A Review of Systemic and Liver-Directed Therapies for Metastatic Neuroendocrine Tumors of the Gastroenteropancreatic Tract

Jonathan R. Strosberg, MD, Asima Cheema, MD, and Larry K. Kvols, MD

Background: Treatment options for metastatic gastroenteropancreatic neuroendocrine tumors (NETs) have evolved in recent years. The somatostatin analogs octreotide and lanreotide have long been used for management of symptoms such as flushing and diarrhea associated with hormonally active NETs. New evidence demonstrates that these agents can also inhibit tumor growth. Other novel agents targeting the VEGF and mTOR pathways have recently been investigated in multicenter phase III studies.

Methods: The authors review the recent literature on treatments for metastatic gastroenteropancreatic NETs and summarize new therapeutic developments.

Results: Novel agents targeting somatostatin receptors and the VEGF and mTOR pathways are capable of significantly prolonging progression-free survival in certain NET subtypes. New temozolomide-based chemotherapy regimens have demonstrated considerable activity in pancreatic NETs. Liver-targeted therapies, including surgical resection, radiofrequency ablation, and hepatic artery embolization, are effective options for patients whose metastases are predominantly confined to the liver. Embolization of 90Y-embedded spheres (radioembolization) represents a novel approach to managing liver metastases.

Conclusions: Treatment options are expanding rapidly for patients with metastatic gastroenteropancreatic NETs, driven largely by randomized, collaborative clinical trials. Future clinical trials should compare the efficacy of emerging therapies and evaluate combination vs sequential approaches.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms composed of carcinoid tumors and pancreatic NETs. The majority are characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones and other vasoactive substances, giving rise to diverse clinical syndromes. Histologically, carcinoid tumors arise from the endocrine (enterochromaffin) cells of the gastrointestinal tract and airways.

Carcinoid tumors have distinct features depending on their site of origin. In the 1960s, Williams et al\(^1\) classified carcinoid tumors based on embryologic derivation, distinguishing between foregut (bronchial, stomach,
duodenal), midgut (jejunal, ileal, cecal, appendiceal), and hindgut (distal colon and rectal). As a rule, metastatic midgut carcinoid tumors produce serotonin and other vasoactive substances that give rise to the typical carcinoid syndrome. This syndrome manifests primarily as diarrhea and flushing, a vasomotor phenomenon that causes redness and warmth in the face and upper torso. Carcinoid heart disease, characterized by fibrosis of the tricuspid and pulmonic heart valves, can also occur in patients with severe and prolonged elevations of circulating serotonin. In contrast, hindgut carcinoid tumors are rarely, if ever, associated with a hormonal syndrome.

Tumor growth rates also correlate with the site of origin. In the metastatic setting, midgut carcinoid tumors tend to behave in an indolent fashion, whereas NETs originating in the foregut or hindgut regions tend to behave more aggressively once they have metastasized.

Pancreatic neuroendocrine tumors (PNETs) arise from the islets of Langerhans. These heterogeneous neoplasms can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP). The annual incidence of PNETs is approximately 1 per 100,000. In contemporary studies, most PNETs are unassociated with a hormonal syndrome and are termed nonfunctioning. Among the hormone-producing tumors, insulinomas tend to behave in a benign fashion and have a malignancy rate of only 10%. The majority of gastrinomas, VIPomas, glucagonomas, and nonfunctioning tumors are metastatic at presentation.

Treatment options for metastatic NETs have evolved in recent years. The somatostatin analogs (SSAs) octreotide and lanreotide were initially developed to palliate hormonal symptoms such as flushing and diarrhea caused by the carcinoid syndrome. More recently, accumulating data have supported their role as antiproliferative agents, capable of stabilizing tumor growth in patients with metastatic neuroendocrine malignancies. Emerging evidence supports the use of other targeted agents, although none yet is considered standard of care. Sunitinib, a multitargeted tyrosine kinase receptor inhibitor, has recently been demonstrated to prolong progression-free survival (PFS) in patients with metastatic PNETs. Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), has shown promise in several phase II studies. In a recent randomized, placebo-controlled phase III trial, everolimus demonstrated prolongation of progression-free survival in patients with advanced PNETs. Bevacizumab, an inhibitor of circulating vascular endothelial growth factor (VEGF), is also being tested in phase III studies based on encouraging phase II evidence. While cytotoxic chemotherapy appears to produce high response rates in metastatic PNETs, responses in carcinoid tumors have been discouraging.

