CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2006;4:526–547

# 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.


1542-3565/06/$32.00
doi:10.1016/j.cgh.2005.12.008

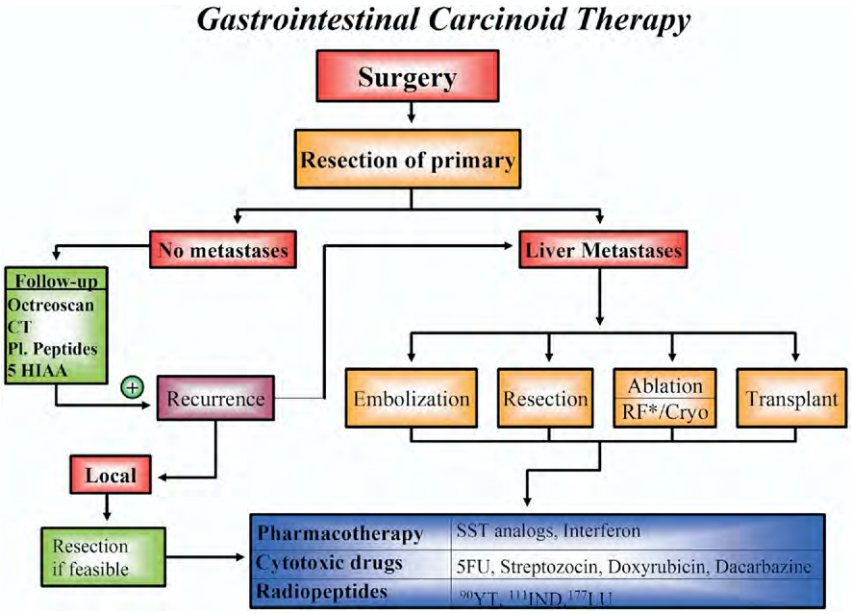


**Figure 1.** Therapeutic algorithm: management algorithm for gastrointestinal carcinoids. RF, radiofrequency; PL, plasma; YT, yttrium; IND, indium; LU, lutetium.

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

tumors larger than 2 cm, a right hemicolectomy with mesenteric excision should be performed but factors including location of the lesion (base of the appendix), histologic evidence of atypia, presence of mucin, and evidence of invasion override the arbitrary 2-cm size delineation.[14] Colonic and small intestinal lesions show the worst prognosis among gastrointestinal carcinoids and warrant a classic en bloc resection. Bowel resection should ensure extensive lymphadenectomy and wide removal of the mesentery, and should include a careful exploration for multicentric disease.[15] Surgical management of gastric carcinoids depends mainly on the type of the lesion and the extent of the lesion. Sporadic carcinoids (type III) may be regarded as akin to neuroendocrine carcinoma and usually behave aggressively and should be managed as for gastric adenocarcinoma. Lesions larger than 2 cm associated with local invasion require subtotal gastrectomy or extended local resection.[16] However, types I and II gastric carcinoids (associated with hypergastrinemia) may be managed by repeated endoscopic or local wedge excisions, unless the lesions are excessive in number or evidence of invasion is shown. Large lesions that ulcerate or bleed may require more extensive surgical resection, particularly if the patient is young and evidence of diffuse gastric microcarcinoidosis is evident. Although initially proposed as a physiologic solution to resolve the hypergastrinemia and thereby resolve enterochromaffin-like cell proliferation, the effect of an antrectomy may be unpredictable if the enterochromaffin-like cell lesions have become gastrin autonomous.[17]

In patients with metastatic carcinoids (hepatic, mesenteric, and peritoneal), conservative resections of the intestine, mesenteric tumors, and fibrotic areas may improve symptoms and quality of life considerably. However, the definitive role of surgery in metastatic disease is not established clearly. In principle, however, if the condition of the patient is such that surgery is not a greater risk than the disease, the primary tumor should be resected to obviate the inherent dangers of an unpredictable emergency presentation with obstruction, perforation, or bleeding.[18]

Although it is commonly accepted that resection of at least 90% of the tumor burden is required to achieve palliation, approximately 60% of patients will experience symptom recurrence (surgery alone), and the 5-year survival rate is between 35% and 80%, depending on the experience of the center.[10,11] The benefits of surgical treatment of gastrointestinal carcinoid tumors therefore should be weighed carefully in each patient against the potential risks inherent in an open exploration, especially because treatment with somatostatin analogues can achieve similar rates of symptom relief with fewer adverse effects. Tumor debulking, however, may render pharmacologic therapy more effective by decreasing the secretion of bioactive substances.

## Biotherapy

The development of long-acting somatostatin analogues and depot formulations has proven instrumental in the amelioration of the carcinoid syndrome and have led to a substantial improvement in quality of life with relatively mild adverse effects.[19,20] There have been sporadic reports of cytostatic effects of such agents although rigorous data are lacking. Indeed it has been proposed that such agents have been responsible for an overall increase in life expectancy in symptomatic patients.[21] Intravenous somatostatin analogues are effective in the management of carcinoid crises, usually precipitated by anesthesia or surgical or radiologic interventions.[22] Recombinant leukocyte interferon (IFN)-α alone or in combination with somatostatin analogues has been used in disseminated carcinoid disease to alleviate diarrhea, flushing, and in some patients has been noted to induce some degree of tumor regression.[23] Its use, however, also can be associated with significant toxic side effects.[19,24]

**Somatostatin analogues.** Although somatostatin first was isolated by Brazeau et al[25] in 1973 from the sheep hypothalamus, it subsequently has been recognized as a major neurotransmitter expressed throughout the central nervous system, thyroid and adrenal glands, kidneys, peripheral tissues, endocrine pancreas, and gastrointestinal tract. Most of the inhibitory effects of somatostatin on neurotransmission, motor and cognitive functions, smooth muscle contractility, glandular and exocrine secretions, intestinal motility, and absorption of nutrients and ions are mediated by cAMP inhibition.[26,27] Particularly appealing has been the experimental observations of its cytostatic effect on tumor cells.[28,29] Mechanistically this involves hyperphosphorylation of the retinoblastoma gene product and G1 cell-cycle arrest, but also can result from somatostatin receptor subtype 3–mediated (and to a lesser extent, subtype 2–mediated) apoptosis.[28,30] Somatostatin itself also appears to show some antiangiogenic properties.[31,32]

By the early 1980s a number of short synthetic analogues of somatostatin including SMS201-995 (octreotide), RC-160 (vapreotide), BIM 23014 (lanreotide), and MK 678 (Seglitide) were developed.[26] These cyclic octapeptides are more resistant to peptidases and their half-lives and hence their biological activities are substantially longer than native somatostatin (1.5–2 h vs 1–2 min).[33] In the 1990s, 5 somatostatin receptor sub-

**Table 1.** Effects of Octreotide in Gastrointestinal Carcinoids

| Study | Year | Number of patients | Biochemical response % | Tumor response % | No disease progression % | | Symptomatic response % | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Biochemical | Tumor | Diarrhea | Flushing |
| Kvols et al[32] | 1986 | 25 | 72 | 0 | 28 | 62 | 88 | 92 |
| Kvols et al[39] | 1987 | 19 | 63 | 0 | — | — | — | — |
| Vinik and Moattari[40] | 1989 | 14 | 75 | 0 | 25 | 50 | 75 | 100 |
| Oberg et al[41] | 1991 | 23 | 27 | 9 | 36 | — | 50 | |
| Saltz et al[42] | 1993 | 20 | | 0 | | 50 | 71 | |
| Janson et al[43] | 1992 | 24 | 45 | 0 | 17 | 62 | — | — |
| Janson and Oberg[44] | 1993 | 55 | 37 | 2 | 49 | — | 69 | 70 |
| Arnold et al[21] | 1996 | 64 | 33 | 0 | — | 55 | 64 | 75 |
| di Bartolomeo et al[45] | 1996 | 31 | 77 | 3 | 23 | — | 40 | 50 |
| Nilsson et al[34] | 1998 | 10 | 33 | | 77 | — | — | — |
| O'Toole et al[46] | 2000 | 28 | 50 | | — | — | 79 | 48 |
| Garland et al[47] | 2003 | 27 | 25 | 0 | 25 | 48 | 81 | |
| Kolby et al[19] | 2003 | 35 | 0 | 0 | 46 | | — | — |
| Welin et al[20] | 2004 | 12 | 17 | 0 | 75 | 75 | — | — |
| Median | | 24 | 37 | 0 | 28 | 55 | 71 | 71 |
| Range | | 10–64 | 0–77 | 0–9 | 17–77 | 48–75 | 40–88 | 48–100 |

NOTE. Pooled data of 14 trials spanning the past 2 decades reflect a median biochemical response rate of 37%, with only 4 trials showing decreased urinary 5-HIAA levels in more than half of the patients studied. Objective tumor responses were shown in only 3 trials (individual rates ranging between 3% and 9%), with the cumulative tumor response rate at 0%. Octreotide therapy has a better effect on slowing the progression of carcinoid disease, with 28% and 55% of patients manifesting biochemical or tumor stability. The beneficial effects of octreotide are limited to symptom relief, with 71% of patients experiencing resolution of diarrhea or flushing.
—, not reported/no data available.

