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REVIEW

Therapeutic Options for Gastrointestinal Carcinoids

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Although wide surgical resection is the optimal curative therapy for carcinoid tumors, in most patients the presence of metastatic disease at diagnosis usually renders excision a palliative procedure. This nevertheless decreases tumor burden, facilitates symptom control, and prevents complications caused by bleeding, perforation, or bowel obstruction resulting from fibrosis. In the stomach (types I and II) and rectum endoscopic excision may be adequate provided the lesion(s) are local. Long-term therapy is focused on symptom alleviation and improvement of quality of life using somatostatin analogues, particularly in a subcutaneous depot formulation. In some instances interferons may have a role but their usage often is associated with substantial adverse events. Conventional chemotherapy and external radiotherapy either alone or in a variety of permutations are of minimal efficacy and should be balanced against the decrease in quality of life often engendered by such agents. Hepatic metastases may be amenable to surgery, radiofrequency ablation, or embolization either alone or in combination with chemotherapeutic agents or isotopically loaded microspheres. Rarely hepatic transplantation may be of benefit although controversy exists as to its actual use. Peptide-receptor–targeted radiotherapy for advanced disease using radiolabeled octapeptide analogs (^{111}In/^{90}Yt/^{177}Lu-octreotide) appear promising but data are limited and its status remains investigational. A variety of antiangiogenesis and growth factor–targeted agents have been evaluated, but as yet have shown little promise. The keystone of current therapy remains the long-acting somatostatin analogues that alleviate symptomatology and substantially improve quality of life with minimal adverse effects.

This review article provides a comprehensive assessment of progress that has been made in the management of carcinoid tumors over the past 3 decades. Although the disease was described in morphologic terms early in the 20th century, it has only been in the past 50 years that the clinical and biochemical basis of carcinoid neoplasia has been defined. In 1888, Lubarsch[1] initially noted the microscopic features of ileal carcinoids but considered them to be carcinomas. Thereafter, Ransom[2] described the first observation of the classic presentation of carcinoid syndrome in a patient with a lesion of the ileum. However, it was Oberndorfer[3] in 1907 who coined the term *karzinoid* (carcinoma-like) to describe these tumors, which showed a more benign behavior than adenocarcinomas. Little more than sporadic reports were available thereafter until 1963 when Williams and Sandler,[4] in seeking to provide a logical framework to describe what appeared to be a ubiquitous collection of lesions, classified carcinoids by their embryologic site of origin as follows: (1) foregut (respiratory tract, stomach, duodenum, biliary system, and pancreas), (2) midgut (small bowel, appendix, cecum, and proximal colon), and (3) hindgut (distal colon and rectum). Although useful in the context of contemporary biological knowledge of that time, current considerations of the morphologic and biological heterogeneity of these lesions has led to the introduction of more generic terminology that embraces all neuroendocrine tumors (NET) including carcinoid tumors. Thus, carcinoid tumors of the gastrointestinal tract currently are regarded as gastroenteropancreatic NETs (GEP-NETs) because it is apparent that the term *carcinoid* fails to define adequately the spectra of tumors that are derived from different neuroendocrine cell types, secrete a diverse spectrum of hormones, and have vastly differing clinical presentations.[5]

The incidence of gastrointestinal carcinoids has increased over the past 20 years, most likely as a result of increased awareness and detection.[6,7] The tumors can be either sporadic or occur as part of familial syndromes, mainly multiple endocrine neoplasia I and II, von Hippel–Lindau disease, and neurofibromatosis. Overall, they occur most frequently (74%) in the gastrointestinal tract,

Abbreviations used in this paper: CTGF, connective tissue growth factor; 5-FU, 5-fluorouracil; GEP, gastroenteropancreatic; HDAC, histone deacetylase; 5-HIIA, 5-hydroxyindoleacetic acid; IFN, interferon; LAR, long-acting repeatable; ^{131}I-MIBG, Iodine-131-Meta-Iodobenzylguanidine; NET, neuroendocrine tumors; NP, neuropilin; SST, somatostatin; VEGF, vascular endothelial growth factor.