Hepatic-directed therapies are appropriate for patients whose tumors are predominantly metastatic to the liver. Options for patients with limited metastases include resection or ablative techniques such as radiofrequency ablation. Modern surgical techniques now enable tumor cytoreduction in patients with multiple bilobar metastases. For patients with diffuse hepatic tumors, intra-arterial embolization techniques such as hepatic artery embolization, chemoembolization, or radioembolization are often utilized.

Tumor differentiation and grade are important predictive and prognostic factors. While often used interchangeably, differentiation and grade are not identical terms: differentiation refers to the similarity between the tumor histology and tissue of origin, whereas grade is calculated based on markers of proliferation such as mitotic rate and Ki-67 proliferative index. In general, poorly differentiated (high-grade) tumors are characterized by an elevated mitotic rate (> 10 to 20 mitoses per 10 high-powered fields), a high Ki-67 proliferative index (typically > 20%), extensive necrosis, and pleomorphism.

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Table 1. Summary of Clinical Trials Evaluating the Antisecretory Effect of Somatostatin

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Disease</th>
<th>No. of Patients</th>
<th>Drug</th>
<th>Symptom Response</th>
<th>Biochemical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kvols® (1986)</td>
<td>Carcinoid</td>
<td>25</td>
<td>Octreotide 450 mg/d</td>
<td>88%</td>
<td>72%</td>
</tr>
<tr>
<td>di Bartolomeo (1996)</td>
<td>Carcinoid PET</td>
<td>31</td>
<td>Octreotide 1500-3000 mcg/d</td>
<td>73%</td>
<td>77%</td>
</tr>
<tr>
<td>Maton (1989)</td>
<td>VIPoma, Insulinoma, Glucagonoma</td>
<td>7, 6, 15</td>
<td>Octreotide</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>Rubin (1999)</td>
<td>Carcinoid</td>
<td>93</td>
<td>Octreotide vs depot-octreotide 10-30 mg</td>
<td>58% vs 66%</td>
<td>–</td>
</tr>
<tr>
<td>O’Toole (2000)</td>
<td>Carcinoid</td>
<td>33</td>
<td>Octreotide 300-600 mcg/d vs lanreotide 30 mg</td>
<td>68% vs 54%</td>
<td>50% vs 58%</td>
</tr>
</tbody>
</table>

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aggressive tumors are associated with a substantially worse prognosis than well-differentiated NETs despite their increased sensitivity to cytotoxic chemotherapy. Most targeted agents have not been formally tested in poorly differentiated tumors.

The overall survival of patients with metastatic gastroenteropancreatic NETs appears to have improved substantially in the past three decades. One potential factor may be the expansion of therapeutic options, particularly the widespread use of SSAs. This review summarizes the standard and investigational agents used for treatment of these rare and challenging malignancies.

**Somatostatin Analogs**

SSAs have had a profound impact on patients with the carcinoid syndrome and other hormonal symptoms associated with functioning NETs. The development of SSAs arose from the recognition that native human somatostatin functions as an inhibitor of endocrine activity. For example, in the digestive tract, it decreases portal blood flow, reduces gastrointestinal secretion, inhibits peristalsis, and downregulates the secretion of other gastrointestinal hormones. Somatostatin exerts its effects through interaction with five somatostatin receptors (ssts1–5) belonging to a family of G-protein coupled receptors. The clinical use of native human somatostatin is impeded by its short half-life of approximately 2 minutes. Consequently, synthetic SSAs have been designed to increase molecular stability by eliminating enzymatic cleavage sites while retaining binding affinity to somatostatin receptors.

The SSAs currently used in clinical practice are octreotide and lanreotide, cyclic peptides with half-lives of approximately 2 hours. Both analogs bind avidly to sst1 and moderately to sst2. In a landmark study, octreotide was tested in 25 patients with malignant carcinoid syndrome. Flushing and diarrhea were substantially palliated in 22 patients (88%), and major reductions in urine 5-HIAA were reported in 18 cases (72%). Numerous subsequent trials have validated the antisecretory effects of octreotide and lanreotide in patients with the carcinoid syndrome as well as other neuroendocrine hormonal syndromes, notably the VIPoma and glucagonoma syndromes (Table 1).

