

## Gastrointestinal carcinoid tumors: diagnosis and treatment

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### Rezumat

#### *Tumori carcinoide gastrointestinale: diagnostic și tratament*

Tumorile carcinoide sunt proliferări maligne provenind din celule neuroendocrine, întâlnite obișnuit la nivelul tractului gastrointestinal, cu o frecvență de 64%, majoritatea interesând ileonul. Anumite sindroame genetice includ în fenotipul lor unele, tumori carcinoide. Aceste neoplazii pot fi mai degrabă asimptomatice, deși unele au manifestări zgomotoase. Tumorile carcinoide sunt diagnosticate tipic din cauza efectelor locale, ce apar într-un stadiu avansat de evoluție, sau simptomelor determinate de secreția de hormoni (sindrom carcinoid). Este necesară o mai bună cunoaștere a biologiei moleculare și comportamentului acestor tumori, astfel încât să fie diagnosticate precoce și tratate eficient.

**Cuvinte cheie:** afectare carcinoidă, celule neuroendocrine, sindrom carcinoid, carcinoidoză ileală

### Abstract

Carcinoid tumors are malignancies originating from neuroendocrine cells, most commonly encountered in the gastrointestinal tract, in a rate of 64%, with the majority affecting the ileum. Certain genetic syndromes sometimes include carcinoid tumors in their phenotype. These malignancies may

be rather asymptomatic, although occasionally they behave aggressively. They are typically diagnosed due to the effects of a locally advanced disease, or when producing symptoms because of hormone secretion (carcinoid syndrome). A better understanding of their molecular biology and behavior is demanded so that these tumors to be diagnosed precociously and managed effectively.

**Key words:** carcinoid disease, neuroendocrine cells, carcinoid syndrome, ileal carcinoids

### Introduction

Carcinoid tumors are distinct neuroendocrine tumors arising from enterochromaffin (EC) and related cells found in epithelial organs throughout the body. The vast majority of all carcinoid tumors (64%) originate in the gastrointestinal (GI) tract. Gastrointestinal carcinoids are enigmatic malignancies which, although slow growing compared with adenocarcinomas, can behave aggressively. They constitute the most common neuroendocrine tumors of the GI tract (1,2). These tumors present as a spectrum from small 'benign' tumors to the classical 'carcinoid syndrome' of local tumor invasion with liver metastases and systemic symptoms (3).

The pathologic entity that is known as carcinoid was first characterized by Lubarsh in 1888 (4). However, the term 'carcinoid' was introduced in 1907 to describe a group of GI tumors that were notably less aggressive but looked similar to adenocarcinoma (5). In the 1920s Masson established the origin of carcinoids (6), while the first description of the malignant carcinoid syndrome (MCS) dates to Cassidy's report in 1934 (7).

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## Discussion

The incidence of carcinoid tumors varies according gender, age, and race. The overall incidence in the United States is estimated to be 2 cases per 100000 people (8). Carcinoid tumors are often diagnosed in a person's fifth or sixth decade of life (8,9). Except in appendiceal and bronchopulmonary sites, African Americans have a higher incidence than other ethnic groups. The entity is slightly more common in females (55% of all cases) than males (8, 10). Within the GI tract, small intestine is the most common primary site (25%) followed by appendix (12%) and rectum (14%).

Carcinoid tumors are derived from dispersed neuroectodermal cells. ECL cells, also known as Kulchitsky's cells, are the most common endocrine cells and are most numerous in the duodenum, the terminal ileum, and the appendix. Thus, carcinoid tumors are neoplasms of peptide- and amine-producing cells, and their variable hormone profiles are based on the site of origin (11). They produce and secrete a large number of substances (12-15). Most individuals with carcinoid tumors have abnormal metabolism of tryptophan (16). Normally, dietary tryptophan is oxidized to nicotinic acid. In individuals with carcinoid tumors, up to 60% of tryptophan instead undergoes 5-hydroxylation into 5-hydroxytryptophan (5-HTP). The bulk of serotonin is metabolized in the liver or kidney to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine.