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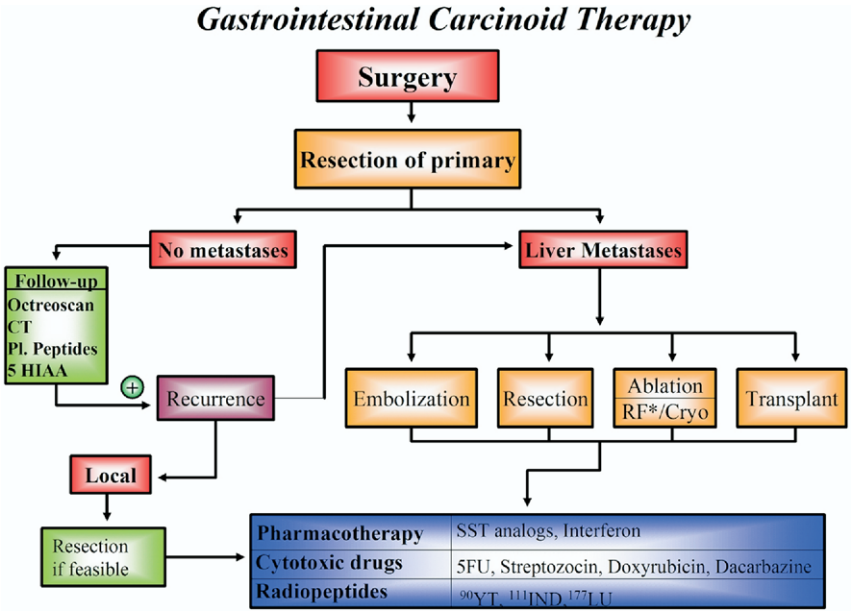

Figure 1. Therapeutic algorithm: management algorithm for gastrointestinal carcinoids. RF, radiofrequency; PL, plasma; YT, yttrium; IND, indium; LU, lutetium.

of which 38% are in the small intestine, 18% are in the appendix, 21% are in the rectum, 12% are in the colon, and 6% are in the stomach.[7] Clinically, their local manifestations include bleeding, obstruction, or perforation caused by either direct tumor invasion or fibrosis induced by the tumor. Indeed, in many instances, carcinoids are detected incidentally at surgery performed for another gastrointestinal disorder or during emergency surgery for appendicitis or obstruction, bleeding, or perforation. Systemic manifestations (flushing, sweating, diarrhea, bronchospasm) often are paroxysmal and the result of the secretion of biological mediators by either the primary lesion or metastases, or the consequences of cardiac failure engendered by tricuspid or pulmonary valvular fibrosis.

Although in general the understanding of gastrointestinal carcinoids has improved, they usually are misdiagnosed and their treatment often is delayed. Fortunately, their growth rate usually is relatively indolent (although some are aggressive) compared with most adenocarcinomas and appropriate treatment can be associated with quite reasonable outcomes in some circumstances.

This review provides an overview of the modalities that have been used in the treatment of these diverse tumors in the past and assesses current therapy and provides information regarding options currently under investigation.

Methods

A retrospective survey of the world's literature over the past 26 years (1979-2005) was undertaken to evaluate the development of therapeutic approaches to gastrointestinal carcinoid tumors. The key words used for this PubMed (www.pubmed.gov) search included "carcinoid," "therapy," and more specific terms including but not limited to: "biochemical markers," "tumor size," "disease stability," and "symptom improvement." When possible, only data that pertain to patients with gastrointestinal carcinoids were extracted from series of GEP-NET studies. Data were pooled and median values were calculated for each therapeutic modality reviewed.

Results

Primary Surgical Resection

Resection of the primary tumor and local lymph nodes is the only potentially curative therapy for gastrointestinal carcinoid tumors and usually is possible in up to 20% of patients (Figure 1).[8–10] Moreover, resection of nonhepatic tumor primaries has been associated with an increased median survival duration from 69 to 139 months.[11,12] The extent of resection, however, depends on the identity of a given tumor (presently defined by site of origin, which in the future likely will be replaced by more precise molecular definition), its location, and the involvement of surrounding structures and the extent of metastases. Overall, tumors of the appendix and rectum have the best prognosis (largely owing to earlier presentation) and therefore a local excision is the most appropriate treatment for most patients with lesions smaller than 1 cm and with no lymph node involvement.[13] In the case of rectal lesions this may be accomplished endoscopically provided endoscopic ultrasonography confirms that disease is localized. For appendiceal