types were cloned and their distribution in various types of normal and tumor tissues was described.[34] Fifty percent of the amino acids in these receptors are identical among the 5 subtypes. In addition to being expressed in neuroendocrine tumors of the GEP axis, somatostatin receptors also are expressed at high densities in meningiomas; medulloblastomas; medullary thyroid carcinomas; adenocarcinomas of the breast, ovary, and colon; and on inflammatory and immune cells.[35] Undifferentiated tumors tend to express somatostatin receptors less often and at a lower density than well-differentiated (less-malignant) neoplasias. The currently available somatostatin analogues display high-affinity binding for type 2 and type 5 receptors, low affinity for type 1 and type 4, and medium affinity for type 3.[26] The more recently described analogue (SOM230) shows nanomolar potency for types 1, 2, 3, and 5, with no agonist activity at the type 4 receptor.[26,36] In contrast to octreotide, this novel analogue (currently in phase II clinical trials for midgut carcinoids) shows a high affinity for type 5 receptors, which may prove therapeutically advantageous.[36–38]

*Octreotide.* The somatostatin analogue octreotide (Sandostatin; Novartis, East Hanover, NJ) was the first biotherapeutic agent used in the management of carcinoid tumors. Pooled data from 14 trials spanning the past 2 decades and including close to 400 patients reflected a median biochemical response rate of 37% (range, 0%–7%), with only 4 trials showing decreased urinary 5-hydroxyindoleacetic acid (5-HIAA) levels in more than half of the patients studied (Table 1).[19,20,32,34,39–48] Objective tumor responses were shown in only 3 trials (range, 3%–9%), with the cumulative tumor response rate at 0%. In contrast, octreotide therapy appears better at slowing the progression of carcinoid disease, with a median of 28% and 55% of patients manifesting biochemical or tumor stability in these studies, respectively. In general, the beneficial effects of octreotide are limited to symptom relief, with 71% of patients experiencing resolution of diarrhea or flushing. There are no rigorous clinical data to support an inhibitory effect on tumor growth and to date only about 30 patients experienced partial tumor regression with somatostatin analogue therapy.[10]

*Lanreotide.* Lanreotide (Somatuline; Ipsen, Slough, UK), a long-acting somatostatin analogue administered every 10–14 days, has a similar efficacy to octreotide in the treatment of carcinoid tumors, but its formulation is easier and more comfortable for patients to use.[49] The therapeutic effects of lanreotide have been studied in 11 groups, totaling about 300 patients over the past decade, with little overall improvement in responses over shorter-acting octreotide, although the decreased need for injection is advantageous (Table 2).[46,50–60] The median biochemical response rate of the entire patient population treated with lanreotide is 42% (vs 37% with octreotide), with 3 trials reporting objective improvements in tumor size in 5%–9% of patients. Com-

**Table 2.** Effects of Lanreotide on Gastrointestinal Carcinoids

| Study | Year | Number of patients | Biochemical response % | Tumor response % | No Disease progression % | | Symptomatic response % | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Biochemical | Tumor | Diarrhea | Flushing |
| Canobbio et al[57] | 1994 | 8 | 62 | 0 | 38 | 90 | 100 | 87 |
| Scherubl et al[50] | 1994 | 12 | — | 0 | — | 58 | 42 | 86 |
| Eriksson et al[51] | 1996 | 19 | 54 | 0 | — | 90 | — | — |
| Ruszniewski et al[52] | 1996 | 33 | 42 | 0 | 46 | — | 38 | 53 |
| Wymenga et al[53] | 1999 | 48 | 27 | 8 | 52 | 81 | 38 | |
| Faiss et al[58] | 1999 | 19 | — | 9 | — | 52 | — | |
| Tomasetti et al[54] | 2000 | 10 | — | 0 | — | 90 | 90 | 80 |
| Ducreux et al[59a] | 2000 | 38 | 40 | 5 | 24 | 54 | — | 40 |
| O'Toole et al[46] | 2000 | 28 | 50 | — | — | — | 89 | 41 |
| Ricci et al[55] | 2000 | 12 | 42 | 8 | — | — | 36 | 100 |
| Rohaizak and Farndon[56] | 2002 | 10 | 0 | 0 | 83 | — | 90 | |
| Ruszniewski et al[60] | 2005 | 55 | 30 | — | — | — | 75 | 81 |
| Median | | 19 | 42 | 0 | 46 | 81 | 75 | 80 |
| Range | | 8–55 | 0–62 | 0–9 | 46–83 | 58–90 | 36–100 | 38–100 |

NOTE. The median biochemical response rate of the entire patient population treated with lanreotide is 42% (vs 37% with octreotide), with only 2 trials reporting objective improvements in tumor size. Compared with octreotide, lanreotide has better effects on tumor stability, with 52% and 85% of patients maintaining biochemical and tumor size status quo (vs 28% and 55% of patients treated with octreotide). The effects of lanreotide on symptom relief, particularly diarrhea, are less pronounced compared with octreotide. Although 80% of patients treated with lanreotide reported decreased flushing, only 42% reported resolution or decrease of diarrhea. In the population treated with octreotide, the median rate of symptom relief of both was 71%.

—, not reported/no data available.

[a]Overlapping patient population with Ruszniewski et al, 1996.[52] Response defined as >30% decrease in biochemical markers.

pared with octreotide, lanreotide has somewhat better effects on tumor stability, with 46% and 81% of patients maintaining biochemical and tumor size status quo, respectively. The effects of lanreotide on symptom relief are comparable with those of octreotide, with 75%–80% of patients reporting decreased diarrhea and flushing, respectively.

*Depot formulations.* The development of a depot formulation of octreotide, Sandostatin LAR (Novartis) (long-acting repeatable), administered up to 30–60 mg once every 4 weeks has to a large extent eliminated the need for daily injections. However, symptom breakthrough in the weeks before a steady state is achieved or in the last week of the cycle sometimes necessitates rescue with an additional 50 or 100 μg (up to 1000 μg) doses of a short-acting analogue such as Sandostatin, or by increasing the dose and/or frequency of the depot injection. A new slow-release depot preparation of lanreotide, Lanreotide Autogel (Ipsen), administered subcutaneously up to 120 mg once a month has been introduced in Europe. Ruszniewski et al[60] evaluated the efficacy and safety of this 28-day aqueous prolonged release formulation of lanreotide in 75 patients in a 6-month dose-titration study. Thirty percent of patients showed a biochemical response and 75% and 80% of patients reported resolution of diarrhea and flushing, respectively, which is comparable with the reported effects of other lanreotide preparations. The median decrease in levels of urinary 5-HIAA and serum chromogranin A was 24% and 38%, respectively. The response was higher in patients who had not been treated previously with somatostatin analogs (46% vs 34%).

Although studies have indicated comparable efficacies of the immediate-release octreotide, the 28-day LAR octreotide, and the lanreotide 30-mg microparticle formulation at steady-state levels, there have been no reports directly comparing the 28-day prolonged release formulations of lanreotide and octreotide.[46,61] A recent report comparing subcutaneous immediate-release octreotide with monthly octreotide LAR reported an increased median survival from the time of metastatic disease diagnosis (143 vs 229 months in favor of the LAR form).[62] This represents a 66% lower risk for death among patients treated with the long-acting formulation. In addition, most recent data from a study with ultra-high dose octreotide (Onco-LAR; Novartis) at 160 mg intramuscularly every 2 weeks for 2 months followed by the same dose once monthly, appear to show some promise.[33] The preliminary results in 12 patients showed tumor size stabilization in 9 and biochemical responses and/or stability in 11. No significant tumor reduction was noted. At 6 months, the median plasma concentrations of octreotide were 25–100 times higher than those obtained by using octreotide LAR at regular doses. The protocol also showed significant inhibition of angiogenesis through the down-regulation of proliferative factors

such as vascular endothelial growth factor (VEGF) and fibroblast growth factor.[33] In general, the highest response rates were reported using octreotide in doses greater than 30 mg/day or lanreotide in doses greater than 5 mg/day (and up to 15 mg/day).[58]

An interim analysis of a phase II trial of SOM230 in 21 patients with metastatic carcinoid tumors whose symptoms (diarrhea and flushing) were refractory/resistant to octreotide LAR showed symptom relief in 33%.[63]

Although the biochemical and tumor responses to somatostatin analogues vary with the frequency and type of analogue used, the typical length of treatment with these compounds is approximately 12 months as a result of the development of tachyphylaxis (reported less frequently with longer-acting formulations) and/or increased tumor burden.[19,64,65] Nevertheless, treatment with somatostatin analogues generally is well-tolerated and their efficacy in symptom relief is unparalleled. Adverse effects such as nausea, cramping, loose stools, steatorrhea, cardiac conduction abnormalities and arrhythmias, endocrine disturbances (hypothyroidism, hypoglycemia, or, more commonly, hyperglycemia), and infrequently gastric atony may occur.[33,66] Cholelithiasis and biliary sludge occur in up to 50% of patients, but few (1%–3%) develop acute symptoms requiring cholecystectomy.[67]