A useful and practical classification system for carcinoids has not yet been adopted. Carcinoid tumors are usually classified by their embryonic gut origin, and the ubiquitous, yet inconsistently defined, classification of 'typical' vs 'atypical' carcinoids has become prevalent within the literature, usually in reference to their degree of differentiation. 'Typical' carcinoids have a characteristic histologic appearance of monotonous sheets of small round cells with uniform nuclei and cytoplasm without pleomorphism or mitoses. 'Atypical' carcinoids have features associated with more aggressive behavior, such as greater nuclear atypia, higher mitotic rates, and/or necrosis. Classification based on embryological origin (foregut, midgut, and hindgut) is an outdated but somewhat useful distinction because the features of carcinoid tumors derived from each respective location differ clinically, histologically, and immunochemically. Foregut carcinoids have a low serotonin content, and thus clinical syndromes are rare. These tumors occasionally secrete 5-HTP or ACTH and are associated with atypical carcinoid syndrome. Midgut carcinoids have a high serotonin content and frequently cause a classical carcinoid syndrome. Hindgut carcinoid tumors rarely contain serotonin, rarely cause carcinoid syndrome, and rarely secrete 5-HTP or ACTH. Carcinoids may be subclassified histologically based on their growth patterns as insular (22%), trabecular (18%), undifferentiated (4%), glandular (2%), or mixed (43%). This classification has been largely replaced by identification of the secretory peptides chromogranin, synaptophysin, and neuron-specific enolase, which are highly specific for neuroendocrine tumors (17).

The genetics of carcinoid tumorigenesis have yet to be

completely elucidated. A number of genetic syndromes including multiple endocrine neoplasia syndrome-type 1 (MEN 1), von Hippel-Lindau syndrome (VHL), and neurofibromatosis-type 1 (NF1) may be associated with gut neuroendocrine (NE) tumors. The best defined of all is MEN 1, an autosomal dominant disorder associated with loss of the tumor suppressor gene MEN1 on chromosome 11q13 (18). Carcinoids, particularly gastric carcinoids, occur in 10% of individuals affected with MEN1. In the normal cell, the above mentioned genes play a role in tumor suppression; aberrations in these regulatory genes can lead to the development of neoplasms, including carcinoids. For midgut carcinoids, the major areas of chromosomal loss are 18q (54%), 9p (15%), 11q (13%), and 16q (12%). Finally, interesting familial and hereditary mutations of p53, K-ras-2, C-raf-1, Bcl2, MEN1, n-myc, and c-jun, abnormal bcl-2:bax ratio, and DNA ploidy have been implicated in connection with prognostic factors of carcinoid tumors (19-23).

### *Clinical manifestations*

Because of their inconspicuous size and submucosal location, primary carcinoid tumors are rarely diagnosed before metastasis. In most instances, they are discovered incidentally at the time of surgery for other abdominal disorders, and their presence may be undetectable for years without obvious signs or symptoms. When symptoms do occur, they are due either to local tumor mass effects, the effects of tumor-engendered fibrosis, or to the secreted bioactive products from the neoplasm. Overall symptom interpretation is difficult because the symptoms can be both of variable intensity as well as paroxysmal, responding intermittently to a particular 'trigger' agent, such as alcohol, cheese, coffee (serotonin-rich foods), or exercise. Vague abdominal pain (invasion, intussusception, fibrous adhesions, hypermotility) is the main symptom caused by local tumor effects. Peritumoral fibrosis leads to intestinal obstruction by adhesions of intestinal loops or luminal stricture (24). The presenting symptoms include feeding-related or crampy abdominal pain, cessation of diarrhea, a palpable abdominal mass, or weight loss (25). Fibrosis around mesenteric metastases causes fixation of the ileal mesentery to the retroperitoneum, with fibrous bands obstructing the small intestine and transverse colon (26). Carcinoid-associated retroperitoneal fibrosis may lead to hydronephrosis and renal failure secondary to stenosis of the ureters (27).

Carcinoid syndrome is the hormonal manifestation of carcinoid tumors and is associated with poor survival. Carcinoid syndrome results from synergistic interactions between 5-HTP metabolites, kinins, and prostaglandins. Studies which include patients with localized and incidental tumors report the incidence of carcinoid syndrome to be about 10% to 18% (16,28). The syndrome is usually observed (with incidence being 40% to 50%) in patients with metastatic disease or when the primary tumor site allows the secreted amines to escape enteral hepatic circulation (29). It is characterized by flushing, diarrhea, abdominal cramping, and less often, wheezing, heart-valve dysfunction, and pellagra. Two

