Colorectal neuroendocrine tumors

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ABSTRACT

Gastrointestinal neuroendocrine tumors originate from amine precursor uptake and decarboxylation cells in the digestive tract and have the ability to undergo multiple differentiation and secrete various active hormones, leading to significant differences in biological behaviors and prognosis. Previous studies have indicated a low incidence rate, but recently epidemiological investigations in the USA showed that the incidence rate was significantly higher. Gastrointestinal neuroendocrine tumors have received much attention in recent years with regard to their diagnosis, classification, prognosis and treatment.

Keywords: neuroendocrine tumors, gastrointestinal tract, colorectal cancer, carcinoid

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), as part of neuroendocrine tumors, are a heterogenous group of tumors derived from neuroendocrine cell compartments in various organs including pancreas, stomach, colorectum and biliary tract. Data from recent population-based studies demonstrate a significant increase in the incidence of NETs over time which ranges from 2.5 to 5 cases per 100000 in Caucasian population. This is attributable to increasing awareness, improved diagnostic strategies for NETs and possibly other undetermined environmental and genetic factors (1). There is a slight overall higher incidence of neuroendocrine tumors for males (5.35) compared with females (4.76). Regarding race, a white predominance (89%) has been demonstrated (2,3).

According to the Surveillance, Epidemiology and End results (SEER) database, more than half of all NETs are gastroenteropancreatic NETs (GEP-NETs) (61%), with the highest frequency being observed in the rectum (17.7% of NETs), small intestine (17.3% of NETs) and colon (10.1% of NETs), followed by pancreas (7.0%), stomach (6.0%), and appendix (3.1%) (2).

The new World Health Organization (WHO) Classification of Tumors of the Digestive System presented in 2010 defines the entire group of tumors as neuroendocrine neoplasms and divides them into neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma (MANEC), hyperplasia and pre-neoplasm. Mixed adenoneuroendocrine carcinoma (MANEC) is morphologically recognizable as both gland-forming epithelial and neuroendocrine phenotype, with each component representing at least 30% of the lesion. The monomorphous endocrine cells of MANEC have a characteristic of bidirectional differentiation. So, exocrine glandular cells are the key points of MANEC distinguish from other neuroendocrine neoplasms. MANEC are further classified into collision and composite types. Mixed histology tumors are more often found in the appendix and cecum. The poorly differentiated NECs have two subtypes small cell and large cell neoplasms (4).

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The grading system is based on mitotic activity and the percentage of Ki-67 labeled proliferating cells: Grade 1, grade 2 and grade 3 (= neuroendocrine carcinoma) are defined by mitotic counts of < 2/10 high power fields (HPF), 2-20/10 HPF and > 20/10 HPF, respectively, and/or by Ki-67 indices of ≤ 2%, 3%-20% and > 20%, respectively (4).

The European Neuroendocrine Tumor Society has proposed a tumor–node–metastasis staging and grading system for various types of GEP-NETs (5).

Among neuroendocrine tumors, the ones developing in the colon and the rectum are grouped together in the WHO classification and are distinguished from those of the appendix or the ileum. Colorectal carcinoids are described as "low-grade malignant", even in the presence of metastasis. The WHO classification defines colorectal carcinoids as 'benign' if the tumors measure 20 mm or less, are localized in the submucosa and have no vascular invasion. Although most colorectal carcinoids are localized at the time of diagnosis and have low malignant potential, rectal carcinoids measuring less than 1cm in size still have malignant potential with a recorded incidence of metastasis ranging from 1.7 to 3.4%. Rectal carcinoids are defined as tumors located within 15cm of the anal verge, whereas tumors more than 15cm above the anal verge are considered colonic carcinoids (6,7).

Extraappendiceal colonic NE tumors, including tumors of the rectosigmoid junction but excluding those of the rectum, are rare malignancies accounting for 1% of colonic neoplasms, 9.6% of all NE and 14.1% of gastrointestinal NE tumors. The predominance of right-sided carcinoid tumors may be due to a greater number of enterochromaffin cells in the right colon, or to the fact that tumors from the appendiceal base extend into the cecum (3,8).

