoid tumors: factors that predict outcome.
Citation
World Journal of Surgery, 2004, 28(4): 387-392.

Authors
Van Gompel, J.J., Sippel, R.S., Warner, T.F., & Chen, H.
Abstract
Gastrointestinal (GI) carcinoids are neuroendocrine tumors originating in multiple locations throughout the GI tract. The prognosis for patients with GI carcinoid tumors is diverse. To determine the factors that significantly affect prognosis, we reviewed our experience. Between 1992 and 2000 a total of 70 patients with GI carcinoid tumors underwent surgical resection at our institution. The patients were grouped into three categories based on the origin of the carcinoid tumor: foregut, midgut, hindgut. The mean age of the patients was 56 +/- 2 years. All patients with foregut carcinoids had symptoms upon presentation, whereas 61% of those with midgut carcinoids and only 37% of those with hindgut carcinoids had symptoms ($p < 0.001$). The factors that most strongly affected survival on univariate analysis were a symptomatic presentation and the site of origin. Patients with foregut or midgut lesions had lower 5-year disease-free survivals than those with hindgut tumors. Moreover, the size of the primary tumor and the presence of liver metastases were not independent predictors of survival. Despite the larger tumor size and the higher incidence of liver metastases, patients with foregut carcinoids appear to have the same prognosis as those with midgut carcinoids. These data therefore suggest that the outcomes of patients with carcinoid tumors are highly dependent on the presence of symptoms and the site of origin.

http://www.ncbi.nlm.nih.gov/pubmed/14603164
Gastrointestinal carcinoids. Prognosis and survival.
Citation
Minerva Chirugica, 2003, 58(4): 523-528, 529-532.

Authors
Caprotti, R., Angelini, C., Mussi, C., Romano, F., Sartori, P., Scaini, A., Muselli, P., & Uggeri, F.
Abstract
BACKGROUND: Gastrointestinal carcinoid tumors are rare and little is known about factors related to prognosis in patients with carcinoid disease. Aim of this study is to determine the impact of clinical presentation variables on the management and survival. METHODS: We have evaluated 31 consecutive patients with gastrointestinal carcinoid tu-mours who underwent surgical intervention at the I Department of Surgery of Milano-Bicocca University over 15 years (1985-1999). Tumor distribution, hormone production, prognostic factors and survival were analysed. RESULTS: Carcinoid syndrome was the only clinical pattern diagnostic of carcinoid tumour. Most common symptoms were abdominal pain (64%), nausea and vomiting (48%). High levels of urinary 5-hydroxyindolacetic acid were significantly associated with carcinoid syndrome and metastatic disease. Tumor size, depth and gender were significant predictors of metastases. Age, gender, tumor size, metastatic spread and location were statistically significant predictors of death. CONCLUSIONS: Clinical presentation was non specific except for those patients affected by carcinoid syndrome. Ten

years overall survival was 43%, with 52% metastatic spread incidence. The extent of surgical resection should be modulated on patient related risk factors. Poor prognostic factors affecting survival were: age, gender, metastatic disease, depth of invasion and tumour size.

http://www.ncbi.nlm.nih.gov/pubmed/11296182

Typical and atypical pulmonary carcinoids : outcome in patients presenting with regional lymph node involvement.

Citation
Chest , 2001, 119(4): 1143-1150.

Authors
Thomas, C.F. Jr., Tazelaar, H.D., & Jett, J.R.

Abstract
STUDY OBJECTIVE: Typical pulmonary carcinoid tumors are well-differentiated neuroendocrine tumors that are associated with good patient survival rates, while atypical carcinoid tumors are more aggressive and have worse patient survival rates. Because these tumors rarely involve the thoracic lymph nodes at presentation, it is currently unknown to what extent the presence of thoracic lymph node metastases at the time of diagnosis influences patient survival. METHODS: A computerized search of the medical records for pulmonary carcinoid tumor at the Mayo Clinic from 1976 to 1997 revealed 517 patients, from which we identified 36 patients with pulmonary carcinoid tumors involving regional thoracic lymph nodes but without distant disease. For each patient, we reviewed the tumor histology, stage, and outcome. In addition, because the histologic criteria for the diagnosis of carcinoid tumors had changed significantly during the time of the study, we reexamined all of the histologic specimens using the current World Health Organization (WHO) criteria for classifying pulmonary neuroendocrine tumors. RESULTS: After reclassification with the WHO criteria for neuroendocrine tumors, 23 patients had typical carcinoid tumors with thoracic lymph node involvement. At the last follow-up, 19 patients had no evidence of disease (NED), 2 patients had developed systemic metastases (SM) and are still alive, and 2 patients had died. Eleven patients had atypical carcinoid tumors with thoracic lymph node involvement. At the last follow-up, four patients had NED, seven patients had developed SM within a median time of 17 months, and six patients with SM died shortly thereafter (median survival time, 25.5 months), while one is still alive. Two patients had been reclassified with large cell neuroendocrine carcinoma at the time of this review; both of these patients had developed SM (at 4 months and 21 months after diagnosis) and had died (at 15 months and 21 months after diagnosis, respectively). CONCLUSIONS: These data suggest that patients with atypical pulmonary carcinoid tumors with regional lymph node metastases have a high likelihood of developing recurrent disease if treated with surgical resection alone and have significantly worse outcome ($p < 0.001$) compared to those patients with typical carcinoid tumors with thoracic lymph node involvement.