**Interferons.** IFN-α, IFN-γ, and human leukocyte IFN all have been used in the pharmacologic management of carcinoid tumors.[24,67] Although the exact mechanism of their action is understood poorly, it variously may include immune cell–mediated cytotoxicity and delayed progression of the cell cycle from S to G2 phase as a result of a reduction in cellular cyclin B and inhibition of Cdc2 kinase activity.[68] Recent reports also have suggested a direct antiproliferative effect and inhibition of tumor angiogenesis mediated by suppression of VEGF gene expression, although a serum analysis of 29 patients with carcinoid tumors found no correlation between IFN treatment and serum VEGF levels.[68,69] IFNs tend to have substantial adverse effects including alopecia, anorexia, fatigue, weight loss, fever, a flu-like syndrome, and myelosuppression, but may show greater antitumor activity (sic) than somatostatin analogues.[49]

*Interferon-α.* In addition to somatostatin analogues, IFN-α is the most well-researched biotherapeutic agent in the treatment of carcinoid disease. Its therapeutic effects are largely identical to those of somatostatin analogues, with marginally better tumor responses.[23,24,70–81] Pooled data from 14 groups that totalled more than 350 patients showed a median biochemical response rate of 42% (range, 17%–75%), which is comparable with octreotide (37%) and lanreotide (42%), with 6 centers reporting reductions in biochemical markers (>50%) in half or more of the patients treated. Although the median tumor response rate of patients treated with somatostatin analogues was 0%, treatment with IFN-α resulted in approximately 10% of patients experiencing objective tumor regression. The median time to progression from the start of therapy is 12 months, whereas median survival ranged from 44 to 80 months.[10] Biochemical and tumor stability were achieved in 40% and 66% of patients, respectively. Similar to somatostatin analogues, the most pronounced effects of IFN-α are inhibition of disease progression and symptom relief, with approximately 75% of patients reporting resolution of diarrhea or flushing.

*Human leukocyte interferon.* The effects of human leukocyte interferon are somewhat comparable with the reported outcomes of IFN-α trials.[67,82–85] Pooled data from more than 70 patients treated at 3 Scandinavian centers in the mid- and late 1980s showed median biochemical and tumor responses in 29% and 14% of patients, respectively (vs 42% and 11% of patients treated with IFN-α, respectively). Approximately 50% of patients treated with human leukocyte IFN maintained disease stability at the time of follow-up evaluation. However, human leukocyte IFN seems to have less pronounced effects on carcinoid symptoms, with only 46% and 36% of patients reporting resolution and/or decrease in diarrhea and flushing, respectively.

*Interferon-γ ± interferon-α.* A recent phase II trial with IFN-γ in 51 patients with carcinoid tumors failed to produce significant antitumor effects and the median time to progression in the 3 patients (6%) who had a partial response was 5.5 months.[86] The combination of interferon-α and interferon-γ appears to be no more effective, with 1 trial of 12 patients showing no biochemical or tumor responses but achieving disease stability in 58% and 92% of patients, respectively, with half of the patient population reporting symptom relief.[87]

**Interferon-α + octreotide.** It is debatable whether somatostatin analogues and IFNs show a synergistic effect in carcinoid syndrome symptom management. Dual therapy with octreotide and interferon-α is limited by the small number of trials, but the median biochemical response rate of 75% for the cumulative population of more than 80 patients is far higher than the rates for each of the individual agents.[19,43,44,88] Although biochemical responses were reported in 77%, 72%, and 75% of patients, none of the trials reported any improvement in tumor size, and a median of

**Table 3.** Effects of Single-Agent Cytotoxic Therapies on Gastrointestinal Carcinoids

| Agent (study) | Years | Number of patients | Response, % |
|---|---|---|---|
| Fluorouracil[92,101] | 1979–1983 | 49 | 20 |
| Doxyrubicin[92,94,101] | 1983–1984 | 114 | 21 |
| Dacarbazine[92,95,96,101,103] | 1983–1995 | 95 | 16 |
| Streptozocin[92,97,101] | 1983–1987 | 13 | 15 |
| Dactinomycin[95] | 1983 | 17 | 6 |
| Cisplatin[98] | 1986 | 15 | 7 |
| Carboplatin[99,100] | 1990–1993 | 20 | 0 |
| Cyclophosphamide[101] | 1979 | — | 0 |
| Etoposide[102] | 1987 | 17 | 12 |
| Melphalan[92,101] | 1983 | 7 | 0 |
| Docetaxel[104] | 2004 | 21 | 31[a] |
| Median (range) | | 17 (7–114) | 12 (0–31) |

NOTE. The most thoroughly researched chemotherapeutic modality is dacarbazine, with 4 trials achieving a trial-defined response rate of 16%. Approximately 1 in 5 patients treated with 5-FU and doxyrubicin achieved therapeutic responses, whereas only 15% of patients treated with streptozocin, 12% of patients treated with etoposide, 7% of patients treated with cisplatin, and 6% of patients treated with dactinomycin were reported to have successful therapeutic outcomes. Trials with cyclophosphamide, carboplatin, and melphalan reported no clinically significant improvements. The median response rate of the entire patient population treated with single-agent chemotherapy was 12%.

—, not reported/no data available.

[a]Biochemical response.

25% of patients achieved biochemical stability. The most recent study reported no significant difference in survival between patients treated with octreotide alone compared with a group managed with combination therapy.[19] The median 5-year survival rates were 36.6% and 56.8%, respectively. Symptom response data were available for 1 group of 19 patients; 47% reported improvement.

**Tamoxifen.** Tamoxifen initially was reported to provide symptom relief in 2 patients with carcinoid syndrome.[89,90] In a subsequent study in the early 1980s that included 16 patients, tamoxifen therapy showed no biochemical or tumor responses.[91]

## Chemotherapy

The majority of single-agent chemotherapeutic protocols (5-fluorouracil, streptozocin, doxorubicin, actinomycin D, dacarbazine) show little beneficial effect. Subsequent combination trials have not resulted in additional increases in response rates.

**Single-agent therapy.** Numerous trials of single-agent chemotherapy with 5-fluorouracil (5-FU), dacarbazine, doxorubicin, streptozocin, and dactinomycin, among others, were conducted in the 1980s. No modality showed response rates greater than 31% (Table 3).[92–104] The most thoroughly researched chemotherapeutic modality is dacarbazine. Trial-defined response rates of 16% were noted in approximately 100 patients studied.[92,93,95,96,103] Approximately 20% of patients treated with 5-FU or doxorubicin achieved therapeutic responses, whereas only 15% of patients treated with streptozocin, 12% of patients on etoposide, 7% of patients on cisplatinum, and 6% of patients treated with dactinomycin were reported to have successful therapeutic outcomes.[92,95,97,98,101,102] Trials with cyclophosphamide, carboplatin, and melphalan reported no clinically significant improvements.[93,99–101] The most recently published data on the effects of docetaxel in 21 patients with metastatic carcinoid disease reported biochemical responses in 31% of evaluable patients and tumor size stabilization in 81% of patients, albeit without significant tumor regression.[104] The median progression-free survival time was 10 months and the median overall survival time was 24 months. The median response rate of the entire patient population treated with single-agent chemotherapy was approximately 10%.

**Multiple-agent therapy.** Of the numerous permutations of chemotherapeutic agents, the combination of 5-FU and streptozocin with or without cyclophosphamide is the most extensively studied.[101] Pooled data from 5 trials that included a total of 165 patients treated with 5-FU and streptozocin reflected a median response rate of 39%.[84,94,97,101,105] Triple therapy with 5-FU, cyclophosphamide, and doxorubicin achieved a similar response rate (38%), but the addition of streptozocin to this combination did not result in an improved outcome.[106–108] The only 2 trials that reported improved outcomes in a more significant proportion of patients (80% and 50%) were double-agent studies of 5-FU with lomustine and cisplatin with doxorubicin. These studies, however, were limited by the relatively small population sizes of 5 and 6 patients, respectively.[109,110] The median response rate of the entire patient population treated with these combination chemotherapies was 22%, which reflects little improvement over the efficacy of single agents (0%–21%).

Overall there is little robust evidence available to advocate the use of single-agent or multiagent chemotherapeutics in this essentially chemoresistant disease because no protocol has shown objective tumor response rates greater than 15%. The only 2 groups of tumors for which chemotherapy has shown some results, albeit transient, are pancreatic and undifferentiated NETs.[111]

## Biochemotherapy

The addition of chemotherapeutics to biotherapy with interferon-α has been studied in 2 small trials. Triple therapy with interferon-α, streptozocin, and doxorubicin resulted in no measurable biochemical or objec-

tive tumor responses in 11 patients.[76] The addition of fluorouracil to interferon-α in 14 patients resulted in 2 of 8 patients experiencing a biochemical response and 1 of 14 patients experiencing a reduction in tumor size.[112] The addition of chemotherapeutic agents to biotherapy protocols does not appear to improve on results of individual modalities.

