Current Status of Gastrointestinal Carcinoids

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Gastrointestinal (GI) carcinoids are ill-understood, enigmatic malignancies, which, although slow growing compared with adenocarcinomas, can behave aggressively. Carcinoids are classified based on organ site and cell of origin and occur most frequently in the GI (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%). Local manifestations—mass, bleeding, obstruction, or perforation—reflect invasion or tumor-induced fibrosis and often result in incidental detection at emergency surgery. Symptoms are protean (flushing, sweating, diarrhea, bronchospasm), usually misdiagnosed, and reflect secretion of diverse amines and peptides. Biochemical diagnosis is established by elevation of plasma chromogranin A (CgA), serotonin, or urinary 5-hydroxyindoleacetic acid (5-HIAA), while topographic localization is by Octreoscan, computerized axial tomography (CAT) scan, or endoscopy/ultrasound. Histological identification is confirmed by CgA and synaptophysin immunohistochemistry. Primary therapy is surgical excision to avert local manifestations and decrease hormone secretion. Hepatic metastases may be amenable to cytoreduction, radiofrequency ablation, embolization alone, or with cytotoxics. Hepatic transplantation may rarely be beneficial. Chemotherapy and radiotherapy have minimal efficacy and substantially decrease quality of life. Intravenously administered receptor-targeted radiolabeled somatostatin analogs are of use in disseminated disease. Local endoscopic excision for gastric (type I and II) and rectal carcinoids may be adequate. Somatostatin analogues provide the most effective symptomatic therapy, although interferon has some utility. Overall 5-year survival for carcinoids of the appendix is 98%, gastric (types I/II) is 81%, rectum is 87%, small intestinal is 60%, colonic carcinoids is 62%, and gastric type III/IV is 33%.

This review provides a broad outline of progress that has been made in the elucidation of the biology and management of gastrointestinal (GI) carcinoid tumors. Because these lesions exhibit a high degree of morphologic and biologic heterogeneity, there is a lack of clarity regarding their individual characteristics. A more generic term, *neuroendocrine tumor* (NET) has been introduced to replace the term *carcinoid*, and such lesions are currently referred to as *gastroenteropancreatic (GEP) NETs* (GEP-NETs).[1] Although an improvement on the group colloquation "carcinoid," the classification still requires to be extended and further refined because a substantial group of NETs are of indefinable malignant potential and represent an indistinct biologic group whose behavior cannot be accurately predicted. This reflects the fact that traditional morphologic criteria of neoplasia have limited applicability. Molecular characterization (as yet lacking) is required to refine and further differentiate GEP-NETs. To date, the gene responsible for MEN-1 on chromosome 11q13, which is also mutated in up to 40% of sporadic GEP-NETs,[2] has been identified, and comparative genomic hybridization and allelic loss have detected a large number of genomic regions with loss or gain of genetic material.[3,4] Such

Abbreviations used in this paper: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptophan; ACTH, adrenocorticotropic hormone; AFP, α-fetoprotein; AP-1, activator protein-1 complex; CAG/A, chronic atrophic gastritis-type A; CBD, common bile duct; CCD, carcinoid cardiac disease; CEA, carcinoembryonic antigen; CgA, chromogranin A; CGH, comparative genomic hybridization; CTGF, connective tissue growth factor; DCC, deleted in colorectal carcinoma; EC, enterochromaffin; EM, electron microscope; FDG, fluoro-2-deoxy-Dglucose; FGF, fibroblast growth factor; G, gastrin; GC, gastric carcinoids; GCC, goblet cell carcinoma; GE, gastroesophageal; GEP, gastroenteropancreatic; hCG, human chorionic gonadotrophin; HLI, human leukocyte interferon; IGF-1, insulin-like growth factor; KNO, knockout; LI, labeling index; LOH, loss of heterozygosity; MEN-1, multiple endocrine neoplasia syndrome-type 1; MIBG, metaidobenzylguanidine; MRI, magnetic resonance imaging; MSI, microsatellite instability; NCAM, neural cell adhesion molecule; NETS, neuroendocrine tumors; NF1, neurofibromatosis-type 1; NSE, neuron-specific enolase; PA, pernicious anemia; PDCD4, programmed cell death protein 4; PDGF, platelet-derived growth factor; PET, pancreatic endocrine tumor; PLCB3, phospholipase CB3; PP, pancreatic peptide; PTC, percutaneous transhepatic cholangiography; SDHD, succinate ubiquinone oxidoreductase subunit D; SEER, surveillance epidemiology and end results; SI, small intestines; SPECT, single positron emission computed tomography; SRS, somatostatin receptor scintigraphy; SSTomas, somatostatinoma; SSTR, SST receptor; UGI, upper gastrointestinal; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau syndrome; VIP, vasoactive intestinal polypeptide; ZE, Zollinger–Ellison.

