

Solid Tumour Section Review

Carcinoid Tumors

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Classification

Carcinoid tumors are the most common type of neuroendocrine (NE) tumor and comprise approximately half of all NE tumors of the gastrointestinal (GI) tract. They arise from enterochromaffin cells of the diffuse NE cells of the gut. Carcinoids are commonly classified according to their presumed derivation from the embryonic gut:

Foregut: Lung, bronchial, and gastric

Midgut: Small intestine and appendiceal

Hindgut: Rectal

Leotlela and colleagues suggested that only NE tumors which secrete serotonin, those of midgut embryologic origin, should be referred to as "carcinoids". In 2000, the World Health Organization developed a classification system that dropped the term "carcinoid" entirely, recommending "neuroendocrine tumor" instead. This classification system uses three subsequent classifications based on malignant potential as assessed histologically:

1. Well-differentiated neuroendocrine tumor
2. Well-differentiated neuroendocrine carcinoma
3. Poorly differentiated neuroendocrine carcinoma.

Despite these recommendations, the term carcinoid continues to be used by many clinicians and researchers.

The incidence of carcinoid tumors is estimated at 1 to 2 cases per 100,000 people per annum. Because carcinoids often have an indolent clinical course, they are often misdiagnosed, and their true incidence is likely higher. A Swedish study, in which the incidence of carcinoid tumors was evaluated in surgical specimens and autopsies, estimated the true incidence of carcinoids to be 8.4 cases per 100,000. Sixty four percent of all carcinoids originate in the GI tract, and

28% originate in the lungs or bronchi. Within the GI tract, small intestinal carcinoids represent 29%, rectum 14%, stomach 5%, and appendix 5%.

Clinics and pathology

Note

The diagnosis of a carcinoid tumor is based on histology and confirmed with immunohisto-chemical staining for neuroendocrine markers. Unfortunately, histological analysis alone cannot predict the aggressiveness or metastatic potential of carcinoids. Up to 75% of patients have metastases at the time of diagnosis. The following substances are secreted by carcinoid tumors:

5-HT; 5-Hydroxytryptophan; Synaptophysin; Chromagranin A and C; Neuron-specific enolase; Insulin; Growth hormones (TGF- β , Platelet-derived growth factor, basic fibroblast growth factor); Bombesin; Kallikrein; Neurotensin; ACTH; Gastrin; Pancreatic polypeptide; Calcitonin; Substance P; Tachykinin; Histamine; Vasoactive intestinal peptide; Bradykinin.

Carcinoid tumor production and release of these substances can lead to various symptoms in patients, including the "carcinoid syndrome", which is characterized by skin flushing, wheezing and shortness of breath, diarrhea, and facial skin lesions. Another serious complication that can develop in patients with carcinoid tumors is valvular heart disease. These symptoms and complications related to carcinoid endocrinopathy can have a deleterious effect on patient quality of life.

Disease

Bronchial / Lung Carcinoid.

Etiology

Lung and bronchial carcinoids are diagnosed most commonly in septuagenarians and are associated with smoking.

Epidemiology

Lung and bronchial carcinoids make up about 28% of carcinoids, and 2% of all primary lung tumors.

Clinics

The tumors are usually central in location and cause cough, hemoptysis, wheezing, and recurrent pneumonia. These tumors can be classified based on histological features as typical (two thirds) or atypical (one third).

Atypical lung and bronchial carcinoids are generally larger at time of diagnosis than other carcinoids. These tumors are metastatic in up to 50% of cases and have a 5-year survival rate of only 40% to 75%.

Typical lung and bronchial carcinoid tumors are found most often in a peripheral location, in the fifth decade of life, and rarely associated with the carcinoid syndrome. They are associated with ectopic adrenocorticotrophic hormone (ACTH) secretion resulting in Cushing's syndrome. These tumors are metastatic in 12% of cases and have a 5-year survival rate of 93%.

Pathology

One third of bronchial carcinoids demonstrate atypical histologic features and the more aggressive phenotype.

Treatment

For localized typical bronchial/lung carcinoids the preferred treatment is wedge or segmental lung resection. For histologically atypical carcinoids of the bronchi/lungs, more aggressive treatment is recommended such as lobectomy.