## Management of Hepatic Metastases

**Overview.** The presently available pharmacologic interventions usually have not addressed hepatic carcinoid metastases specifically, but as noted earlier are somewhat ineffective overall and often show severe adverse effects. Similarly, an invasive surgical approach often is risky, sometimes has serious associated adverse events, or may be unfeasible technically. Intervention depends on the extent of hepatic disease and its anatomic (segment) localization. This may range from wedge resection to hemihepatectomy or the use of local ablative techniques (cryofrequency or radiofrequency ablation) if multiple metastases precluding segmental resection are present. In instances of diffuse metastasis or multiple metastases with dominant lesions, selective angiography-guided occlusion or embolization of the hepatic arterial tree has been developed as an alternative modality for patients in whom safe or effective surgical excision is unattainable. This relatively minimally invasive approach is based on the premise that most of the vascular supply to metastases originates from branches of the hepatic artery. Normal hepatic parenchyma, on the other hand, receives additional blood supply from the portal venous system.

Initially, the devascularization and necrosis of hepatic metastases was achieved through open surgical ligation of the common hepatic artery. However, the outcomes were inconsistent, short-lasting (development of collaterals), and frequently unacceptably costly because of both the need to repeat the procedure and high perioperative mortality rates of up to 20%.[113] The subsequent development of interventional radiologic approaches that involve highly selective embolization of tumor vasculature has led to a significant reduction of reactive angiogenesis and collateral formation, and most importantly has shown much less morbidity, thus obviating the need for open surgical ligation.[15,114]

Currently, most vascular occlusion protocols involve transcatheter arterial chemoembolization by injection of an emulsion of a cytotoxic drug (usually streptozocin or doxorubicin) into the branches of the hepatic artery, followed by embolization with gelatin sponge particles or microspheres until a significant decrease in blood flow is achieved. The therapeutic injection is preceded by superior mesenteric and celiac trunk arteriography to assess the arterial distribution and portal vein patency and to evaluate tumor blood flow.[113,115] The underlying principle behind the combination of intra-arterial chemotherapy and hepatic artery embolization is based on the notion that a combination of reduced vascularization and anoxia will increase local drug concentrations and decrease wash-out time in the metastasis.[116,117] In situ cryofrequency or radiofrequency ablations usually are reserved for patients with localized or residual disease, and often are used as adjuncts to primary resective surgery. Hepatic embolization with concurrent local irradiation with radiolabeled microspheres (brachyradiotherapy) and alcohol injection directly into liver foci also have been used for metastases of various tumors, but the experience with gastrointestinal carcinoids is limited.[118,119]

**Surgical resection.** There have been more than a dozen trials or reports over the past decade on the effects of surgical resection on hepatic metastases. Most series, however, do not discriminate carcinoid tumors from NETs and GEPs and very few report biochemical/objective response rates. This notwithstanding, the median response rate of the entire pool (≃400 patients) is more than 90%, with about 60% of patients experiencing decreased urinary 5-HIAA levels after surgery. Symptomatic improvement is reported in 90% of patients and the median duration is between 19 and 45 months.[120] The median time to progression varies between 16 and 20 months, depending on whether the surgical resection was palliative or complete.[121] McEntee et al[11] retrospectively reviewed the Mayo Clinic experience of hepatic resection for patients with metastatic NETs who underwent resection between 1970 and 1989 (37 patients; 24 patients had a carcinoid). Of the 10 patients with carcinoid who underwent resection with curative intent, 9 achieved complete clinical response; similarly, of the 13 patients who underwent palliative resections, 6 of 7 (86%) showed biochemical responses.[11] In a 1996 series of 64 patients with disseminated midgut carcinoids, 14 patients (22%) who underwent hepatic resections achieved anatomic and biochemical cure by surgery alone, with a mean reduction of urine 5-HIAA secretion of 78% and a 5-year survival rate of 100%. Forty patients with bilobar hepatic disease underwent embolization in combination with octreotide. In this group, 5-HIAA levels were reduced by 55%, 17 patients (43%) showed objective tumor response, and the 5-year survival rate was 56%.[122] The largest review to date that included 120 carcinoid patients reported a biochemical response rate of 96% among patients whose hepatic metastases were resected surgically.[121] This was associated with a

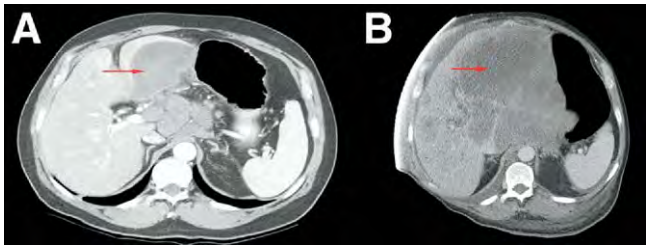


**Figure 2.** Hepatic metastasis prehepatic and posthepatic artery embolization. (*A*) Computed tomography (preembolization): axial section reveals large metastatic focus involving the left hepatic lobe with a small area of central necrosis. Note para-aortic/mesenteric adenopathy. (*B*) Positron emission tomography–computed tomography (postembolization): large attenuated mass in the left hepatic lobe consistent with necrosis with recent known embolization of the metastatic carcinoid tumor.

5-year survival rate of 61%, which is slightly less than the median rate of 72% for the entire patient population treated surgically for hepatic metastases surveyed in this review. In contrast, the 5-year survival rate without surgical therapy is approximately 30%.[10]

**Hepatic artery embolization.** The use of occlusive agents with or without concurrent chemoembolization is associated with biochemical responses in 5%–75% and tumor responses in 8%–60% of patients.[70,79,123–136] The most frequently used single-agent modality is gelatin powder, and in more than 60 patients with carcinoid tumors the use of gelatin powder resulted in 34% and 42% of patients achieving biochemical and tumor-diminution responses, respectively.[123–125] In a separate series of 23 patients, embolization with either gelatin powder, polyvinyl alcohol, or coils resulted in effective biochemical responses in 52% of patients.[126]

Trials using transcatheter arterial occlusion with chemoembolization have reported biochemical responses in 12%–75% of patients, with a median response rate of approximately 60%.[70,79,127–136] Reported tumor response rates are 8%–60%, with a median of 50% of patients showing objective tumor regression (Figure 2). In a group of 42 patients treated with hepatic-artery occlusion followed by systemic chemotherapy, the median overall decrease in 5-HIAA levels among responders was 75% with hepatic artery occlusion alone and 89% with added chemotherapy.[132] The most thoroughly researched combination occlusion modality, hepatic artery ligation with Gelfoam (Pharmacia, Peapack, NJ) and doxorubicin (4 trials and 66 patients), resulted in biochemical responses in 71% of patients and tumor regression in approximately 50% of patients.[127–130] Other combination modalities of chemotherapeutic agents (5-FU/cisplatin/mitomycin) with occlusive agents (gelfoam, polyvinyl alcohol, coils) have not been associated with any increased therapeutic advantage.[79,131,133,134,136] At this time it is unclear whether combinations of chemotherapeutic agents and vascular occlusive material such as gelfoam, starch particles, lipiodol, or radioisotope-loaded spheres result in any significant survival benefits.

The most beneficial aspect of vascular occlusion therapy is symptom control, with approximately 90% and 100% of patients experiencing relief from diarrhea and flushing, respectively. Nevertheless, despite the short-term efficacy the duration of the response after hepatic-artery occlusion or embolization can be short-lived. The duration of symptom relief is between 14 and 22 months, with mean survival times of 24–32 months.[127–130] In 1 study of 23 patients treated with hepatic-artery occlusion without chemoembolization, 20 patients (87%) responded to embolization with a median response duration of 11 months.[126]

Although surgery is a more formidable procedure, embolization can be associated with a series of adverse effects that may range from transient symptoms (pain, nausea, fever, fatigue), which occur in 30%–70% of patients, to liver enzyme abnormalities, which occur in up to 100% of patients (transaminitis, postembolization syndrome), to florid and potentially lethal carcinoid crisis with massive release of vasoactive substances.[10] The latter scenario can be obviated by the prophylactic use of somatostatin analogues before embolization.[137] Other unwanted effects include gastrointestinal bleeding, acute pancreatitis, ischemic necrosis of the gallbladder and small bowel, liver abscesses, gastric and duodenal ulceration, sepsis, renal failure, hepatorenal syndrome, portal vein thrombosis, sclerosing cholangitis, arterial thrombosis, and arrhythmias.[134] These usually reflect erroneous embolization of nonhepatic vessels or bacterial infection of necrosed tumor.