DIAGNOSIS

Colorectal neuroendocrine tumors grow slowly and are often clinically silent for many years before becoming manifest. They frequently metastasize to the regional lymph nodes, liver, and, less commonly, to the bones. Colonic carcinoid tumors typically present in the seventh decade with nonspecific digestive tract symptoms – abdominal pain, abdominal distention, diarrhea, constipation, anorexia, weight loss or hematochezia (8,9).

Although carcinoids classically are tumors of enterochromaffin and argentaffin cells of the digestive tract, the term carcinoid tumor can be expanded to cover gut tumors of paracrine- and endocrine-like cells of unknown function. It is now established that these tumors have a neuroendocrine origin and derive from a primitive stem cell. They may differentiate into any one of a variety of adult endocrine secreting cells: βcell and insulinoma, α cell and glucagonoma, δ cell and somatostatinoma, and the PP cell and PPoma, or cells capable of producing ACTH, growth hormone-releasing hormone, VIP, SP, calcitonin, gastrin-releasing factor, Ghrelin, serotonin and the peptide motilin. These cells may secrete one humor at any one point in time whereas at others, the peptide or amine secreted may differ and generate an entirely different clinical syndrome. Metastases are known to secrete hormones that differ from the primary tumor, and different metastases may secrete different hormones (2,6,10).

The carcinoid syndrome, which occurs in less than 10% of patients with carcinoid tumors, comprises multiple signs and symptoms associated with hypersecretion of vasoactive substances (serotonin, histamine, prostaglandins and tachykinins) by the carcinoid tumor. It includes cutaneous flushing (in 84% of patients), gastrointestinal hypermotility with diarrhea (70%), heart disease (37%), bronchial constriction (17%), myopathy (7%), and an abnormal increase in skin pigmentation (5%). Urinary 5-HIAA (24-hour collection) is an useful laboratory marker for carcinoid tumors (8-11).

Thus, NETs can be classified into functional or nonfunctional tumors according to the symptoms associated with peptides and hormones production. Carcinoid syndrome, Whipple triad Zollinger-Ellison syndrome, Verner-Morrison syndrome and glucagonoma syndrome are typical symptoms of functional NETs. Most colorectal carcinoids are non-functioning, carcinoid symptomatology being less than 5% (12,13).

The mean tumor size of colonic carcinoid tumors at presentation has been reported at approximately 5 cm. The cecum is the most frequent location and the tumors are often diagnosed at the late stages of IIIb or IV, with lymph node involvement and distant metastases (3,8). Al Natour and colleagues (14) described a recent trend of increased incidence of smaller and more superficial colonic carcinoid tumors. This is a result of the expanding use of screening colonoscopy, leading to earlier detection of clinically occult colonic lesions. Colonoscopy is the most useful method of diagnosing and treating rectal NETs. Macroscopically, typical NETs ap-

pear as yellowish, sessile, submucosal tumors, but some have unusual morphology with irregular surfaces or being hyperemic and pedunculated (15).

Definitive diagnosis of GEP-NETs mainly relies on pathological examination. The family of neuroendocrine GEP-NETs, even if it is a heterogenous group, share a common phenotype with immunoreactivity for the pan-neuroendocrine markers including chromogranin A and synaptophysin. Neuroendocrine cells in non-neoplastic and neoplastic tissue of the gastrointestinal tract and nerve elements express a panel of identical antigens, which are used as neuroendocrine markers. The markers chromogranin A, B and C, synaptophysin, HISL-19, proprotein convertases PC2 and PC3, neuron-specific enolase (NSE), lymphoreticular epitope Leu-7 and the neural cell adhesion molecule (CD56) are sufficient to sustain neuroendocrine differentiation independent of hormone production (14-16). The most important of these markers, chromogranin A (CgA), is a 49-kDa acidic polypeptide present in the secretory granules of neuroendocrine cells. Plasma CgA is elevated in 50% to 100% of patients with either functioning or nonfunctioning NETs. The sensitivities and specificities of CgA for the detection of NETs range between 70% and 100% (17).

A detailed description of the macroscopic, microscopic and immunohistochemical findings is mandatory to support the diagnosis of NETs allowing thus a proper classification, grading and staging. Immunohistochemistry for Ki-67 is mandatory to grade the tumor according to the new WHO classification.