As with all carcinoids, bronchopulmonary carcinoids usually do not respond to radiation therapy or chemotherapy, and use of these modalities should be considered experimental in this patient population.

Evolution

Typical carcinoid tumors are usually indolent, with metastases reported in less than 15% of cases.

Atypical carcinoids pursue a more aggressive course, metastasizing to mediastinal lymph nodes in 30% to 50% of cases.

Prognosis

Long-term survival rates for patients with typical lung or bronchial carcinoid tumors following surgical resection exceed 85%. Long-term survival rates are significantly shorter for patients who undergo resection for atypical carcinoids - about 52% according to McCaughan et al.

Disease

Gastric Carcinoid.

Etiology

Gastric carcinoid tumors are classified into 3 types:

Type 1: Associated with chronic atrophic gastritis;

Type 2: Associated with the Zollinger-Ellison syndrome;

Type 3: Sporadic.

Epidemiology

Gastric carcinoid tumors account for less than 1% of all gastric cancers. They comprise 5% of all GI carcinoids.

Type 1 gastric carcinoids are the most common type, accounting for up to 75% of cases. Up to 10% of gastric carcinoids are Type 2, associated with Zollinger-Ellison syndrome. Between 15% and 25% of gastric carcinoids are sporadic, Type 3 gastric carcinoids.

Treatment

Most gastric carcinoids can be resected endoscopically. Cases involving larger, recurrent tumors require more extensive surgical resection.

Antrectomy has been used in patients with chronic atrophic gastritis to eliminate the gastric production, and may cause the carcinoids to regress. The use of somatostatin analogs has resulted in gastric carcinoid tumor regression in patients with Zollinger-Ellison syndrome. In patients with sporadic Type 3 gastric carcinoids, which have a more aggressive biology, radical gastrectomy is the recommended treatment.

Evolution

Type 1 and 2 gastric carcinoids pursue an indolent course and generally do not metastasize. Sporadic Type 3 gastric carcinoids have a more aggressive course than Type 1 or Type 2. Most Type 3 gastric carcinoids are metastatic at presentation, portending a poor prognosis.

Disease

Small Intestinal Carcinoid.

Epidemiology

Small intestinal carcinoid tumors account for approximately one third of all small bowel tumors. They comprise 29% of GI carcinoids. Small intestinal carcinoids are most commonly diagnosed in the sixth and seventh decades of life.

Clinics

Patients with small intestinal carcinoids frequently present with abdominal pain or small bowel obstruction. Approximately 5% to 7% of patients manifest symptoms of the carcinoid syndrome, and in these cases hepatic metastases are usually present.

In patients with endocrinopathies, standard imaging techniques such as computed tomography (CT) and small bowel barium contrast studies often fail to localize the primary tumor. Small intestinal carcinoids are most frequently located in the distal ileum.

Treatment

Small intestinal carcinoids are treated by resection of the small bowel primary tumor together with associated mesenteric metastases. Most patients who have small bowel carcinoids are ultimately treated with octreotide, which is associated a high incidence of cholelithiasis. Because of this, cholecystectomy should be considered when carcinoids are surgically resected.

Prognosis

Tumor size is a poor predictor of metastases, and metastases have been reported in association with tumors smaller than 5 mm. The 5-year survival rate is 60% for patients with localized disease. It is 73% for those with regional metastases, and 36% for patients with distant metastases.

Disease

Appendiceal Carcinoid.

Etiology

Approximately two-thirds of appendiceal carcinoid tumors arise in the tip of the appendix, where they are unlikely to cause symptoms of obstruction. Ten percent of appendiceal carcinoids occur in the base where they are more prone to obstruct the appendix and cause acute appendicitis. It has been proposed that the incidence of appendiceal carcinoid tumors parallels the activity of subepithelial NE cells, the source of these tumors. The density of these NE cells peaks in the second decade of life and then decreases.

Epidemiology

Carcinoid tumors are the most common tumor of the appendix, accounting for more than half of all appendiceal malignancies and discovered in seven of every 1,000 appendectomy specimens. They account for 5% of GI carcinoids and are more common in women than men. The mean age at presentation is 49 years. This may reflect the common patient age at appendectomy, when the tumors are often incidentally discovered.

Treatment

Simple appendectomy is indicated in patients with tumors less than 2 cm in diameter, based on historical data suggesting a low probability of metastasis. For tumors larger than 2 cm in diameter, right hemicolectomy is recommended.