thirds of patients with carcinoid syndrome have carcinoid heart disease, characterized by fibrous thickening of the endocardium, usually involving the right side (30). Carcinoid crisis constitutes a life-threatening form of carcinoid syndrome triggered by specific events such as anesthesia, surgery, or chemotherapy, presumably stimulating release of an overwhelming amount of biologically active compounds. Symptoms include flushing, diarrhea, tachycardia, arrhythmias, hypertension or hypotension, bronchospasm, and altered mental status. Gastrointestinal carcinoids may present with multiple synchronous primary tumors or with synchronous second malignancies (31). The metastatic risk for carcinoids is least for appendiceal tumors and greatest for rectal primaries. The risk is lowest for subcentimeter-sized tumors and rises with increased size, regardless of the site. Common sites of metastasis are the liver, lung, and bone. The diagnosis of carcinoid tumors should be confirmed using biochemical tests, followed by topographic localization of the primary tumor and any metastatic tumors that may be present. The 24-hour urinary 5-HIAA collection is a widely available laboratory test yielding a specificity of approximately 88% (32). A 24-hour collection is necessary due to a high variability of 5-HIAA in the urine. This time-consuming process, together with the problems of urine collection (such as inconvenience), makes it a very cumbersome test. In addition, foods rich in serotonin, such as bananas, tomatoes, and eggplant, should be avoided (33). The sensitivity of 5-HIAA is reported to be as low as 35% (34). Interestingly, a high concentration of urinary 5-HIAA has been found to be associated with carcinoid heart disease (35).

Another tumor marker, chromogranin A (CgA), contained in the neurosecretory vesicles of neuroendocrine tumor cells, is detectable in the plasma of patients with endocrine neoplasms. Because it does not rely on serotonin secretion, serum CgA is a more sensitive and broadly applicable marker than urinary 5-HIAA (36).

Although plasma CgA levels are very sensitive (99%) markers of carcinoid tumors, they are nonspecific as they are also elevated in other types of neuroendocrine tumors, such as pancreatic, small cell lung, and even sporadic prostate carcinomas. False-positive increased CgA concentrations can be found in renal impairment, liver failure, atrophic gastritis, and inflammatory bowel disease. Studies have noted an association between plasma CgA levels and the location of the tumor (37), and an association with the severity of the disease as well (38).

In addition to its diagnostic value, plasma CgA levels are also well correlated to the tumor volume and burden, and may be used to monitor the outcome of treatment. It is also considered to be an important prognostic marker (39), particularly for mid-gut carcinoid tumors.

There are many other biochemical markers that are associated with neuroendocrine tumors, but none have the specificity or predictive value of CgA or 5-HIAA, and their measurement is complex compared with the latter. Current markers of interest include substance P, neurotensin, bradykinin, human chorionic gonadotropin, neuropeptide K, and PP, and as such, research into these areas is ongoing.

### ***Small intestine carcinoids***

The ileum is the most common site for carcinoid tumors, composing 28% of all carcinoids, and constitutes the most frequent neoplasm in the small intestine (40,41). The lesions occur 6.5-8.2 times more frequently in the ileum than in the duodenum and jejunum (40,42), and their relative frequency increases aborally.

As far as duodenum and upper jejunum are concerned, most tumors are discovered incidentally at endoscopy for dyspepsia or during the investigation of an upper GI bleed. There are five pathological types of duodenal carcinoids. Particular features of these tumors include the exclusive expression of Xenin and their association with von Recklinghausen's disease, ZE syndrome, and MEN (43,44). Small duodenal lesions may be resected endoscopically with a good outcome, although the risk of bleeding does exist (45). If the ampulla is in close cohesion with the lesion, or if local spread or lymph node involvement is detected, pancreatico-duodenectomy may be advisable to ensure complete resection of the lesion (46). Tumor size greater than 2 cm, involvement of the 'muscularis propria', and the presence of mitotic figures constitute negative prognostic features and imply a generalized disease (47).

Jejuno-ileal carcinoids differ from those occurring in other locations of the gut because they are usually at an advanced stage at the time of presentation. Due to slow progress, patients may have non-specific abdominal pain and diarrhea for several years before prognosis. Many patients get increased abdominal pain attacks with time, and approximately 40% are discovered at emergency surgery for intestinal obstruction. In other patients the diagnosis is settled after detection of liver metastases, sometimes together with features of the carcinoid syndrome (the syndrome occurs in up to 18% of patients with jejuno-ileal carcinoids) (26). Ileal carcinoids are nonlocalized in 64.1% of patients, the second highest percentage after the colon of carcinoids of the GI tract (40). Transmural invasion and extensive fibrosis are common features contributing to the aggressive local behavior of the lesion, and local and distant metastases are frequent (41). The tumor cells are characteristically argyrophil and argentaffin positive, and over 85% of the lesions exhibit positive reactions for CgA, Leu-7, NSE, and serotonin (42,47). An association with other noncarcinoid neoplasms is evident in 29% of patients, which is the highest percentage among all carcinoids of the GI tract (48).