Octreotide was originally developed as an immediate-release subcutaneous formulation and tested at doses of 100 to 500 mcg administered two to three times daily. During the past decade, a long-acting repeatable (LAR) depot formulation of octreotide (Sandostatin LAR) has been available, which enables monthly intramuscular dosing. The initial clinical trial of octreotide LAR for treatment of the carcinoid syndrome investigated doses of 10, 20, and 30 mg every 4 weeks. In clinical practice, higher doses of up to 60 mg are frequently administered to patients who develop refractory hormonal symptoms. Doses exceeding 60 mg are unlikely to be of additional palliative benefit, given saturation of somatostatin receptors. Patients who experience exacerbation of symp-

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**Table 2. — Summary of Nonrandomized Clinical Trials Evaluating the Antiproliferative Effect of Somatostatin Analogs**

<table>
<thead>
<tr>
<th>Analog</th>
<th>Study (yr)</th>
<th>No. of Patients</th>
<th>Complete/Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients With Documented Tumor Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Faiss (2003)</td>
<td>22</td>
<td>1</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Aparicio (2001)</td>
<td>35</td>
<td>1</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Arnold (1996)</td>
<td>52</td>
<td>0</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Saltz (1993)</td>
<td>34</td>
<td>0</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Octreotide</td>
<td>di Bartolomeo (1996)</td>
<td>58</td>
<td>2</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>201</td>
<td>4 (1%)</td>
<td>90 (45%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients Without Documented Tumor Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Wymenga (1999)</td>
<td>31</td>
<td>2</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Ducieux (2000)</td>
<td>39</td>
<td>2</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Eriksson (1997)</td>
<td>19</td>
<td>1</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Tomassetti (1998)</td>
<td>18</td>
<td>0</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Tomassetti (2000)</td>
<td>16</td>
<td>0</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Ricci (2000)</td>
<td>15</td>
<td>1</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>138</td>
<td>6 (4%)</td>
<td>92 (67%)</td>
</tr>
</tbody>
</table>
toms toward the end of each treatment cycle may benefit from more frequent drug administration (every 2 to 3 weeks). A long-acting lanreotide formulation (Somatuline autogel) is also available, and it is administered as a deep subcutaneous injection at doses ranging from 90 to 120 mg every 4 weeks.

Pasireotide, a novel SSA, is currently in clinical development. It binds avidly to four of the five somatostatin receptors (sst1, sst2, sst3, sst5). An open-label trial evaluated the activity of subcutaneous pasireotide in patients with carcinoid syndrome whose symptoms were inadequately controlled on octreotide. Preliminary data indicated activity in this refractory population. A randomized clinical study is currently evaluating the ability of a depot formulation of pasireotide (LAR) to palliate flushing and diarrhea in patients who are refractory to octreotide.

The Antiproliferative Effects of SSAs
SSAs were initially developed for control of hormonal syndromes associated with NETs. In recent years, increasing data have supported the hypothesis that they can also function as antineoplastic agents capable of inhibiting tumor growth. In vitro evidence demonstrates that SSAs can inhibit tumor growth through direct and indirect mechanisms. Direct mechanisms involve interaction with somatostatin receptors on tumor cells. It appears that all somatostatin receptor subtypes can mediate inhibition of cellular proliferation, whereas specific receptors can also stimulate cellular apoptosis. Although the precise signaling transduction pathways have not been fully elucidated, the primary steps appear to involve activation of phosphotyrosine phosphatases (PTPs) and inhibition of adenylate cyclase. Indirect inhibitory effects on tumor growth occur through suppression of circulating growth factors like VEGF, insulin-like growth factor (IGF), and growth hormone.

Until recently, evidence of the antiproliferative effects of SSAs derived from single-arm phase II trials documenting a relatively high rate of disease stabilization among patients with NETs treated with octreotide or lanreotide (Table 2). Higher-level evidence supporting the antiproliferative effect of octreotide emerged recently after publication of the PROMID study, a randomized phase III trial comparing octreotide LAR 30 mg vs placebo in 85 patients with metastatic midgut NETs. The study reported a clinically and statistically significant prolongation in median time to progression from 6 months in the placebo arm to 14.3 months in the octreotide LAR 30 mg arm. (Figure). Serious adverse events were evenly balanced (11 patients in the octreotide LAR group and 10 patients in the placebo arm). The small number of deaths in both treatment arms and the high rate of crossover precluded any meaningful analysis of overall survival differences. A randomized trial evaluating lanreotide vs placebo in nonfunctioning gastroenteropancreatic NETs is ongoing.