Prognosis

Ninety-five percent of appendiceal carcinoid tumors are less than 2 cm in diameter. The incidence of metastases in these cases is low. In contrast, about 33% of patients who have appendiceal carcinoid tumors measuring more than 2 cm in diameter have either nodal or distant metastases. When disease is localized, the prognosis of appendiceal carcinoids is good. The 5-year survival rate is 94% for local disease, 85% for

regional disease, and 34% when distant metastases are present.

Disease

Rectal Carcinoid.

Epidemiology

Rectal carcinoids comprise 1-2% of all rectal cancers, and 14% of all GI carcinoids. Tumors less than 1 cm in diameter make up about 33% of all rectal carcinoids.

Clinics

Half of all rectal carcinoids are asymptomatic and are incidentally found during endoscopy performed for other indications, such as screening for colorectal cancer. Patients who are symptomatic usually present with rectal bleeding, pain, or constipation.

Treatment

For tumors less than 1 cm in diameter, local excision is indicated. Tumors between 1 and 2 cm in diameter, especially in combination with other factors such as symptoms at diagnosis, probably warrant more aggressive surgical treatment. Tumors over 2 cm in diameter are generally treated with a low anterior resection or abdominoperineal resection.

Prognosis

The size of the primary lesion is predictive of metastatic disease. Metastases occur in less than 5% of tumors that are less 1 cm in diameter but at a much higher rate when the primary lesions is greater than 2 cm in diameter. The 5-year survival rate is 81% for local disease, 47% when regional metastases are present, and 18% with distant metastases.

Genes involved and proteins

MAP2

Location: 2q34

Note

Microtubule-associated protein 2 (MAP2) has been shown to be expressed specifically in neuronally differentiated cells, and is a useful marker for distinguishing non-neuroendocrine carcinomas of the lung from neuroendocrine lung tumors such as carcinoids.

Protein

MAP2 is a microtubule-associated protein important for the assembly of cytoskeletal components.

RAF1

Location: 3p25

Note

Raf-1 activation using an estrogen-inducible Raf-1 construct in human GI (BON) carcinoid cell line led to a marked reduction in neuroendocrine phenotypic markers such as human achaete-scute complex like-1 (ASCL1) and bioactive hormones and tumor markers 5-HT, chromogranin A (CgA), and synaptophysin. Treatment of GI carcinoid cells with Raf-1 activator

ZM336372 led to a decrease in bioactive hormone levels, suppression of cellular proliferation, and an increase in cell cycle inhibitors p21 and p18, as well as a decrease in the neuroendocrine phenotypic marker ASCL1.

CTNNB1

Location: 3p21

Note

Alias: β -catenin

Cytoplasmic accumulation of the β -catenin protein is present in about 30% of GI carcinoids and is absent in non-GI carcinoids. However, in tumors with accumulation of the protein, mutation in the β -catenin gene was not present.

Protein

β -catenin is part of the Wnt/ β -catenin/APC signaling pathway which is complex and affects numerous cellular processes. The role of the gene product is varied and poorly understood in both GI and non-GI carcinoids.

HES1

Location: 3q29

Note

An increase in HES-1 expression in vitro causes suppression of pulmonary carcinoid cell growth.

CDKN1A

Location: 6p21

Note

Alias: p21

Protein p21 up-regulation has been reported in appendiceal carcinoids. Its down-regulation or absence has been reported in pancreatic GI carcinoids.

Protein

A tumor suppressor, p21 is a cyclin-dependent kinase inhibitor.

VEGFA

Location: 6p12

Note

Alias: VEGF

Vascular endothelial growth factor (VEGF) expression has been demonstrated in a variety of bronchopulmonary and GI carcinoids. Tumor VEGF expression level corresponds to presence and number of metastases.

Multiple genes in the VEGF pathway reside in regions of frequent mutation in neuroendocrine and carcinoid tumors. The VEGF pathway is important in angiogenesis, and is implicated in a multitude of neoplasms. Reduction in VEGF expression causes reduction in tumor microvessel density and growth.

CDKN2A

Location: 9p21

Note

Alias: p16.

Loss of heterozygosity in the p16 gene is present in 23% of carcinoids.