Biochemically, CgA and 24-hour urine 5-HIAA levels are both sensitive for these tumors, and can also be used to monitor the effects of treatment. Abdominal ultrasonography may detect hepatic metastases, and confirmation is provided by fine-needle biopsy. Moreover, capsule endoscopy is well established as a sensitive investigation for the diagnosis of small bowel tumors (49). Octreoscan is definitive for identification of the primary and staging, pointing out spread to the liver and to extra-abdominal sites. Bone metastases are identifiable by MRI scanning and can be used to assess tumor volume. Cardiac echo to identify carcinoid heart disease should be performed on a regular basis (50).

### **Midgut carcinoids**

Midgut carcinoids can be recognized at laparotomy by typical features of a small ileal tumor and large mesenteric metastases surrounded by fibrosis (51). Because multicentric lesions, liver metastases, and other noncarcinoid malignancies may occur, even in the presence of small primaries, surgery should involve diligent assessment of the abdomen. The primary tumor should be removed by wedge resection of the mesentery with dissection of lymph-node metastases around the mesenteric artery and vein aiming to preserve intestinal vascular supply and limit the intestinal resection. The operation is difficult due to fibrosis between regions of intestine, and mistakes may result in fistulation, intestinal devascularization, or creation of a short bowel (52). Patients should undergo careful and life-long surveillance, since eventual recurrence of liver metastases can be expected in approximately 85% of them. For advanced carcinoids, treatment with long-acting somatostatin analogues, octreotide, and interferon- $\alpha$  can often provide efficient control of the carcinoid syndrome. Finally, surgery in patients with the carcinoid syndrome may initiate a carcinoid crisis. This is prevented by routine preoperative administration of intravenous somatostatin analogue.

Survival of patients with midgut carcinoids has improved with active and combined medical and surgical management, but depends highly on the extent of the disease. Jejunio-ileal, in particular, have a poor 5-year survival rate (60,5%) compared with other GI carcinoids (40). The 5-year survival rate of patients with hepatic tumor spread is 18%-32% (1,40,52). An increased median survival (4,4 years) is present in patients with jejunio-ileal carcinoids, which show a mixed insular/glandular pattern (53). In contrast, patients with an undifferentiated pattern have a median survival of only 6 months.

### **Carcinoids of the appendix**

Appendiceal carcinoids have decreased in incidence to comprise approximately 8% of carcinoids (40,54-56), but they are still the most prevalent tumors of the appendix. Identification of the lesion occurs in 5 or 6 per 1000 appendectomies (57) and presents in a younger patient population than other GI carcinoid tumors with a median age of 49,3 years (40). Although a marked female predominance has been reported (58), the female predominance of appendiceal carcinoids has decreased from 77% to 57% in the latest SEER data analysis (40). According to a study by Shaw, 70%-80% of appendiceal carcinoids occur at the tip, 5%-20% in the body, and only 7%-8% at the base of the organ (59,60).

Carcinoid tumors of the appendix are usually small, clinically apparently benign lesions and are often discovered as an incidental finding during surgery for appendicitis or gynecological procedures. The diagnosis is frequently established at laparotomy or laparoscopy, undertaken to evaluate nonspecific symptoms, although abdominal ultrasound may occasionally provide a preoperative diagnosis. A minority present with clinical features of acute appendicitis,

while the carcinoid syndrome or symptoms are extremely rare.

The majority of appendiceal carcinoids measure  $< 1$  cm in diameter and are invariably cured by appendectomy (61). Tumors  $> 2$  cm require hemicolectomy and ileocaecal lymph-node clearance. This type of management is also suggested for tumors in the appendix base, since they may originate in the colon and cause local recurrence. For tumors measuring 1-2 cm hemicolectomy is recommended if there is invasion in the mesoappendix or residual tumor in the resection margins, as well as in the presence of lymph-node metastases. Same-size lesions confined to the appendiceal wall, require appendectomy alone. However, hemicolectomy may be recommended when operative specimens exhibit high proliferative activity, high mitotic index, or signs of angioinvasion (55,56).

