limited in number (usually less than five) and size (usually <3.5 cm in diameter). It can be used at the time of surgery (either general or laparoscopic) or using radiologic guidance.

Response rates are >80%, the responses can last up to 3 years, the morbidity rate is low, and this procedure may be particularly helpful in patients with functional pNETs that are difficult to control medically. Although RFA has not been established in a controlled trial, both the European and North American Neuroendocrine Tumor Society guidelines (ENETS, NANETS) state it can be an effective antitumor treatment for both refractory functional syndromes and for palliative treatment.

Chemotherapy plays a different role in the treatment of patients with pNETs and GI-NETs (carcinoids). Chemotherapy continues to be widely used in the treatment of patients with advanced pNETs with moderate success (response rates 20–70%); however, in general, its results in patients with metastatic GI-NETs (carcinoids) has been disappointing, with response rates of 0–30% with various two- and three-drug combinations, and thus, it is infrequently used in these patients. An important distinction in patients with pNETs is whether the tumor is well differentiated (G1/G2) or poorly differentiated (G3). The chemotherapeutic approach is different for these two groups. The current regimen of choice for patients with well-differentiated pNETs is the combination of streptozotocin and doxorubicin with or without 5-fluorouracil. Streptozotocin is a glucosamine nitrourea compound originally found to have cytotoxic effects on pancreatic islets, and later in studies with doxorubicin with or without 5-fluorouracil, it produced response rates of 20–45% in advanced pNETs. Streptozotocin causes considerable morbidity, with 70–100% of patients developing side effects (most prominent being nausea/vomiting in 60–100% or leukopenia/thrombocytopenia) and 15–40% of patients developing some degree of renal dysfunction (proteinuria in 40–50%, decreased creatine clearance). The combination of temozolomide (TMZ) with capecitabine produces partial response rates as high as 70% in patients with advance pNETs and a 2-year survival of 92%. The use of TMZ or another alkylating agent in advanced pNETs is supported by studies that show low levels of the DNA repair enzyme O^6-methylguanine DNA methyltransferase in pNETs, but not in GI-NETs (carcinoids), which increases the sensitivity of pNETs to TMZ. In poorly differentiated NETs (G3), chemotherapy with a cisplatin-based regimen with etoposide or other agents (vincristine, paclitaxel) is the recommended treatment, with response rates of 40–70%; however, responses are generally short-lived (<12 months). This chemotherapy regimen can be associated with significant toxicity including GI toxicities (nausea, vomiting), myelosuppression, and renal toxicity.

In addition to the effectiveness in controlling the functional hormonal state, long-acting somatostatin analogues such as octreotide and lanreotide are increasingly used for their antiproliferative effects. Whereas somatostatin analogues rarely decrease tumor size (i.e., 0–17%), these drugs have tumoristatic effects, stopping additional growth in 26–95% of patients with NETs. In a randomized, double-blind study in patients with metastatic midgut carcinoids (PROMID study) octreotide-LAR demonstrated a marked lengthening of time to progression (14.3 vs 6 months, $p = .000072$). This improvement was seen in patients with limited liver involvement. This study did not assess whether such treatment will extend survival. A double-blind, randomized, placebo-controlled, phase III study in patients with well-differentiated, metastatic, inoperable pNETs (45%) or GI-NETs (carcinoids) (55%) (CLARINET study) showed that monthly treatment with lanreotide-autogel reduced tumor progression or death by 53%. Somatostatin analogues can induce apoptosis in GI-NETs (carcinoids), which probably contributes to their tumoristatic effects. Treatment with somatostatin analogues is generally well-tolerated, with most side effects being mild and uncommonly leading to stopping the drug. Potential long-term side effects include diabetes/glucose intolerance, steatorrhea, and the development of gallbladder sludge/gallstones (10–80%), although only 1% of patients develop symptomatic gallbladder disease. Because of these phase III studies, somatostatin analogues are generally recommended as first-line treatment for patients with well-differentiated metastatic NETs.