![Figure](image-url)

Interferon Alfa

Interferons can exert antitumor effects through a variety of mechanisms, including stimulation of T cells, induction of cell cycle arrest in the G1 and G0 phases, and inhibition of angiogenesis.57 In NETs, interferons can also induce upregulation of somatostatin receptors.58 Interferon alfa (IFN-α), also known as leukocyte IFN, has been the type of interferon primarily studied in NETs. Early trials of IFN-α in hormonally functional NETs took place prior to the introduction of SSAs and reported significant palliation of hormonal symptoms such as flushing and diarrhea along with reductions of tumor markers in over 50% of patients.59 Or61 Objective tumor response rates have generally been in the 4% to 10% range, with high rates of tumor stabilization.

With the development of SSAs, in vitro studies suggested synergism between IFN-α and SSAs, leading several investigators to evaluate the combination of the two therapies. One trial of patients with carcinoid syndrome who had become refractory to octreotide reported symptomatic improvement in 49% of patients after the addition of IFN-α.62 Another study reported a 67% rate of disease stability in patients with progressive NETs treated with a similar combination.55

Three randomized clinical trials have investigated SSAs alone or in combination with IFN-α. In one multicenter study of 68 patients evaluating subcutaneous octreotide alone or in combination with IFN-α at 3 million units 5 times per week, the 5-year survival rate was prolonged in the combination group (57% vs 37%) but not in a statistically significant fashion (P = .13).64 Another three-arm trial compared subcutaneous lanreotide to IFN-α 5 million units 3 times per week alone or in combination. Objective response rates were rare (≤ 7%) in all three arms, and tumor progression rates were nearly identical.65 A third randomized study of 109 patients compared subcutaneous octreotide alone or in combination with IFN-α at 4.5 million units 3 times per week. Survival in the combined arm was prolonged (51 vs 35 months) but did not achieve statistical significance (P = .38). Response rates in both arms were < 6%.56

The underpowered nature of the above-mentioned randomized studies precludes any definitive conclusions regarding the effects of IFN-α on overall survival. Moreover, an optimal dosing regimen has never been established. Enthusiasm for IFN-α therapy is tempered by potential side effects such as fevers, chills, myalgias, depression, and myelosuppression. However, toxicities have been relatively tolerable at the dose ranges studied in NETs.

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a conserved serine/threonine kinase that regulates cell growth, proliferation, and metabolism in response to environmental factors.57 In addition, it appears to play a role in the control of apoptotic cell death. The mTOR enzyme lies downstream of the PI3K/AKT pathway and is upregulated in a variety of malignancies in response to stimulation by growth factors and cytokines. The tuberous sclerosis complex (TSC1, TSC2) is an endogenous inhibitor of mTOR. The importance of mTOR in neuroendocrine cancers is highlighted by the fact that patients with germline mutations of TSC2 are prone to develop PNETs.68

The mTOR inhibitors temsirolimus and everolimus have both been studied in NETs. In a phase II study of metastatic NETs, temsirolimus was associated with an intent-to-treat response rate of 5.6% with a median time to progression of 6 months.69 Everolimus was associated with a more promising response rate of 20% and a median PFS of 15 months in a phase II study of 60 patients.10 In a follow-up multicenter study of 160 patients with advanced, progressive PNETs (RADIANT 1), patients were evaluated in two strata: everolimus monotherapy (n = 115) or everolimus plus octreotide (n = 45).11 Response rates and median PFS were 9% and 9.7 months, respectively in the monotherapy arm vs 4% and 16.7 months in the combined therapy arm.