Colonic carcinoids exhibit one of the worst prognoses of all gastrointestinal carcinoid tumors. Prior studies from the 1970s to 1990s reported 5-year survival rates between 23% and 42%. A more recent analysis of 477 patients from the SEER database reported 5-year survival rates for extraappendiceal colonic carcinoid tumors ranging from 59% to 87%. The poor prognosis of colonic carcinoid tumors is considered to be a result of the large tumor diameter, higher rates of regional and distant metastatic disease at the time of diagnosis and higher rate of undifferentiated histologic pattern with more aggressive clinical features than carcinoids at other sites (3,8,13).

Patients with a small neoplasm size, shallow invasion, no lymph node metastasis, a low pathological grading and no expression of CgA have a better prognosis. Tumor size was often cited as the most important prognostic indicator for carcinoid tumors, but the best indicators are the evidence of invasive growth and the presence of regional or distant metastasis. Colonic carcinoids exhibit one of the highest rates of nonlocalized disease at presentation of all carcinoid tumors with an overall rate of lymph node metastasis of 48% to 72% and distant metastasis present at the time of diagnosis in 25% to 31% of the patients. (9,13,14)

Given this propensity for metastatic spread, widely accepted consensus guidelines recommend a formal segmental colectomy with oncologic resection of the lymph drainage. Isolated hepatic metastases should be resected if possible (14,18,19). Rectal carcinoids have a risk of lymph node metastasis and distant metastasis varies depending on tumor size A population-based study in Japan reported lymph node metastasis of 3.7% for rectal carcinoids with sizes of 5 mm or less and 9.7% lymph node metastasis for tumors with sizes of less than 10 mm (6,20,21). Analysis of the Connecticut Tumor Registry data found that one out of 6 tumors <2 cm was nonlocalized, compared to metastasis in two thirds of patients with tumors >2 cm. Al Natour and colleagues utilizing the SEER database analyzed predictors of lymph node metastasis based on tumor size and depth of invasion. They found that tumor size (stratifying tumors <1, ≥1 and <2, or ≥2 cm) and depth of invasion (intramucosal, submucosal, or muscularis propria) highly correlated with regional lymph node metastasis Furthermore, patients with intramucosal tumors <1 cm had only a 4.0% rate of lymph node metastasis (13,14,18,19).

Endoscopic ultrasound is excellent for determining exact tumor size and to exclude infiltration of the NETs into the muscular wall (muscularis propria). Endoscopic ultrasound is not mandatory for NETs measuring less than 1 cm, because those do generally not infiltrate the muscular layer.

THERAPEUTIC APPROACHES

Endoscopic removal, followed by endoscopic surveillance is the treatment of choice in NETs/carcinoids of the gastrointestinal tract that are ≤ 10 mm in size, have a low proliferative activity (G1), do not infiltrate the muscular layer and have no angioinvasion. In all the other intestinal NETs, optimal treatment needs surgery and/or medical therapy depending on type, biology and stage of the tumor (20,21).

New developments in the endoscopic technology allow early detection of mucosal abnormalities that are amenable to endoscopic. Resection-based modalities consist of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). ESD is a newly developed technique that allows en bloc resection of larger (usually more than 20 mm) mucosal as well as subepithelial gastrointestinal lesions above the muscularis propria with the use of cutting devices (22).

For tumors with size between 10 and 20mm local excision is usually recommended, but radical surgery should be considered if there is evidence of lymph node metastasis or lymphovascular invasion on biopsy. Controversy resides since no established treatment guideline exists. In contrast, radical surgery is recommended for tumors larger than 20 mm, where the risk of metastasis is known to be 60 to 80%. Shields et al. (23) reported that a tumor size of more than 10 mm and lymphovascular invasion were significantly associated with the presence of nodal disease, rendering mesorectal excision advisable. Cytoreductive surgery is recommended for palliation and to increase survival for patients with advanced disease. To rule out distant metastasis, imaging studies, such as CT or magnetic resonance imaging, are recommended for patients with rectal carcinoids larger than 20 mm (24).