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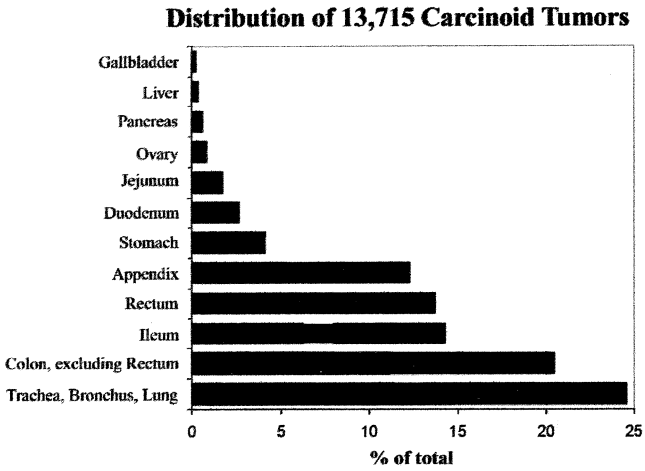

Figure 1. Distribution of 13,715 carcinoid tumors contained by the ERG, TNCS, and the SEER file (1950–1999) by organ site. Adapted from Modlin IM et al.[14]

studies have also confirmed that NETs in different localizations are genetically independent tumors. Hence, foregut NETs often show loss of 11q, which distinguishes them from NETs of the mid- and hindgut, which frequently show losses on chromosome 18q.[5,6] A major goal is to identify a series of molecular signatures that will identify genetic markers or constellations that will facilitate prediction of the biologic behavior of such lesions and enable the delineation of rational therapeutic strategies. This review provides a general outline of the background of GEP-NETs, their clinical diagnosis, and management with specific sections describing each tumor type and its characteristics in detail (Figure 1). The final section evaluates therapeutic strategy.

Concept Evolution

In 1888, Lubarsch described the microscopic features of a patient with multiple carcinoids of the ileum but regarded them as carcinomas.[7] Two years later, Ransom provided the first detailed descriptions of the classical symptomatology of carcinoid syndrome in a patient with an ileal carcinoid tumor and hepatic metastasis.[8] However, it was Oberndorfer in 1907, who coined the term *karzinoide* (carcinoma-like) to describe these tumors, which he believed to behave in a more benign fashion than adenocarcinomas (Figure 2).[9] The recognition of carcinoids as endocrine-related tumors was first outlined by Gosset and Masson in 1914.[10] In 1963, Williams and Sandler classified carcinoids according to their embryologic site of origin as foregut carcinoids (respiratory tract, stomach, duodenum, biliary system, and pancreas), midgut carcinoids (small intestine, appendix, cecum, and proximal colon), and hindgut carcinoids (distal colon and rectum).[11] This classification was the first to emphasize clinicopathologic differences between the tumor groups composing the gastroenteropancreatic neuroendocrine tumors (GEP-NETs) but never achieved general acceptance in routine diagnostic practice because it proved too imprecise to distinguish between the different biologically relevant GEP-NET entities.[12] This was particularly apparent in the foregut NETs, which differ so greatly in morphology, function, and biology that they cannot be classified as a single group.

However, with the introduction of immunohistochemistry, plasma immunoassays for peptides and amines and the development of novel diagnostic methodology (eg, computed tomographic [CT] scan, magnetic resonance imaging [MRI], SST receptor [SSTR] scintigraphy, and positron emission scanning), the management of NETs has advanced significantly in the last 2 decades. Furthermore, it has become apparent that the term "carcinoid" fails to convey the diverse spectrum of neoplasms with widely different secreting products that originate from different NE cell types. Although the precise identification of the specific cell type of each NE tumor of the GI tract is far from complete, the widespread use of

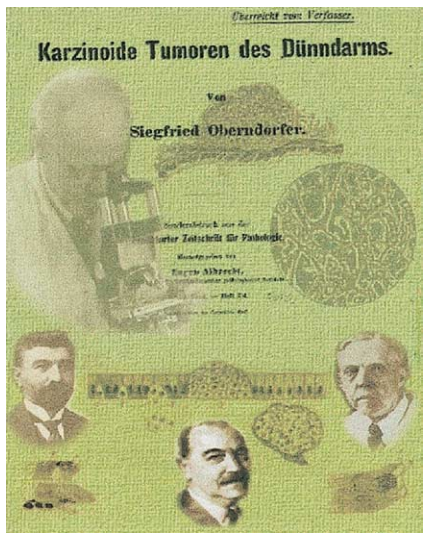

Figure 2. Siegfried Oberndorfer (1876-1944) (*top left*) presented his observations of multiple "benign carcinomas" (*Karzinoide*) of the small bowel at the German Pathological Society meeting of 1907 in Dresden (*top*). P. Masson and A. Gosset (*bottom left and right*, respectively) demonstrated the argentaffin staining properties of appendiceal carcinoid tumors in 1914 and suggested that gut enterochromaffin (EC) cells (*lower left*; *bottom right*) formed a diffuse endocrine organ. In 1928, they described these cells to be neural in origin and proposed them as progenitors of neuroendocrine tumors of the gut (carcinoids). The first description of the diffuse neuroendocrine system (DNES) was provided in 1938 by F. Feyrter (*bottom*), who described argentaffin or argyrophil "clear cells" ("*Helle Zellen*") in the gut and pancreas and proposed that such cells produced hormones that acted locally.