http://www.ncbi.nlm.nih.gov/pubmed/11038218

Gastrointestinal carcinoid tumors: long-term prognosis for surgically treated patients.

Citation
World Journal of Surgery, 2000, 24(11): 1431-1436.

Authors
Söreide, J.A., van Heerden, J.A., Thompson, G., Schleck, C., Ilstrup, D.M., & Churchward, M.

Abstract
To evaluate long-term survival of patients with gastrointestinal carcinoid tumors and to assess factors that may influence prognosis, 154 patients (49% females, 51% males), median age 62 years (range 12-84 years) treated at our institution during 1972-1982 have been followed long term. Tumor location included the foregut (7%), midgut (62%), and hindgut (30%). Ninety-five percent of the patients underwent surgical or endoscopic excision of the primary tumor, with overall operative mortality and postoperative morbidity rates of 2. 6% and 11%, respectively. At follow-up, 60 patients (39%) were alive (median follow-up 18 years; range 1-26 years). The main causes of death included carcinoid tumor burden (32%), unrelated causes (45%), other malignancy (19%), and unknown causes (4%). Observed overall 5- and 10-year survivals were 69% and 53%, respectively. Survival was not related to gender or symptoms at presentation. However, age, embryologic origin, tumor size, depth of invasion, nodal status, and stage of disease proved to be of statistical significance (log-rank). In a multivariate Cox' model, only older age (> 62 years) [P = 0. 001, odds ratio (OR) = 3.4) and embryologic origin (midgut versus foregut) (P = 0.045, OR = 0.45) provided independent prognostic power when death from any cause was taken as the end-point. This study confirms that patient's age and the site of the primary tumor have prognostic significance. Carcinoid tumors are neuroendocrine tumors with a relatively good prognosis, and long-term survival is possible despite advanced stages of disease.

http://www.ncbi.nlm.nih.gov/pubmed/10999844
Prognostic markers in patients with typical bronchial carcinoid tumors.
Citation
Journal of Clinical Endocrinology & Metabolism, 2000, 85(9):3425-3430.

Authors
Granberg, D., Wilander, P., Oberg, K., & Skogseid, B.

Abstract
Typical bronchial carcinoids are usually considered fairly benign tumors. Metastases do however occur, and up to 10% of the patients ultimately die from their disease. To identify prognostic markers, we immunostained 43 typical bronchial carcinoids with antibodies against 8 possibly relevant hormones, oncogenes, tumor suppressor genes, adhesion molecules, and proliferation markers. Altogether 12 patients (28%) had metastatic disease, of whom 10 had regional lymph node metastases at diagnosis. Distant metastases have occurred in 5 patients (12%); all of these have died from their disease. Patients with high expression of Ki-67 had shorter survival time (P < 0.01). None of the immunostained hormones correlated to distant metastases or shorter survival time, but gastrin-releasing peptide correlated to metastatic disease (P < 0.05). All patients who died had CD44-negative tumors (P < 0.001). Nuclear nm23 staining correlated to decreased risk for metastatic disease and distant metastases per se (P < 0.01). Bcl-2 and p53 were associated with increased risk for distant metastases (P < 0.05 and P < 0.01, respectively). We conclude that some patients with typical bronchial carcinoids die from their disease and that gastrin-releasing peptide, Bcl-2, and p53 may be of importance for the malignant transformation of the tumor. Moreover, CD44, nm23, and Ki-67 may give valuable prognostic information and help identify the patients at risk of disease-related death.