Surgical treatment, dependent on neoplasm size, site and depth of invasion, is required to resect the primary site of the neoplasm, any sites of metastasis and lymph nodes in order to improve survival rates. Carcinoids of the appendix are often found incidentally during appendectomy. The majority of appendiceal carcinoids are small (<1 cm), located at the tip of the appendix and often cured with appendectomy. A radical right hemicolectomy is recommended when the primary tumor is ≥2 cm, incompletely resected, invades the base of the appendix or meso-appendix, displays lymphovascular invasion, lymph node metastases and unfavorable histology or grade. The need for right hemicolectomy in appendiceal carcinoid of 1-2 cm in size remains controversial, and decided on a case by case basis. In cecal carcinoids, usually presenting as a bulky mass causing intestinal obstruction or hemorrhage, an oncologic resection is also recommended (25). Cytoreductive surgery should be considered when metastatic disease is localized or if >70% of tumor load is thought resectable, which may decrease endocrine and local symptoms and help improving systemic treatment. There are no randomized clinical trials comparing the efficacy of locoregional therapies and palliative liver surgery. The choice of the ablative or locoregional procedure such as radiofrequency ablation (RFA), laser-induced thermotherapy or selective hepatic transcatheter arterial embolization (TAE), chemoembolization (TACE) and selective internal radiotherapy (SIRT) depends on the local expertise, number and size of lesions and location of liver involvement. These types of locoregional therapies are usually used in combination with systemic medical treatment (26,27).

An R0 situation should be the aim of hepatic surgery, but also patients with R1 or R2 resection show a good survival benefit.

In GEP-NET there is a wide array of other therapeutic options, such as interventional radiology, somatostatin analogues, interferon, peptide-receptor radionuclide therapy, targeted agents (sunitinib, everolimus, bevacizumab) and chemotherapy to palliate symptoms and increase survival (18). Biotherapy and molecular targeted therapy have good prospects in the treatment of patients with progressive NET. Chemotherapy is mainly used to treat patients with NEC or MANEC, while NETs have low sensitivity to chemotherapy

The use of somatostatin analogs is standard therapy in functional NETs of any size. Interferon alpha may also be used for symptoms control in some patients, but is usually used as second line therapy due to its toxic profile. The antitumor efficacy of somatostatin analogs appears weak with respect to objective tumor response (5-10%). However, disease stabilization of up to 50-60% has been reported. In a prospective randomized placebo-controlled trial of octreotide long-acting release (LAR), an antiproliferative efficacy has been confirmed. The median time to tumor progression was 14.3 months with octreotide LAR versus 6 months with placebo.

Somatostatin analogs are the recommended first line therapy in functional as well as nonfunctional progressive G1/G2 NETs. In contrast, in metastatic NEC G3 somatostatin analog treatment is not recommended (III, B). Other specific therapies in GEP-NETs are the mTOR-inhibitor everolimus, alone or in combination with a somatostatin analog. In the RADIANT-2 trial which was a randomized phase III trial in patients with NETs (carcinoids), everolimus demonstrated a significant antitumor effect compared with placebo.

Tyrosine kinase inhibitors, sunitinib and pazopanib, have demonstrated significant antitumor efficacy in pancreatic NETs.

Chemotherapy is recommended in metastatic NET G2 and in NEC G3 of any site. A combination of streptozotocin and 5-fluorouracil (5-FU)/ doxorubicin is indicated in patients with inoperable progressive hepatic metastases from G1/ G2 NETs leading to objective response rates of 35-40%. Chemotherapy using cisplatinum/ etoposide is recommended in cases of high-grade NEC G3 with liver metastases regardless of the site of the primary tumor There is no established second-line therapy for poorly differentiated endocrine carcinoma, but recent retrospective studies have demonstrated the efficacy of temozolomide alone or in combination with capecitabine ± bevacizumab. Encouraging results have been obtained with 5-FU i.v. or capecitabine orally combined with oxaliplatin or irinotecan (12,28-30).

Promising data have evolved with regard to peptide receptor targeted radiotherapy (PRRT) using 90Yttrium and 177 Lutetium (31) in the treatment of NETs with liver metastases. PRRT may be considered in both functional and non-functional NETs with positive somatostatin receptor scintigraphy irrespective of the primary tumor site. Based on phase II trials, the objective response rates range between 20% and 40%. The highest objective response rate has so far been obtained in metastatic rectal NETs. Prospective randomized trials are still lacking but in progress.