**Cryoablation and radio frequency ablation.** Radiofrequency ablation induces cellular destruction by the conversion of high-frequency alternating current into heat, achieving temperatures in excess of 60°C. Cryotherapy involves cycles of freezing and thawing by means of a cryoprobe placed within the tumor foci.[138] In 1 series of patients who underwent cryotherapy, close to 90% experienced complete relief of symptoms for a median interval of 11 months and approximately 60% showed decreased 5-HIAA secretion.[139] Interestingly, during the follow-up period of approximately 2 years, about 90% of patients experienced recurrence. Approximately 50% of recurrences were observed in the previously ablated foci. Another study of 13 patients treated with cryoablation for neuroendocrine liver metastases reported a 92% survival rate at a median follow-up time of 13.5 months.[140]

One series of 32 patients who underwent laparoscopic radiofrequency ablation for hepatic metastases from neuroendocrine tumors, including 13 gastrointestinal carcinoids, showed a partial or significant decrease in tumor markers in 65% of patients at a mean follow-up period of 1.6 years.[141] Forty-one percent of patients showed no evidence of disease. Local recurrence in the liver occurred in 13%, existing lesions progressed in 13%, new lesions developed in 28%, and new extrahepatic disease developed in 25% of patients. The symptomatic response to radiofrequency ablation lasted for a mean of 10.1 months (range, 6–24 mo). The study reported no perioperative mortality and the mean hospital stay was 1.1 days. Likewise, 3 patients with unresectable hepatic carcinoid metastases treated with radiofrequency ablation showed decreased symptoms in the first 3 months after treatment.[142] All 3 patients had decreased octreotide requirements postprocedure, including 1 patient who discontinued octreotide treatment for symptom control. All 3 patients showed objective tumor shrinkage on computed tomography. In general, cryotherapy and radiofrequency ablation are of limited use in tumors larger than 35 mm and in patients with multifocal (>5) hepatic metastases.[113]

**Orthotopic liver transplantation.** At present, the indications for hepatic transplantation are to achieve symptom relief from unresectable neuroendocrine liver metastases in the presence of no other evidence of metastases.[143] However, the benefit of this procedure in the treatment of metastatic carcinoids has yet to be established rigorously because there are few centers that offer the procedure and experience is limited to small series. Overall, approximately 50 liver transplantations have been described, with symptomatic relief occurring in 90%–100% of patients. Given the relatively short follow-up times available, the 5-year survival rates of 36%–73% represent for the most part actuarial calculations.[144] One of the first case reports on this subject included a patient with a small-bowel carcinoid who maintained biochemical response for close to 10 months after surgery and showed no radiologic evidence of recurrence at 20 months posttransplant.[145] The first prospective series included 9 patients with carcinoid tumors but only 3 patients were followed-up for longer than 3 years. The reported 5-year survival rate was 81%.[146] A number of early series reported high perioperative mortality rates and frequent tumor recurrence. Thus, in the series by Lang et al[148] of 12 patients, there was 1 intraoperative mortality and 2 patients died in the postoperative period as a result of sepsis and/or tumor recurrence. Similarly, in a series of 6 hepatic transplantations for carcinoid the median survival was 20 months, with disease recurrence occurring in 5 patients at a median follow-up period of 11 months.[148] In a separate series of 4 liver transplants for carcinoids, 3 patients were alive at 15–62 months.[149] The largest series to date (15 patients with carcinoids in a group of 31 patients with metastatic NETs) undergoing orthotopic liver transplantation reported a 5-year survival rate of 73%, with only 47% of patients disease-free at follow-up evaluation.[150] Of note, however, was the overall postoperative mortality rate of 19%, with 50% of the carcinoid transplant patients suffering at least 1 major complication (peritoneal bleeding, acute/chronic rejection, or acute pancreatitis). Studies that excluded patients with noncarcinoid tumors or extrahepatic disease reported significantly higher success rates. One such series reported actuarial 5-year and disease-free survivals of 70% and 53%, respectively.[151] Overall, the outcome of liver transplantation for carcinoid hepatic metastases remains less than satisfactory, reflecting both morbidity of transplantation and the intrinsic nature of the disease, and the recrudescence based on the use of immunosuppressive agents in the presence of undetected or minimal metastatic disease. In this respect a recent cumulative review of 103 patients reported that up to 40% manifested extrahepatic disease spread before transplant.[152]

## Radionuclides

The response rate of carcinoid tumors to external beam radiation therapy is very limited.[153] Palliative therapy, however, has some efficacy for bone and brain metastases and in the management of spinal cord compression.[154] The more recent introduction of systemic receptor–targeted (a variety of radiolabeled somatostatin analogues) or metabolically directed radiotherapy using a variety of isotopes for the treatment of inoperable or metastatic GEP tumors has engendered early optimism.[155] This technique involves targeting of a molecule-radionuclide conjugate to specific surface receptors on tumor cells. On binding to the receptor, the radioisotope-molecule complex is endocytosed. Thus, a very focal and effective dose of radiation theoretically can be administered to tumor or peritumoral cells only, leaving the majority of surrounding nonneoplastic tissue intact. In addition, by using isotopes with different emission wavelengths the extent of local irradiation to a certain extent can be tailored to the size range of the lesions. Although renal exposure is of concern, kidney irradiation can be decreased substantially by pretherapy amino-acid infusion

**Table 4.** Effects of Peptide Receptor Radionuclide Therapy in Gastrointestinal Carcinoids

| Investigator | Year | Number of patients | Agent | Tumor response % | No disease progression % | |
|---|---|---|---|---|---|---|
| | | | | | Biochemical | Tumor |
| Otte et al[158] | 1999 | 9 | $^{90}$Yt | 0 | - | 100 |
| Waldherr et al[159] | 2001 | 12 | $^{90}$Yt | 8 | - | 92 |
| Virgolini et al[160] | 2002 | 34 | $^{90}$Yt | 0 | - | 62 |
| McCarthy et al[161] | 1998 | 10 | $^{111}$In | 20 | - | 40 |
| De Jong et al[162] | 1999 | 10 | $^{111}$In | 17 | - | 50 |
| Valkema et al[163] | 2002 | 9 | $^{111}$In | 0 | - | 89 |
| Anthony et al[164] | 2002 | 17 | $^{111}$In | 13 | - | 81 |
| Buscombe et al[165] | 2003 | 10 | $^{111}$In | 20 | - | 5 |
| Modlin et al[166] | 2005 | 29 | $^{111}$In | 0 | 54 | 79 |
| Hoefnagel et al[178,a] | 1994 | 52 | $^{131}$MIBG | 15 | - | 69 |
| Taal et al[167] | 1996 | 30 | $^{131}$MIBG | 0 | 52 | 74 |
| Taal et al[167] | 1996 | 20 | $^{131}$MIBG | 0 | 40 | 65 |
| Mukherjee et al[168] | 2001 | 18 | $^{131}$MIBG | 11 | 62 | 72 |
| Safford et al[172] | 2004 | 98 | $^{131}$MIBG | 15 | - | - |
| Kwekkeboom et al[169] | 2003 | 12 | $^{177}$Lu | 3 | - | 79 |
| Teunissen et al[170] | 2004 | 26 | $^{177}$Lu | 48 | - | 88 |
| Kwekkeboom et al[171,b] | 2005 | 65 | $^{177}$Lu | 46 | - | 82 |
| Median (range) | | 17 (9–98) | | 3 (0–48) | 53 (40–62) | 79 (5–100) |

NOTE. Four radiolabeled somatostatin analogues have been studied in the past decade for their potential therapeutic effects on neuroendocrine tumors ($^{90}$Yt, $^{111}$In, $^{131}$MIBG,$^{177}$Lu). Two of the 3 yttrium trials showed complete absence of objective tumor regression. Similarly, 2 of the 4 trials with $^{131}$MIBG showed no effect on tumor size. Four of the 6 trials of $^{111}$In showed response rates between 13% and 20%. The most recent $^{177}$Lu trial (Teunissen et al, 2004[170]) showed better tumor responses (48%), but the median response rate of the entire patient population remained at 2%. The effects of radionuclide therapy are better at maintaining the status quo, with 53% and 79% of patients achieving biochemical or tumor size stability, respectively.

[a]Collective review of 5 centers.