Currently, two large phase III studies comparing everolimus 10 mg daily vs placebo in metastatic functional carcinoid tumors (RADIANT 2) and pancreatic NETs (RADIANT 3) have completed accrual. The RADIANT 3 trial demonstrated a statistically significant improvement in PFS from 4 months on the placebo arm to 11 months in the active treatment arm.12 The RADIANT 2 trial demonstrated an improvement in PFS from 11 months on the placebo arm to 16 months on the active treatment arm. On central radiologic review, the statistical significance of this trial was borderline (P = .026).70

Angiogenesis Inhibitors

Neuroendocrine tumors are highly vascular and frequently overexpress the VEGF ligand and receptor (VEGFR).71 Moreover, elevated circulating VEGF has been associated with tumor progression in NETs. Consequently, inhibition of the VEGF pathway has been a promising treatment target.

Bevacizumab is a monoclonal antibody to circulating VEGF. In a randomized phase II trial, 44 patients with metastatic carcinoid tumors were randomly assigned to treatment with bevacizumab or pegylated IFN-α2b (PEG-IFN) for 18 weeks after which they received both agents in combination.13 At the week-18 time point, the PFS rate was 95% on the bevacizumab arm vs 68% on the PEG-IFN arm. Moreover, the objective radiographic response rate in the bevacizumab arm was 18%, indicating a high degree of clinical activity. An ongoing phase III study led by the Southwest Oncology Group (SWOG) is comparing bevacizumab to IFN-α in patients with metastatic carcinoid tumors, with a primary endpoint of PFS.

The tyrosine kinase receptor inhibitor sunitinib is an inhibitor of VEGFR-1, -2, and -3, as well as platelet-derived...
growth factor (PDGF), KIT, and FLT3. In a two-cohort phase II study of 109 patients, the objective response rates associated with sunitinib monotherapy were 16.7% and 2.4% in PNETs and carcinoid NETs, respectively. Based on the relatively high response rates in PNETs, a multinational phase III study was launched comparing sunitinib (37.5 mg daily) to placebo. The study, which was discontinued on interim analysis after enrollment of 171 patients, demonstrated a median PFS of 11.1 months on the sunitinib arm vs 5.5 months on the placebo arm. The objective response rate associated with sunitinib was 9.3%.

Cytotoxic Chemotherapy

The sensitivity of NETs to cytotoxic chemotherapy appears to correlate with primary tumor location and tumor grade. PNETs have long been effectively treated with the nitrosourea streptozocin (STZ). Two randomized trials conducted by the Eastern Cooperative Oncology Group (ECOG) in the 1970s and 1980s reported response rates of 63% with STZ plus 5-fluorouracil (5-FU) vs 36% with STZ monotherapy and response rates of 69% with the combination of STZ and doxorubicin vs 45% with STZ and 5-FU (Table 3). These high response rates have been subsequently questioned due to the partial reliance on nonradiographic response criteria after enrollment of 171 patients, demonstrated a median PFS of 11.1 months on the sunitinib arm vs 5.5 months on the placebo arm. The objective response rate associated with sunitinib was 9.3%.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Author (yr)</th>
<th>Complete/Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>STZ + 5-FU vs STZ</td>
<td>88</td>
<td>Moertel (1980)</td>
<td>63% vs 36%</td>
</tr>
<tr>
<td>STZ + doxorubicin vs STZ + 5-FU</td>
<td>125</td>
<td>Moertel (1992)</td>
<td>69% vs 45%</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>50</td>
<td>Ramanathan (2001)</td>
<td>34%</td>
</tr>
<tr>
<td>STZ + 5-FU + doxorubicin</td>
<td>84</td>
<td>Kouvaraki (2004)</td>
<td>39%</td>
</tr>
<tr>
<td>TMZ + thalidomide</td>
<td>11*</td>
<td>Kulke (2006)</td>
<td>45%*</td>
</tr>
<tr>
<td>TMZ + capecitabine</td>
<td>30</td>
<td>Strosberg (2010)</td>
<td>70%</td>
</tr>
</tbody>
</table>

* Out of 29 patients with metastatic NETs, 11 were pancreatic in origin. STZ = streptozocin, 5-FU = 5-fluorouracil, TMZ = temozolomide.

Low-grade carcinoid tumors appear significantly more resistant to the effects of cytotoxic chemotherapy. Contemporary studies employing strict radiographic response criteria demonstrate low response rates. For example, the combination of temozolomide and thalidomide has been associated with a response rate of only 7% in carcinoid tumors. One potential explanation is increased expression of MGMT, a DNA repair enzyme, in carcinoid tumors compared to PNETs.