Follow-up investigations should include biochemical parameters and conventional imaging. In cases with R0/R1 resected NET G1/G2 a CT or MRI is recommended every 3-6 months and in NEC G3, every 2-3 months. Somatostatin receptor imaging, either Octreoscan or PET/CT might be included in the follow-up and is recommended after 18-24 months if expression of somatostatin receptor 2a has been proven in the tumor cells. If chromogranin A is not elevated NSE represents an alternative biomarker (32).

In localized tumors, the 5-year survival is 94%, decreasing to 64% with regional lymph node involvement and 18% with distant metastases. An analysis of overall survival stratified by TNM staging (33) revealed that 5-year survival rates were 100% for stage I and II tumors vs. 91% for stage III (locoregionally advanced) and 72% for stage IV tumors. The median overall survival for stage IV tumors was 103 months. Nodal-negative rectal NETs that are ≤ 1 cm in size without angioinvasion or infiltration of the muscular layer have an excellent 5-year-survival rate of 98.9-100%. For nodal-positive rectal carcinoid disease (without distant metastases detected at the time of diagnosis) the 5-year-survival rate is 54-73%. In rectal NETs with distant metastases, the 5-year-survival rate ranges between 15-30%.

The risk of lymph node metastases of rectal NETs/carcinoids is not lower than the metastatic risk of rectal adenocarcinoma of the same size. Neither is the prognosis of patients with metastatic rectal NET disease better than that of patients suffering from metastastic rectal adenocarcinoma of the same size (33,34). Recent Korean studies suggest that the endoscopic treatment of small (<10 mm) rectal NETs without evidence of regional or distant metastasis can achieve highly favorable long-term outcomes. In contrast, the risk of recurrence is markedly increased in rectal NET patients with metastatic lymph nodes, even after radical surgery (35).

A particulary group of poor survival neuroendocrine tumors is represented by the high-grade neuroendocrine carcinomas, defined as those having a high mitotic rate >10 mitotic figures by 10 high-powered fields, or a Ki-67 proliferative index >20%. They are managed primarily with platinum-based chemotherapy and have a 5-year overall survival of 15% and median survival of 10 months (36)

An important aspect in patients with carcinoid tumors is the increased risk (13% to 41%) of developing a secondary noncarcinoid malignancy compared to the general population. The secreted bioactive agents produce proliferative peptides that may enhance the development of other neoplasia. Most synchronous tumors were observed in the gastrointestinal tract, whereas metachronous tumors were more often observed outside the gastrointestinal tract (13,37).

Colorectal neuroendocrine tumors are reported to have a rate of second primary malignancy in of 5% to 32%. The most common site of associated non-carcinoid malignancies is the gastrointestinal tract, which involves between 32 and 62% of all tumors, followed by the genitourinary tract (9 to 22%) and the lung and/or bronchial system (9 to 13%) (38,39).

Data from many studies strongly suggest that when a carcinoid tumor is identified in a patient, there is a need for close surveillance of the gastrointestinal tract, respiratory system and genitourinary tract. Long-term follow-up is recommended for patients in order to identify delayed metastasis and secondary malignancies. The European Neuroendocrine Tumor Society recommends CT and colonoscopy follow-up

through 10 years, with the frequency of surveillance based on the characteristics of the initial carcinoid tumor (18,40).

CONCLUSIONS

The gastrointestinal tract constitutes the most common site of extra-pulmonary neuroendocrine tumors. Small colorectal neuroendocrine tumors are effectively treated by local resection, which provides good oncological and surgical outcomes. For larger tumors, radical resection provides acceptable oncological outcomes. Regular surveillance is highly recommended for high-risk patients for long-term management.

The treatment of colon and rectal neuroendocrine tumors is complex one and depends of the individuality of each patient. With adequate management, the prognosis can be favorable with long survival, although related to the tumor differentiation degree, efficacy of the chosen treatment and to the patient adhesion to the follow-up after treatment.

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