[b]Partial patient population overlaps with Kwekkeboom et al, 2003[169] and Teunissen et al, 2004[170].

and adequate hydration.[156] The 4 radionuclides most commonly used in the treatment of carcinoid disease are $^{131}$I-MIBG (Iodine-131-Meta-Iodobenzylguanidine), indium-111, yttrium-90, and lutetium-177 (Table 4).[157–171]

β electrons (from isotopes such as iodine-131 and yttrium-90) are able to penetrate about 1 cm of tissue.[172] γ radiation (generated from the decay of iodine-131 and indium-111 isotopes) is the most penetrating of all types of radiation and the photons released engender damage by ionizing molecules they strike. In addition to γ radiation, indium-111 also emits Auger electrons by a process in which an ionized atom emits a second electron rather than a photon. Because such electrons typically generate only a few thousand electron-volts in energy, their effective radius of travel is less than 100 nm and they are effective only if internalized within a cell.[163] Initially iodine and then indium-tagged somatostatin analogues were used but more recently lutetium-177,[173] an emitter of β particles and γ rays, has proved more effective. Lu-177 bound to DOTA0-Tyr3-octreotate has been reported to result in 3- to 4-fold higher uptake in a majority of somatostatin receptor–positive tumors when compared with indium-111.[174] Because Lu-177 has a lower tissue penetration range compared with yttrium-90, it has been proposed that it may be beneficial for the treatment of small neuroendocrine tumors because the therapeutic-dose exposure of cells distant from the bound and internalized somatostatin receptors is minimized.[172]

Although radiopeptide-receptor targeting has been used for only a relatively limited period of time in the treatment of carcinoid disease, overall this strategy has been associated with a reasonable degree of disease stabilization and, of particular importance, shows relatively mild toxic effects.[163]

**Iodine-131–MIBG.** Iodine isotopes (γ emitters) have been used as therapeutic agents since 1942 and initially were used for scintigraphy and thyrotoxicosis.[175] More recently, $^{123}$I and $^{131}$I have been used in the treatment of neuroendocrine tumors.[176] In 1994 an initial review of the cumulative therapeutic data of $^{131}$I-MIBG summarized the experience from 5 European centers that included 52 patients.[177] A tumor response rate of 15% was noted with tumor stability achieved in close to 70% of the pooled populations. Subsequently, Taal et al[167] treated 30 carcinoid patients with $^{131}$I-MIBG and 20 patients with unlabeled MIBG, and reported a biochemical response rate of less than 10% with no objective remission in either group. A recent trial included 18 patients and resulted in an

objective response in 11%.[167] The largest retrospective series that analyzed the use of $^{131}$I-MIBG in the management of metastatic midgut carcinoids (n = 58) reported 3- and 5-year survival rates of 77% and 63%, respectively, as compared with 56% and 47%, respectively, for controls.[178] The largest prospective series to date (n = 98) of patients with metastatic carcinoid tumors reported biochemical responses in 37% of treated patients; however, this was not associated with increased survival rates.[171]

Overall the median tumor response rate for the patients treated with $^{131}$I-MIBG is low (<5%), although the modality appears somewhat more effective in achieving biochemical (~50%) or tumor stability (~70%).

**Indium-111.** More recently, iodine usage has been superseded by the use of indium-111 (half-life, 2.83 days, and both a γ ray and Auger electron emitter) bound to a variety of somatostatin analogues, including octreotide and octreotate.[172] $^{111}$In-labeled somatostatin analogues are the most commonly studied radiopeptides to date in the treatment of carcinoid disease, largely reflecting their availability. Overall tumor response rates are between 13% and 20%.[160–165] Similar to $^{131}$I-MIBG, the benefits of therapeutic protocol mostly were limited to disease stabilization, with a median of 65% in the overall pool of 85 patients experiencing no progression in tumor size and 54% of patients in 1 series experiencing leveling of urinary 5-HIAA levels.[163]

**Yttrium-90.** After the evaluation of indium-labeled somatostatin analogues, the β-emitting yttrium-90 (half-life, 2.67 days) has been assessed as a therapeutic agent for somatostatin-receptor–positive tumors.[172] The use of the somatostatin ligand, DOTA-d-Phe1-Tyr3-octreotide, has been reported to facilitate administration based on its enhanced stability and easy yttrium-90 labeling. The therapeutic effects of $^{90}$Y-octreotide on tumor stabilization appear to be more effective compared with $^{111}$In-labeled analogues. Thus, a median of 92% of patients in a pool of 55 patients maintained stable tumor size.[157–159] However, 2 out of 3 trials were unable to show objective tumor regression whereas 1 trial achieved tumor regression in only 8% of patients. The median time to progression and median overall survival were 30 and 60 months, respectively.

**Lu-177.** The most promising advance in the field of radiopeptide therapy has been the recent development of $^{177}$Lu-octreotate, which emits both β and γ radiation. The $^{177}$Lu-octreotate combination has a half-life of 6.64 days and shows a higher affinity for somatostatin-receptor subtype 2.[179] In 76 patients with GEP tumors, biochemical responses were reported in 30% of patients, whereas stable disease was identified in 40%. Tumor responses were reported in 35% of patients with gastrointestinal carcinoids and between 80% and 90% of patients experienced tumor stabilization.[168,169,180] The data on the largest patient series treated to date with lutetium-labeled somatostatin analogues (n = 131, of which 65 were gastrointestinal carcinoids) found that remission rates were correlated positively with high pretherapy octreotide scintigraphy uptake and limited hepatic tumor load.[170] Median time to progression (>36 mo) was significantly shorter in patients with extensive liver involvement (26 mo).

## Management of Carcinoid-Related Fibrosis

Given the increased longevity of carcinoid patients, the sequelae of tumor-induced fibrosis (both local and systemic) represent a more frequent therapeutic challenge.[181] Thus, bowel obstruction secondary to peritoneal fibrosis is the most common presenting symptom of small intestinal carcinoids, and heart failure secondary to right-sided valvular fibrosis has emerged as one of the most serious extraintestinal manifestations of carcinoid, occurring in 20%–70% of patients with metastatic disease and resulting in as much as 50% of carcinoid mortality.[182,183] As of yet, there is no effective pharmacologic therapy for either clinical problem. In the instance of bowel obstruction, surgical lysis of the adhesions often is demanding technically because of the cocoon effect of extensive fibrosis engendered by the fibrosis-promoting growth factors produced by the tumor cells.[184] Similarly, bowel anastomosis has a high risk for ischemic necrosis given the associated mesenteric vascular fibrosis. Indeed, this biological event may independently culminate in mesenteric ischemia, bowel ischemia, and perforation.[181–183]

There is currently no medical therapy that appears effective in ameliorating carcinoid-induced fibrosis. As a consequence, valvular replacement usually is required to manage carcinoid heart disease, although temporary amelioration can be provided by palliative balloon pulmonary valvuloplasty.[185] Overall, adequate therapy for right-sided valve disease is associated with improvement of symptoms and an increased quality of life despite the relatively high morbidity and mortality rates of cardiac intervention.[186]

## Symptomatic Therapy

Although the long-acting depot formulations of somatostatin antagonists (Somatuline Autogel and Sandostatin LAR) are the principal agents in the alleviation of carcinoid symptoms, other modalities bear some consideration.[184] Nonspecific supportive care of carcinoid patients includes advising the patient to avoid factors

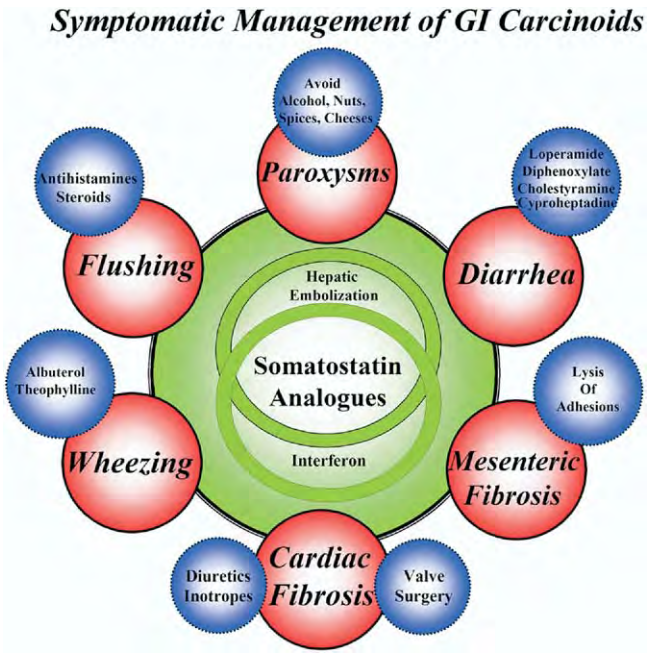


**Figure 3.** Symptom management: management of gastrointestinal carcinoids symptoms. Carcinoid patients often show a constellation of symptoms that may vary in intensity of both duration and expression. Some symptoms may be abrogated by avoiding inciting or provocative agents, and most can be ameliorated by pharmacologic agents that specifically address a specific symptom. This usually results in polypharmacotherapy, which is difficult for patients to manage and has variable efficacy. Overall, somatostatin analogues have the broadest and most effective coverage for all symptoms, particularly when used in a long-acting depot formulation. No effective pharmacologic therapy is available for fibrosis and this currently can be managed only by surgical intervention.

that induce flushing or bronchospastic episodes such as alcohol ingestion, certain cheeses, nuts, stressful situations, or some kinds of physical activity. Intake of agents that exacerbate symptoms (flushing, sweating, and diarrhea) such as capsaicin-containing foods (curry, peppers) should be diminished. Moderate diarrhea generally responds to conventional antidiarrheal agents such as loperamide or diphenoxylate; cholestyramine (bile-salt binder) may be useful if the patient has undergone a distal ileal resection to remove the primary tumor (Figure 3). More pronounced diarrhea can be treated with the 5-HT receptor subtype 2 antagonist cyproheptadine, which is effective in up to 50% of patients, and also may be of benefit in alleviating anorexia or cachexia in those with a malignant carcinoid syndrome.[187,188]