Interferon α, similar to somatostatin analogues, is effective at controlling the hormonal excess symptoms of NETs and has antiproliferative effects in NETs, which primarily result in disease stabilization (30–80%), with a decrease in tumor size in <15% of patients. Interferon can inhibit DNA synthesis, block cell cycle progression in the G_1 phase, inhibit protein synthesis, inhibit angiogenesis, and induce apoptosis. Interferon α treatment results in side effects in the majority of patients, with the most frequent being a flu-like syndrome (80–100%), anorexia with weight loss, and fatigue. These side effects frequently decrease in severity with continued treatment. In addition, patients become accommodated to the symptoms. More serious side effects include hepatotoxicity (31%), hyperlipidemia (31%), bone marrow toxicity, thyroid disease (19%), and rarely CNS side effects (depression, mental/visual disorders). ENETS 2012 guidelines conclude that in patients with well-differentiated NETs that are slowly progressive, interferon α treatment should be considered if the tumor is somatostatin receptor negative or if somatostatin treatment fails.

Selective internal radiation therapy (SIRT) using yttrium-90 (^{90}Y) glass or resin microspheres is a relatively newer approach being evaluated in patients with unresectable NET liver metastases, with approximately 500 NET patients treated. The treatment requires careful evaluation for vascular shunting before treatment and a pretreatment angiogram to evaluate placement of the catheter and is generally is reserved for patients without extrahepatic metastatic disease and with adequate hepatic reserve. One of two types of ^{90}Y microspheres are used: either microspheres with a 20- to 60-μm diameter and 50 Bq/sphere (SIR-Spheres) or glass microspheres (TheraSpheres) with a 20- to 30-μm diameter and 2500 Bq/sphere. The ^{90}Y-microspheres are delivered to the liver by intra-arterial injection from percutaneously placed catheters. In four studies involving metastatic NETs, the response rate varied from 50–61% (partial or complete), tumor stabilization occurred in 22–41%, 60–100% had symptomatic improvement, and overall survival varied from 25–70 months. Side effects include postembolization syndrome (pain, fever, nausea/vomiting [frequent]), which is usually mild, although grade 2 (43%) or grade 3 (1%) symptoms can occur; radiation-induced liver disease (<1%); and radiation pneumonitis (<1%). Contraindications to use include excess shunting to the GI tract or lung, inability to isolate the liver arterial supply, and inadequate liver reserve. Because of the limited data available in the ENETS 2012 guidelines, treatment with SIRTs is considered experimental.

Molecular targeted medical treatment with either an mTOR inhibitor (everolimus) or a tyrosine kinase inhibitor (sunitinib) is now approved treatment in the United States and Europe for patients with metastatic unresectable pNET, each supported by a phase III, double-blind, prospective, placebo-controlled trial. mTOR is a serine-threonine kinase that plays an important role in proliferation, cell growth, and apoptosis in both normal and neoplastic cells. Activation of the mTOR cascade is important in mediating NET cell growth, especially in pNETs. A number of mTOR inhibitors have shown promising antitumor activity in NETs including everolimus and temsirolimus, with the former undergoing a phase III trial (RADIANT-3) involving 410 patients with advance progressive pNETs. Everolimus caused significant improvement in progression-free survival (11 vs 4.6 months, $p <.001$) and increased by a factor of 3.7 the proportion of patients progression-free at 18 months (37% vs 9%). Everolimus treatment was associated with frequent side effects, causing a twofold increase in adverse events, with the most frequent being grade 1 or 2. Grade 3 or 4 side effects included hematologic, GI (diarrhea), stomatitis, or hypoglycemia occurring in 3–7% of patients. Most grade 3 or 4 side effects were controlled by dose reduction or drug interruption. The ENETS 2012 guidelines conclude that everolimus, similar to sunitinib (below), should be considered as a first-line treatment in selected cases of