Appendiceal carcinoids have the best prognosis among all types of carcinoids. The most predictive determinant of survival is the size of the primary tumor. Tumors  $< 2$  cm rarely metastasize ( $< 3\%$ ), whereas the risk of metastatic spread is considerably higher in tumors  $> 2$  cm (30%-60%) (60,62). Five-year survival rates for localized lesions, regional spread, and distant metastases are 80,8%, 88,1%, and 9,6%, respectively, with an overall survival rate of 71% (40).

### **Rectal carcinoid disease**

The rectum is the third most common site for gastrointestinal carcinoids. However, carcinoid tumors comprise only 1%-2% of all rectal tumors (8). There is no specific sex predominance, and the average age at diagnosis is markedly lower than for colonic carcinoids (48-52 years) (40).

Approximately 50% of patients with rectal carcinoids are asymptomatic. Symptoms include discomfort in the anorectal area, constipation, bleeding, or change in bowel habit (63). Rarely, rectal pain (late presentation) and pruritus ani may occur (54,64). Carcinoid syndrome occurs only very rarely in patients with rectal carcinoids (65,66). Overall, rectal carcinoids present with metastases in only 4%-18% of cases (40). Parameters predicting metastatic spread of these tumors include depth of invasion, tumor size, and histopathologic type (67,68).

Biochemically, rectal carcinoids are associated with elevated CgA, but not increased levels of urinary 5-HIAA. Most lesions are discovered endoscopically and a complete colonoscopy should be undertaken to exclude the presence of coexisting colon carcinoma. Any polyps visualized should be biopsied. Endoscopic ultrasound (EUS) is useful in the preoperative assessment of tumor invasion, and can be used in conjunction with CT/MRI. Metastatic lesions can be detected by octreotide scintigraphy (50).

Rectal carcinoids  $< 1$  cm can be safely removed by endoscopic or transanal resection (69). Tumors with a diameter of 1-2 cm, without infiltration or regional metastases can be locally excised; presence of either favors anterior resection and lymph-node clearance (70). Finally, tumors  $> 2$  cm are treated by anterior resection with mesorectal excision and lymph-node clearance (71).

Because of their low propensity to metastasize, classic

rectal carcinoids have a generally favorable prognosis with an overall 5-year survival rate of 88,3% (40).

### **Rare locations of carcinoid tumors**

Less common gastrointestinal carcinoids are those of colon and stomach.

Carcinoid tumors of the colon compose 7,8% of all carcinoids and occur most frequently in the cecum (40,72). Over half of the patients present with nonspecific symptoms such as weight loss and weakness, but occasionally diarrhea or bright red rectal bleeding may occur, suggesting a tumor location distal to the hepatic flexure (64,72).

In general, carcinoids of the colon resemble the rectal lesions and their diagnosis is established in the same way. However, they exhibit a more undifferentiated pattern with clinically more aggressive features (72).

These tumors are generally metastasized at diagnosis and are mainly treated with chemotherapy; only occasional patients require palliative surgery, but have poor survival. Local excision is only recommended in the minority of patients who present with a tumor <2 cm. For lesions >2 cm in size, a wide resection including lymph-node dissection is suggested. Unexpectedly, these tumors exhibit the worst prognosis among all GI carcinoid tumors, with an overall 5-year survival of 33%-42% (1,40). This partially reflects the large tumor size at the time of diagnosis and the high percentage of metastatic spread (40,72).

Gastric carcinoid tumors are rare lesions that represent approximately 8,7% of all gastrointestinal carcinoids (40). These tumors have been classified into three types according to biological behavior and prognoses based on their pathogenesis and histomorphological characteristics (73-76). Type I is most frequent and composes approximately 65% of all gastric carcinoids. Gastric carcinoids exhibit an increased incidence in individuals with atrophic gastritis, pernicious anemia, auto immune diseases, and MEN 1-associated gastrinoma (77).

The clinical presentation of gastric carcinoids can mimic symptoms of gastric ulcers, bleeding gastric polyps, or gastric carcinoma (77,78). Up to 33% of patients can be asymptomatic and present as an incidental finding on endoscopy (79). Literature reports of carcinoid syndrome typically range from 0% to 2% (76,79-81).

Upper GI endoscopy with biopsy is the most useful diagnostic tool, but endoscopic ultrasound is of value in identifying submucosal lesions and determining the degree of transmural spread. Biochemically, CgA is the most sensitive marker for detection. (50).