High-grade (or poorly differentiated) NETs appear to be highly sensitive to platinum-based cytotoxic chemotherapy regimens. These aggressive malignancies are histologically characterized by a high mitotic rate (typically defined as > 10 to 20 mitoses per 10 high-powered fields), extensive necrosis, and pleomorphism. The clinical characteristics of extrapulmonary poorly differentiated NETs are similar to small cell carcinomas of the lung. In one study investigating cisplatin and etoposide in gastroinestinal NETs, a response rate of 67% was observed in poorly differentiated tumors vs 7% in well-differentiated tumors. Another study of cisplatin and etoposide in poorly differentiated NETs of the gastrointestinal tract demonstrated a response rate of 42%. The durations of response in both studies were short (8 to 9 months), with median survivals of only 15 to 19 months.

Radiolabeled SSAs

Nearly 80% of gastroenteropancreatic NETs express somatostatin receptors as evidenced by radiotracer uptake on 111In-pentetreotide scans (OctreoScan). The high incidence of somatostatin receptor expression has provided the rationale for development of radiolabeled SSAs as a means of delivering targeted radiotherapy to NETs.

Early clinical trials of somatostatin-labeled radionuclides used high cytotoxic doses of 111In-pentetreotide,
the isotope used in OctreoScans.\textsuperscript{79,80} While clinical benefit was observed in some cases, objective radiographic responses were rare, possibly due to the short tissue penetration of Auger electrons emitted by the $^{111}\text{In}$ isotope. The next generation of radiolabeled SSAs used yttrium ($^{90}\text{Y}$), a high-energy $\beta$-particle emitter with a maximum tissue penetration range of 12 mm. Objective radiographic response rates associated with $^{90}\text{Y}$-DOTA-Tyr$^3$-octreotide (also known as $^{90}\text{Y}$DOTATOC) were initially reported to be in the 10% to 30% range.\textsuperscript{81,82} However, a large multicenter phase II trial of 90 patients with metastatic carcinoid tumors recently reported an objective response rate of only 4% (with a stable disease rate of 70% and high rate of symptom control).\textsuperscript{83} Adverse events consisted primarily of nausea and vomiting attributed to amino acid solutions that were administered to prevent radiation nephrotoxicity.

The latest generation of radiolabeled SSAs utilizes $^{177}\text{Lu}$-lutetium-octreotate ($^{177}\text{Lu}$-DOTA-Tyr$^3$-octreotate), a $\beta$ and $\gamma$ particle-emitting compound with enhanced affinity for SST$_2$. An objective radiographic response rate of 30% and a median time to progression of 40 months were reported in an ongoing single-center study of 310 patients.\textsuperscript{85} Adverse effects were mild and consisted primarily of nausea and vomiting occurring within 24 hours of radionuclide administration. Selection criteria for radiolabeled SSA therapy include evidence of strong radiotracer uptake on OctreoScan (at least as high as normal liver tissue).

Liver-Targeted Therapies
The liver is the predominant site of metastases in PNETs and gastrointestinal NETs.\textsuperscript{6,20} Patients with liver metastases may experience symptoms such as pain, anorexia, and weight loss related to tumor burden. Additional symptoms include flushing and diarrhea caused by secretion of hormones directly into the systemic circulation. Hepatic-directed therapies include liver resection or ablation, hepatic artery embolization, and liver transplantation. These therapies are generally reserved for patients whose tumors are predominantly confined to the liver.

Liver resection is generally advocated for patients with limited hepatic disease in which more than 90% of tumors can be successfully resected or ablated.\textsuperscript{86,87} Various ablation techniques have been described, including cryoablation, alcohol ablation, and radiofrequency ablation (RFA).\textsuperscript{88,89} RFA involves conversion of radiofrequency waves to heat using a high alternating current that causes ionic vibration after the change in the current direction.\textsuperscript{88} Ablation methods are generally reserved for unresectable metastases smaller than 5 to 7 cm in diameter. Proponents of cytoreductive hepatic resection and ablation cite numerous institutional series reporting palliation of symptoms and prolonged survival durations among patients undergoing surgery with curative or near-curative intent.\textsuperscript{92,96} However, there are no randomized studies comparing surgical to nonsurgical approaches, and prolonged survival durations observed in surgically treated patients may be related to inherently favorable prognostic factors such as low tumor burden.