Protein

The p16 gene is a tumor suppressor. The p16 protein is a cyclin-dependent kinase inhibitor whose loss can lead to cell cycle abnormalities.

NOTCH1

Location: 9q34.3

Note

Notch-1 signaling is minimal or absent in GI Carcinoids.

Protein

Notch-1 protein functions either as a tumor suppressor or oncogenic protein depending on cellular context.

Expression of active Notch-1 via adenoviral vector or inducible retroviral vector in GI carcinoid cells resulted in growth suppression and significant reduction in NE tumor markers such as 5-HT, CgA, synaptophysin, neuron specific enolase (NSE), and ASCL1, confirming the tumor suppressor role of Notch-1 signaling in carcinoid tumors.

Treatment of human carcinoid cancer cells with histone deacetylase (HDAC) inhibitors valproic acid (VPA) and suberoyl bishydroxamic acid (SBHA) resulted in activation of Notch-1 signaling and inhibition of carcinoid cell growth in vitro and in vivo. These findings suggest that Notch-1 activation with HDAC inhibitors may be an attractive approach for the treatment of these tumors.

MEN1

Location: 11q13

Note

Spanning 9 Kb and containing 10 exons.

Carcinoids have been reported in association with multiple endocrine neoplasia type 1 (MEN1) since 1953. The MEN1 gene was sequenced and cloned in 1997. Since this time, a plethora of mutations have been discovered in the MEN1 gene, many with phenotypic consequences. Carcinoids are found in about 16-20% of patients with MEN1.

Protein

The MEN1 gene codes for the 610-amino acid protein menin, whose function is unknown.

CCND1

Location: 11q13

Note

Cyclin D1 up-regulation has been reported in appendiceal carcinoids.

Protein

Cyclin D1 forms a complex with cyclin-dependent kinases and acts to promote the cell cycle.

SDHD

Location: 11q23

Note

Alternatively called PGL and PGL1.

Succinate dehydrogenase complex subunit D (SDHD) is a tumor suppressor gene. Mutations in this gene are reported in 22% of ileal and duodenal carcinoids, and are not typically present in non-midgut carcinoids.

Protein

SDHD is a subunit of the succinate dehydrogenase complex on the inner mitochondrial membrane which is involved in the citric acid cycle and electron transport chain of metabolism. It has been postulated though not confirmed that the loss of functionality of this subunit causes a hypoxic response in affected cells that contributes to the tumor phenotype.

CDKN1B

Location: 12p13

Note

Alias: p27

Protein p27 down-regulation or absence has been reported in pancreatic GI carcinoids.

Protein

A tumor suppressor, p27 is a cyclin-dependent kinase inhibitor.

NF1

Location: 17q11.2

Note

Loss of heterozygosity mutations in the neuro-fibromin 1 (NF1) gene have been reported in association with gastric carcinoids. NF1 is most commonly associated with the disease neurofibromatosis type 1.

Protein

NF1 encodes the protein called neurofibromin, a negative regulator of the Ras oncogene. Loss of NF1 activity also leads to constitutively active mTOR and tumor formation.

BCL2

Location: 18q21

Note

The bcl-2 family of proteins affects the growth of pulmonary carcinoids. The protein bcl-2 is expressed at higher levels in atypical pulmonary carcinoids than in typical pulmonary carcinoids. The protein bcl-x is expressed at higher levels in typical pulmonary carcinoids. It is possible that this balance is responsible for the more aggressive clinical course of atypical pulmonary carcinoids.

Protein

The bcl-2 protein is thought to be anti-apoptotic whereas the bcl-x protein is thought to be pro-apoptotic.

To be noted

Note

Tumor Markers: Elevated urine levels of the serotonin (5-HT) breakdown product 5-HIAA is a highly specific indicator of midgut (small bowel, gastric) carcinoids. It is not useful in monitoring foregut (bronchial, lung) or

hindgut (rectal) carcinoids, as these do not typically secrete serotonin.

Chromogranin A (CgA) is an acidic glycoprotein that is contained in the neurosecretory vesicles of NE cells. It is an elementary tumor marker in NE tumor diseases, including carcinoids. CgA is more sensitive than urinary 5-HIAA and is useful in carcinoids of the fore-, mid-, and hindgut. In the clinical setting, CgA has been used as an indicator of response to treatment.

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