Medical treatment usually consists of dietary modifications to acidify the stomach or octreotide therapy (73,82). For small, solitary Type 1 tumors, endoscopic polypectomy is the treatment of choice (83-86). For patients with multiple tumors or recurrence, surgery is the treatment of choice aiming to reduce the gastrin-producing cell mass of the stomach. In most patients, antrectomy results in regression of neoplastic and hyperplastic ECL cells in the fundic mucosa (82,87,88).

Laparoscopic resection, which has been reported in the literature in a few cases, would seem to be an appropriate option given the generally benign course of Type 1 gastric carcinoid lesions (89,90).

The 5-year overall survival rates for gastric carcinoid tumors with localized disease, regional spread, and distant metastases are 69%, 38%, and 21%, respectively.

Rare GI carcinoid tumors are those of esophagus, pancreas, liver, extrahepatic biliary ducts, gallbladder, and Meckel's diverticulum.

Patients with carcinoid lesions of the esophagus present with multiple symptoms, most commonly dysphagia, weight loss, pain, reflux esophagitis, fatigue, and melanotic stools. An increased number of endocrine cells has been found in the setting of Barrett's metaplasia (91). Diagnostic tools include endoscopy with biopsy and CT scan, while barium studies may be beneficial in ascertaining the extension of the lesion. Most reports indicate esophagogastrectomy or sub-total esophagectomy with gastroesophageal anastomosis as the preferred interventions. Prognosis is designated by an approximate 70% survival rate of at least 6 months with stage I and II lesions and less than a 25% six month survival rate observed in stage III or IV tumors (92).

Carcinoids of the pancreas comprise 0,6% of all carcinoid tumors (40). Abdominal pain, diarrhea, flushing, and nausea are among the most frequently encountered symptoms. Multiple diagnostic modalities, including abdominal ultrasound, computed tomographic scan, and endoscopic retrograde cholangiopancreatography, may be useful to detect these lesions. Pancreatic carcinoids are most frequently managed surgically, usually by pancreatectomy, with a prognosis that depends mostly on the extent of local or distant spread.

Hepatic carcinoids comprise only 0,3% of carcinoid GI tumors (40). Patients may present with pain, weight loss, a palpable mass and even gastric outlet obstruction due to mass effect. The classical carcinoid syndrome occurs in only 5% of patients (92). Octreoscan, abdominal and chest CT scan, MRI, bronchoscopy, hepatic venous sampling, and laparoscopy are all efficient diagnostic tools in anticipation of an intraoperative exploration. To confirm the diagnosis, percutaneous fine needle aspiration or needle biopsy followed by immunological and electron microscopic assessment is recommended. In the majority of cases, hepatic lobectomy is the treatment of choice, though systemic chemotherapy, hepatic artery chemoembolization, and octreotide have also been used alone or in conjunction with surgery in attempts to manage hepatic lesions. Prognosis of these patients is poor (40).

Carcinoid tumors of the extrahepatic biliary duct account for 0,2%-2% of all gastrointestinal carcinoids (40). Biliary obstruction, with pain, jaundice, and pruritis are among the most common symptoms. Serum laboratory investigations can help diagnosis (93,94), while elucidation of the bile duct obstruction is often pursued with abdominal ultrasound, CT, ERCP with biopsy, or even percutaneous transhepatic cholangiography (PTC) in cases of complete obstruction. Surgical excision of the neoplasm remains the

therapy of choice when feasible. In most instances, a complete surgical resection ensures a more favorable prognosis (95).

Most carcinoids of the gallbladder are diagnosed incidentally upon histological examination of gallbladder specimens at autopsy, after cholecystectomy for cholecystitis, or after surgical treatment of patients in whom a biliary malignancy is suspected. Although some lesions have been removed laparoscopically, Z'graggen et al. have expressed certain reservations (96). The 5-year survival is  $60,8\% \pm 14,8\%$  (40).

Carcinoids within Meckel's diverticulum are typically found incidentally and patients remain asymptomatic. However, at the time of onset of symptoms, 77% of these tumors have already metastasized and at least 24% demonstrate metastases at the time of presentation (97). These lesions are generally amenable to aggressive surgical intervention, with an 83% 5-year survival rate reported (98).

## Conclusion

Although nearly a century has passed since the distinctive nature of this class of endocrine tumors was first recognized, the biological resolution of the different types of carcinoid tumor remains a source of considerable difficulty. Consequently, the diagnosis and management of these lesions remain challenging. A better understanding of the molecular biology of the entity may lead to better clinical models for predicting outcome and developing novel treatment strategies for this relatively rare but complex disease.

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