Hepatic artery embolization is typically performed in patients with diffuse, unresectable liver metastases. The rationale for embolization is that liver metastases derive the majority of their blood supply from the hepatic arterial circulation, whereas the normal liver parenchyma derives its blood supply primarily from the portal venous circulation. In patients with bilobar hepatic metastases, staged lobar embolizations are typically performed at 4- to 6-week intervals.

The embolization procedure begins with a celiac angiogram designed to identify the hepatic vasculature, patency of the portal vein, and location of hepatic metastases. Selection criteria for hepatic artery embolization include evidence of strong radiotracer uptake on OctreoScan (at least as high as normal liver tissue).

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>No. of Patients</th>
<th>Disease</th>
<th>Technique</th>
<th>Complete/Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruszniewski\textsuperscript{97} (1993)</td>
<td>24</td>
<td>Carcinoid and PNET</td>
<td>TACE</td>
<td>33%</td>
</tr>
<tr>
<td>Gupta\textsuperscript{99} (2003)</td>
<td>81</td>
<td>Carcinoid</td>
<td>TAE or TACE</td>
<td>67%</td>
</tr>
<tr>
<td>Strosberg\textsuperscript{100} (2006)</td>
<td>84</td>
<td>Carcinoid and PNET</td>
<td>TAE</td>
<td>48%</td>
</tr>
<tr>
<td>Eriksson\textsuperscript{98} (1998)</td>
<td>41</td>
<td>Carcinoid and PNET</td>
<td>TAE</td>
<td>51%</td>
</tr>
<tr>
<td>Therasse\textsuperscript{103} (1993)</td>
<td>23</td>
<td>Carcinoid</td>
<td>TACE</td>
<td>35%</td>
</tr>
<tr>
<td>Loewe\textsuperscript{101} (2003)</td>
<td>23</td>
<td>Carcinoid</td>
<td>TAE</td>
<td>73%</td>
</tr>
<tr>
<td>Rhee\textsuperscript{104} (2008)</td>
<td>42</td>
<td>Carcinoid and PNET</td>
<td>$^{90}\text{Y}$ spheres</td>
<td>51%</td>
</tr>
<tr>
<td>Kennedy\textsuperscript{103} (2008)</td>
<td>148</td>
<td>Carcinoid and PNET</td>
<td>$^{90}\text{Y}$ spheres</td>
<td>63%</td>
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PNET = pancreatic neuroendocrine tumors, TACE = transarterial chemoembolization, TAE = transarterial embolization.
ticulate and occlusive materials have been used including Gelfoam (Pharmacia and Upjohn Co, Kalamazoo, MI), polyvinyl alcohol (PVA) particles, and trisacryl gelatin microspheres (Embospheres; BioSphere Medical Inc, Rockland, MA). Embolization can be performed either with the addition of intra-arterial cytotoxic agents (chemoembolization) or without (bland embolization). For chemoembolization, an emulsion of cytotoxic drugs such as doxorubicin or cisplatin is combined with iodized oil and injected into the selected artery until near-complete stasis of flow. There are no randomized studies comparing bland embolization to chemoembolization techniques and no consensus favoring a particular approach. Reported response rates, derived primarily from institutional series, are relatively equivalent (Table 4).\textsuperscript{97,104} Side effects of hepatic artery embolization include nausea, abdominal pain, fevers, and fatigue, all caused by induction of ischemic hepatitis. Serum transaminases typically increase significantly, peaking 2 to 3 days after each embolization. Most side effects resolve within 1 week of treatment.\textsuperscript{100} Contraindications to the transarterial embolization include liver dysfunction, moderate to severe ascites, and portal venous thrombosis.