Short-term treatment with the selective 5-HT receptor subtype 3 antagonist ondansetron has been shown to ameliorate carcinoid diarrhea and improve gastric emptying. Flushing, however, was not affected.[189] In addition, ondansetron reduces the postprandial colonic hypertonic response in carcinoid diarrhea to normal levels.[190]

Histamine 1 receptor blockade (fexofenadine, loratadine, terfenadine, diphenhydramine) is also sometimes of benefit in suppressing skin rashes, particularly in histamine-secreting gastric carcinoid tumors. Bronchospasm can be managed with theophylline or β-2 adrenergic receptor agonists such as albuterol. Cardiac failure may necessitate diuretics or valvular surgery.[191] Some brief relief can be provided by prednisone in the event of acute exacerbations, particularly in hepatic transplant patients, but its toxicity warrants cautions.[48]

Carcinoid crisis manifested by profound flushing, extreme blood pressure fluctuations, bronchoconstriction, arrhythmias, and confusion or stupor lasting hours or even days may occur, especially during anesthetic induction or an invasive radiologic procedure.[22,192] This potentially fatal syndrome can occur after manipulation of tumor masses (including bedside palpation), after administration of chemotherapy, or after hepatic arterial embolization, especially in patients with extensive disease.[193] The treatment of carcinoid crises differs from other causes of acute hypotension because calcium and catecholamines should be avoided because these agents provoke the release of bioactive tumor mediators that may perpetuate or worsen the syndrome. Blood pressure support usually is achieved by infusion of plasma and octreotide. In general, somatostatin receptor analogues have replaced other pharmacologic interventions in the treatment of crises, and their use has been associated with increased survival rates.[194] Indeed, prophylactic use of subcutaneous octreotide or the administration of a depot injection in a timely fashion before any procedures are attempted is mandatory to prevent the development of a crisis.

## Therapies in Development

**Symptom relief.** The recent development of a peptidomimetic with broader somatostatin-receptor activity may amplify the efficacy of somatostatin-receptor ligand therapy. By using alanine scanning, Bruns et al[37] synthesized SOM230, a compound with high affinity for somatostatin (SST)1-, SST2-, SST3-, and SST5-receptor subtypes, and a lower affinity for SST4. This semi-universal ligand manifests a 30- to 40-fold higher affinity for SST1 and SST5 than octreotide or lanreotide, with particularly potent inhibitory effects on growth hormone and insulin-like growth factor-1 release. Animal studies have indicated that SOM230 can dose-dependently decrease insulin-like growth factor-1 levels for up to 120 days, with a half-life of nearly 24 hours, compared with 2 hours for octreotide. In contrast to octreotide, there is no reversal of the suppressive effect on human insulin-like growth factor-1 levels and no obvious adverse side

effects were noted, including changes in plasma glucose levels.[37,195] Although there are no data to support an antiproliferative effect, SOM230 might be effective in influencing somatostatin receptor 1– and 3–mediated antiproliferative effects (cell-cycle inhibition, induction of apoptosis). This theoretically would confer additional clinical benefit in metastatic carcinoids; islet cell tumors; somatostatin-receptor–positive breast, prostate, and colonic cancers; and malignant lymphomas. This analogue currently is under evaluation in phase II clinical trials for acromegaly and midgut carcinoid therapy.[37]

**Antineoplastic.** The growth and development of metastatic lesions to some extent reflects alterations in local regulatory factors that favor angiogenesis. A critical agent and rate-limiting step in this process is VEGF signaling.[196] Angiogenesis and VEGF expression have been studied in both gastrointestinal and pulmonary carcinoids.[197–199] In 28 gastrointestinal carcinoids evaluated, midgut lesions showed strong VEGF expression but there was no correlation between VEGF expression and tumor stage.[200] Conversely, an evaluation of angiogenesis in rectal carcinoids indicated that microvessel density was correlated with the tumor size, lymphatic or venous invasion, and existence of metastasis.[201] In addition, strong expression of neuropilin (NP)-2, a receptor for angiogenic factors belonging to the VEGF family, has been noted in neuroendocrine cells throughout the digestive tract.[202] NP-2–expressing neuroendocrine cells in the colon were almost identical to the serotonin-producing subpopulation; however, the majority of colon and appendiceal carcinoids did not contain NP-2–secreting cells. Conversely, small intestinal and gastric carcinoids expressed low levels of NP-2 in isolated foci of cells, suggesting that loss of NP-2 expression may accompany tumor progression in carcinoid tumors.

Despite promising preclinical data, phase I trials targeting VEGF with single-agent therapy have not produced substantial clinical benefit. However, recent data noting anti-VEGF therapy enhancement of chemotherapy effects suggests that there may be some use in targeting angiogenic factors.[203] The VEGF-A monoclonal antibody, bevacizumab, has been evaluated in a variety of solid and hematologic malignancies, including renal cell carcinoma, colorectal, breast, prostate, non–small-cell lung, pancreatic, liver, head and neck, and cervical cancers.[204]

An early animal study of VEGF-neutralizing monoclonal antibody in xenotransplanted human duodenal carcinoid lesions reported the development of liver metastases in 16 of 17 control mice compared with only 2 of 19 mice treated with VEGF antibody.[205] Similarly, studies in patients with carcinoid disease reported a decrease in tumor perfusion within 48 hours of treatment with bevacizumab.[206] A phase II trial in patients with metastatic or unresectable carcinoid tumors reported a sustained decrease in tumor perfusion and progression-free survival rate of 95% at 18 weeks.[81] Biochemical responses of 50% or greater were observed in 21% of patients. After at least 9 weeks of treatment, 15% of patients were reported to have responded to therapy, whereas in 80% the disease had stabilized (Table 5).

Carcinoid tumors also have been shown to co-express platelet-derived growth factor and platelet-derived growth factor receptor, a receptor/ligand system important in cell growth and survival.[15] A phase II trial of the platelet-derived growth factor receptor inhibitor, Imatinib (Gleevec; Novartis), in advanced carcinoid tumors achieved tumor stabilization in 63% of patients after a 16-week median follow-up evaluation.[207] A biochemical response of greater than 50% was reported in 15% of patients and the median progression-free survival dura-

**Table 5.** Novel Antineoplastics Currently Under Evaluation

| Agent | Mechanism of action | Evaluated effects | Assessment |
|---|---|---|---|
| Bevacizumab | VEGF-A antibody | PFS 95% at 18 wk<br>PR (biochem) 21%<br>SD 80% at 9 wk | Moderately effective |
| Bortezomib | Proteasome inhibitor | SD 69% at 3 mo | Ineffective |
| Epothilone | Microtubule stabilizer | SD 71% at 3 mo | Minimally effective |
| Gemcitabine | Pyrimidine antimetabolite | Median PFS 8.3 mo | Ineffective |
| Imatinib | PDGFR inhibitor | Median PFS 24 wk<br>PR (biochem) 15%<br>SD 63% at 4 mo | Moderately effective |
| Irinotecan | Topoisomerase I inhibitor | Median PFS 50 wk<br>SD 64% at 6 mo | Minimally effective |
| BB-1091 | CD56 recognition and cytotoxicity | Trial in progress | - |
| CCI-779 | mTOR kinase inhibitor | Trial in progress | - |
| Gefitinib | Tyrosine kinase inhibitor | Trial in progress | - |
| RAD001 | mTOR kinase inhibitor | Trial in progress | - |

NOTE. Some trials are still in progress but it currently appears that most novel antineoplastic therapy can at best be regarded as having achieved temporary tumor stabilization, with median progression-free survival durations of less than 12 months. PFS, progression-free survival; PR, partial response (>50% reduction in tumor markers); SD, stable disease; mTOR, mammalian target of rapamycin.

tion was 24 weeks. The study found no correlation between plasma VEGF and basic fibroblast growth factor, computed tomography flow studies, and patient outcome.

A phase II trial investigated the safety and antitumor activity of epothilone EPO906, a novel microtubule stabilizer, in 26 carcinoid patients and other NETs.[208] Stable disease was reported in 71% of patients after 3 months of therapy.

A small study (n = 11) of topoisomerase I inhibitor irinotecan in patients with advanced carcinoid disease observed no responses, but disease stabilization was reported in 64% of patients at 24 weeks.[209] The median progression-free survival was 50 weeks.

A recent study of the proteasome inhibitor bortezomib (PS-341) in 16 patients with metastatic NETs (12 carcinoids) failed to produce any measurable tumor responses, although 11 patients (69%) experienced disease stabilization at 12 weeks.[210] Of the patients with stable disease, 3 experienced an 11%–24% reduction in serum pancreastatin levels, although serum marker levels were not found to correlate with objective tumor responses.