A novel approach to hepatic metastases involves arterial embolization of \textsuperscript{90}Y embedded in either a resin microsphere (SIR-Spheres, Sirtex Medical Ltd, Lane Cove, Australia) or a glass microsphere (TheraSphere, MDS-Nordion Inc, Ontario, Canada). This technique enables direct delivery of a radionuclide with a long-range tissue penetration of up to 11 mm to hepatic metastases. A preprocedural celiac angiogram is necessary to map the vascular supply to the liver and identify aberrant vessels to the gastrointestinal tract that need to be avoided or embolized before treatment. \textsuperscript{99m}Technetium macro-albumin is then infused intra-arterially with single photon emission computed tomography (SPECT) imaging to evaluate for possible intrahepatic arterial shunting to the lungs or gastrointestinal tract. These procedures are performed to avoid unintentional infusion of radioactive microspheres outside of the liver, which could lead to radiation pneumonitis or enteritis. The actual radioembolization procedure is performed similarly to bland embolization or chemoembolization. However, the microspheres are not infused until stasis of blood flow due to the fact that cell death through radiation requires normal oxygen tension. Consequently, patients with mild to moderate liver dysfunction or portal vein thrombosis who are ineligible for bland embolization or chemoembolization may be able to tolerate radioembolization.

Toxicities associated with \textsuperscript{90}Y microsphere radioembolization appear to be lower than with other embolization techniques, primarily due to the fact that the procedure does not induce ischemic hepatitis. Thus, the procedure can be performed on an outpatient basis. A serious potential complication is radiation enteritis, which can occur if particles are accidentally infused into arteries supplying the gastrointestinal tract. This toxicity appears to occur rarely in high-volume centers. Response rates associated with radioembolization in metastatic NETs have been encouraging. In one retrospective multicenter study of 148 patients treated with SIR-Spheres, the objective radiographic response rate was 63%, with a median survival of 70 months.\textsuperscript{103} Another study of 42 patients treated with either TheraSphere microspheres or SIR-Spheres reported a response rate of 51%. However, only 29 of the 42 enrolled patients were evaluable for response.\textsuperscript{104}

Liver transplantation has been described in metastatic NET patients, but the benefits of transplantation are uncertain. Most centers report a high postoperative mortality rate of 10% to 20%. In the largest reported meta-analysis of 103 patients, the 5-year survival rate was 47%, with only 24% of patients free of disease recurrence.\textsuperscript{105} Another multicenter analysis of 85 cases reported a 5-year survival rate of 47% and recurrence-free survival rate of 20% at 5 years.\textsuperscript{106} Since recurrence-free survival curves have not achieved a plateau, it is unclear whether transplantation can be considered as potentially curative. Negative prognostic factors for recurrence have included hepatomegaly, pancreatic primary site (as opposed to small intestinal), and elevated Ki-67 index.

Conclusions

Therapeutic options for treatment of metastatic gastroenteropancreatic NETs are expanding. SSAs such as octreotide represent the appropriate first-line treatment for most patients with well-differentiated tumors. In the past, SSAs were employed primarily for palliation of secretory hormonal syndromes. More recent data support their role as antiproliferative agents, capable of stabilizing tumor growth in a large percentage of patients and significantly improving PFS regardless of hormonal output. At this time, high-level evidence favors the use of octreotide as an antiproliferative agent in metastatic well-differentiated midgut NETs. The role of SSAs in the treatment of other types of neuroendocrine malignancies is still uncertain.

IFN-α is another agent that can palliate hormonal symptoms and inhibit tumor growth, albeit with higher rates of toxicity than SSAs. Novel targeted agents include sunitinib, bevacizumab, and everolimus. Among these, sunitinib has been proven to improve PFS in a phase III study of PNETs. Phase III data on everolimus and bevacizumab are anticipated in the near future.

Cytotoxic chemotherapy has long been known to be active in poorly differentiated NETs. Accumulating data point to the fact that PNETs are substantially more sensitive than carcinoid tumors to chemotherapy. While STZ-based regimens are associated with high response rates, temozolomide-based regimens appear to be at least equally active and with lower rates of toxicity. Due to the increasing interest in targeted agents, cytotoxic
drugs have not been evaluated in contemporary phase III studies. However, the high response rates reported with temozolomide warrant further studies in larger multicenter studies.

Liver-directed therapies such as surgical cytoreduction, ablation, and embolization are frequently employed for treatment of patients with liver-predominant metastases. New radioembolization techniques utilizing 90Y microspheres are encouraging due to their reduced toxicity.

In this era of expanding treatment options, understanding how to best sequence treatments becomes increasingly vital. One complicating factor is that many patients with asymptomatic indolent tumors require no treatment at all and can be managed with close observation. Future randomized trials comparing various therapies and evaluating combination vs sequential approaches may help in the development of treatment algorithms.

References


101. Loeve C, Schindf M, Cejna M, et al. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and