Two current clinical trials examined the therapeutic role of mammalian target of rapamycin kinase inhibitors, which is involved in the regulation of cell proliferation, survival, motility, and angiogenesis through initiation of gene translation in response to nutrients such as amino acids.[211,212] The first is a phase II study[211] of CCI-779 in patients with progressive metastatic NETs. The second is a phase II study[212] of RAD001, another mammalian target of rapamycin kinase inhibitor, plus depot octreotide in patients with metastatic or unresectable neuroendocrine tumors. Preclinical studies reported dose-dependent inhibition of tumor growth and reduced tumor vascularity.[213]

A separate study examining the role of the tyrosine kinase inhibitor gefitinib (IRESSA; AstraZeneca, Wilmington, DE), currently used as second-line treatment of non–small-cell lung cancer, in patients with metastatic carcinoids and other NETs is underway.[212] Similarly, a phase I/II trial of BB-1091, an immunoconjugate that binds with high affinity to CD56, often expressed on a variety of solid tumors, has been established to examine its therapeutic efficacy in carcinoid tumors.[212]

Recently published data of a phase II trial of gemcitabine, a pyrimidine antimetabolite used in the treatment of patients with advanced pancreatic adenocarcinoma, showed no radiologic or biochemical responses in 18 patients (9 carcinoids) with metastatic neuroendocrine tumors.[214,215] Although 65% of patients achieved disease stabilization as their best response, the median progression-free survival duration was only 8.3 months.

Another novel strategy involves the targeting of histone deacetylases (HDACs), which are key regulators of histone deacetylation, which plays a vital role in the regulation of gene expression.[216] HDACs also may regulate gene expression by deacetylating transcription factors, such as p53, and may participate in cell-cycle regulation.[217] A number of HDAC inhibitors (MS-27–275, oxamflatin, and the hydroxamic acid–based hybrid polar compounds such as pyroxamide and suberoylanilide hydroxamic acid) have been identified that induce tumor cell cultures (neuroblastoma, melanoma, leukemia, breast, prostate, lung, ovarian, colon) to undergo growth arrest, differentiation, and/or apoptotic cell death.[218] In addition, recent studies have shown increased HDAC immunoreactivity in NETs, including carcinoid tumors, suggesting that HDACs may be markers of neuroendocrine differentiation.[219,220] HDAC inhibitors including suberoylanilide hydroxamic acid and MS-275 increase the expression of the cyclin-dependent kinase inhibitor p21WAF1/CIP1, which in turn leads to growth arrest in the G1 phase of the cell cycle and ultimately to differentiation.[221]

Goke et al[222] investigated the effect of the peroxisome proliferator-activated receptor-γ agonist pioglitazone on growth and tumor necrosis factor–related apoptosis-inducing ligand–induced apoptosis in carcinoid cells. Pioglitazone suppressed growth and induced apoptosis of carcinoid cells. Importantly, the enhancement of tumor necrosis factor–related apoptosis-inducing ligand–induced apoptosis was associated with the up-regulation of the cyclin-dependent kinase inhibitor p21waf1/cip1 in pioglitazone-treated carcinoid cells.

Clinical data on the use of HDAC inhibitors in carcinoid disease are very limited. In a dose-titration study that included 1 carcinoid patient, the therapy with the novel oral HDAC inhibitor, CI-994, did not result in objective improvement of disease.[223]

**Antifibrotic.** Connective tissue growth factor (CTGF), a profibrotic cytokine, and transforming growth factor-β are activators of the process that initiates the production of collagen and fibronectin. A recent study showed CTGF overexpression in ileal carcinoids and noted that protein expression was correlated with fibrosis in a tissue microarray.[181] Furthermore, CTGF was secreted by ileal tumor cells and was detectable in the serum of patients with ileal carcinoids.[219] Iloprost is a synthetic prostacyclin analogue that blocks the induction of CTGF and hence the increase in collagen synthesis in fibroblasts exposed to trans-

forming growth factor-β. Its usage in scleroderma resulted in a decrease in dermal interstitial fluid CTGF levels and a marked decrease in dermal skin tightness, suggesting that it inhibits skin fibrosis.[224] Although the use of this agent in treating carcinoid fibrosis is unknown, is appears attractive given the recent identification of a role for CTGF in the evolution of carcinoid fibrosis.[181]

Other agents that may be useful in inhibiting the development of fibrosis include FG-3019, a human monoclonal antibody against CTGF. Phase I clinical trials using this agent in the treatment of idiopathic pulmonary fibrosis and in animal models of lung, kidney, and systemic fibrosis have shown a reduction of scar tissue formation and preservation of organ structure and function.[225] Similarly CAT-192, a monoclonal antibody against transforming growth factor-β currently is under evaluation in phase I/II clinical trials in patients with diffuse systemic sclerosis. Preliminary results have provided no definitive conclusions regarding efficacy.

## Conclusions

The clinical management of carcinoid tumors has evolved though a number of phases in the century since the lesion first was described. Despite the development and implementation of a number of chemotherapeutic, biotherapeutic, radiologic, and surgical strategies, the overall clinical results are disappointing. Indeed, were it not for the development of the somatostatin analogue class of drugs that have been so effective in ameliorating symptoms and improving the quality of life, carcinoid tumor management would have advanced little.

The somatostatin analogues lanreotide and octreotide remain the main symptomatic therapeutic modalities for the management of carcinoid tumors. Generally, their effects are limited to symptom control and stabilization of the disease progress. Although a decrease in tumor size is almost nonexistent, they show marginally better effects on biochemical tumor markers. The effects of other biotherapeutics, such as interferon-α, on tumor cell proliferation are indistinguishable from those of somatostatin analogues, but are associated in many instances with severe adverse effects.

The introduction of longer-acting somatostatin analogues (Somatuline Autogel and Sandostatin LAR) has increased dramatically the duration of therapeutic control from days to weeks, and even may extend therapeutic control to months with the introduction of novel formulations. Thus, advances in drug-delivery systems in conjunction with the development of more stable formulations and slow-release depot formulations have facilitated symptom management and quality of life further. Nevertheless, although the number of injections needed to control symptoms has decreased, instances of breakthroughs requiring rescue treatment still occur.

There is little evidence that any permutation of chemotherapeutics offers increased efficacy over biotherapy, and the frequently severe side effects render chemotherapy much less appealing. Although intellectually promising, the therapeutic effects of radiolabeled somatostatin analogues remain somewhat disappointing. In general, they may be considered to at best maintain the status quo by stabilizing disease progression. Nevertheless, they remain the currently most exciting therapeutic development in the treatment of neuroendocrine tumor disease. Overall, β-emitting radionuclides (eg, $^{131}$I) have greater therapeutic potential because the particles they emit have sufficient energy to cause tumor cell damage without penetrating far into surrounding tissue.[226–228] Those radionuclides emitting primarily γ-radiation (eg, $^{111}$In) or Auger electrons show antiproliferative effects only if cellular DNA is within the particle range. Such compounds therefore may be most effective when given in combination with β-emitters or when used to eradicate micrometastases.[229] As an emitter of both β particles and γ radiation, $^{177}$Lu has been shown to induce significant tumor regression and may be of particular benefit in the treatment of small tumors by minimizing the radiation exposure of cells distant from the bound somatostatin receptors.[172]

Radionuclides decaying by the emission of α-particles ($^{213}$Bi, $^{225}$Ac, and $^{211}$At), which because of their short range have high linear energy transfer (100 keV/μm), offer the possibility of irradiating tissues in the range of only a few cell diameters.[230] In comparison, the mean linear energy transfer for the high-energy β particles emitted by $^{90}$Y is only about .22 keV/μm.[230] In addition, the effectiveness of high linear energy transfer radiation is nearly independent of oxygen concentration, dose rate, and cell-cycle position. Considerable evidence has shown that radiation-induced biological bystander effects can result in the killing of cells that have not been hit directly by radiation.[230–232]

The issue of receptor heterogeneity, which may be responsible for some tumor resistance, theoretically could be overcome by using cocktails of radiolabeled ligands in combination with one another or with other biotherapeutics or chemotherapeutics. One potentially promising approach in patients with micrometastases or tumors of different sizes is treatment with a combination of radionuclides shown to be optimal for treating larger tumors ($^{90}$Yt) and radionuclides shown to be optimal for smaller tumors ($^{177}$Lu).[229,233] Because the side effects of this type

of therapy are infrequent, the duration of response of more than 2 years suggests that such combination cocktail isotope therapy may offer a potentially attractive therapeutic path in the future.

Although primary surgical resection remains the only potentially curative modality currently available, the critical issue remains the need to diagnose the lesion before the development of metastases. At this time no early biomarkers of the disease exist. Therefore, rational surgical management needs to be based on the prediction of the likelihood of aggressive local or metastatic behavior. This requires the identification of tumor-specific molecular signatures that will define the malignant and metastatic potential of an individual lesion and identify covert metastatic disease undetectable by conventional microscopy or immunohistochemistry. Although the management of hepatic metastases initially focused on varieties of hepatic vascular occlusion, embolization often is associated with morbid events. Alternatively, the surgical excision or radiofrequency ablation of hepatic metastases, especially if undertaken by laparoscopic techniques, has a comparable morbidity and mortality with possibly higher rates of perioperative and postoperative complications. The results of liver transplantation for metastatic disease are disappointing, and reflect the usually advanced disease states of transplant recipients.

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**Supported by National Institutes of Health grant R01-CA-097050 (to I.M.M.) and by the Bruggeman Medical Foundation (to M.K.).**