Introduction

For nearly a century, neuroendocrine cancers have been a source of biological curiosity. The term neuroendocrine includes histologic subtypes of both carcinoid and pancreatic neuroendocrine cancers. The majority of gastrointestinal neuroendocrine tumors are carcinoids (55%), with most of these being midgut carcinoids (50% to 70%). They have the greatest potential for metastases to the liver, resulting in carcinoid syndrome. Carcinoid syndrome presents as flushing, diarrhea, bronchial constriction, and heart disease, and it is
related to tumor volume and elevation in urinary levels of 5-hydroxyindoleacetic acid.\(^3\) Although pancreatic neuroendocrine cancers are less common, they may also present with liver metastases and disabling endocrinopathies — insulinomas can cause hypoglycemic events leading to altered mentation, vasoactive intestinal polypeptide-secreting tumors (VIPomas) are associated with life-threatening hypokalemia as a result of severe diarrhea, and patients with gastrinomas are predisposed to gastrointestinal perforation and bleeding, as well as diarrhea.

Compared with most metastatic gastrointestinal and pancreatic adenocarcinomas, gastrointestinal neuroendocrine cancers have a slow clinical progression and patient survival is prolonged.\(^3\) Patients with metastatic neuroendocrine cancers often suffer for months or years with pain from bulky liver disease or from disabling hormonal symptoms. It is known from historical controls that the survival of patients with metastatic neuroendocrine cancers is limited by the extent of their disease. The 5-year survival rate for unresected carcinoid tumors and metastatic islet cell carcinomas is 30% to 40%, with a mean survival of 3 to 4 years.\(^5\) The role of chemotherapeutic agents in treating systemic disease has been limited by poor response, short duration of effect, and toxicity.\(^5\) Cytoreductive therapy has emerged as an attractive option in the treatment of neuroendocrine liver metastases. It is defined as complete removal or reduction of the total tumor volume by at least 90%.\(^1\) Aggressive surgical resection, chemotherapy, radiofrequency ablation (RFA), and embolization have been used either alone or in combination to meet the goal of cytoreduction. Reducing tumor burden has been shown to lessen symptoms in the majority of patients with hormonally active tumors and improve survival.\(^1\) Furthermore, perioperative morbidity and mortality rates for metastasectomies of neuroendocrine tumors are similar to those established for colorectal metastases.\(^1\) Neuroendocrine cancers have certain characteristics that are considered favorable for cytoreduction; these characteristics include slow growth of tumor, liver-only or

Fig 1A-C. — Case 1. (A) Initial presentation demonstrating a primary distal pancreatic neuroendocrine tumor with extensive bilobar hepatic metastases. (B) Response post yttrium-90 labeled somatostatin therapy. (C) Post resection of the primary with concurrent RFA of the remaining liver metastases.
liver-dominant disease, intrahepatic growth pattern without encasement of major hepatobiliary structures, and prolonged patient survival. Several case reports are included to show the beneficial effects of cytoreductive therapy followed by a review of the literature supporting an aggressive surgical approach.

**Case Studies**

**Case 1**
A 51-year-old man presented in 2000 with gastrointestinal symptoms and flushing. Further workup revealed a well-differentiated pancreatic neuroendocrine cancer with diffuse metastatic involvement of the liver (Fig 1A). Hepatic artery embolization was initially attempted for control of his symptoms but could not be performed after finding insufficient portal venous flow. He was then given chemotherapy with 5-fluorouracil and streptozocin, followed by participation in a phase I trial using yttrium-90-labeled somatostatin ([90Y-DOTA, Tyr3]octreotide). Follow-up radiographic studies showed an interval decrease in the size of the hepatic lesions and primary tumor (Fig 1B). His last treatment had been 2 years prior, and no disease progression was evident. Cytoreductive surgery with concomitant resection of the primary tumor was recommended. Four bilobar hepatic metastases were treated with RFA, and a distal pancreatectomy and splenectomy were performed for the primary neuroendocrine lesion in the tail of the pancreas (Fig 1C). Postoperatively, the patient suffered a minor cerebral vascular accident but has had a complete recovery. The patient is 3 months postsurgery and remains free of symptoms and without evidence of radiographic recurrence.

**Case 2**
A 52-year-old woman presented with a VIP-secreting pancreatic neuroendocrine tumor with multifocal liver metastases (Fig 2A). With a life-threatening endocrinopathy, she was referred for cytoreductive surgery. Initial computed tomography (CT) scan revealed a rather large mass measuring 8 cm × 5 cm was seen in the tail of the pancreas and multiple bilobar liver metastases (Fig 2A). The patient underwent an unremarkable distal pancreatectomy with splenectomy and RFA of seven hepatic lesions. An additional lesion located centrally nearing all three hepatic veins was not ablated for fear of causing venous thrombosis and complete outflow obstruction of the liver. A debulking of 80% of the tumor burden was achieved (Fig 2B). The patient is 1 month postsurgery and is now receiving the long-acting release (LAR) formulation of octreotide.

**Case 3**
A 72-year-old woman presented with a 12-year history of metastatic carcinoid disease with unknown primary. Her initial symptoms of flushing and diarrhea were controlled with octreotide therapy. In 2004, it was noted that her symptoms progressed, which were associated with an increase in biologic markers and size of her liver metastases. A liver lesion essentially replacing 60% to 70% of the right hepatic lobe was found by CT (Fig 3A). Two indeterminate lesions were noted in the left hepatic lobe. She also had chronic cholecystitis as a result of long-term octreotide therapy. She underwent an uneventful right hepatectomy and cholecystectomy with complete resection of all tumor burden. A primary tumor was not identified, and the lesions in the left lobe were benign hepatic cysts (Fig 3B). At 12 months of follow-up, the patient remains symptom free with complete biologic and radiographic response. She has also had partial resolution of her facial telangiectasia (Figs 3C-D).

**Case 4**
A 62-year-old woman has been followed since 1993 for metastatic neuroendocrine cancer with an unknown primary. Therapy with octreotide, the somatostatin analog,
was initiated to control her symptoms of diarrhea. Over the ensuing 5 years she had progression of her disease with increasing resistance to somatostatin therapy. In 1998, she experienced a crisis with severe watery stools, and dehydration. Interestingly, her serum VIP level at this time was found to be elevated with a value of 1,130 pg/mL (normal range less than 75 pg/mL). Subsequent to this, she underwent sequential hepatic artery embolization in an attempt to decrease tumor burden. She also participated in an experimental protocol of peptide receptor radionuclide therapy using yttrium-90-labeled somatostatin (\(^{90}\text{Y-DOTA}_6\text{Tyr}^1\text{octreotide}\)). In 2004, she presented with progression of symptoms and findings of a new mass in the left lateral segment of the liver (Fig 4A). Given the extent of her metastases, cytoreductive surgery was initiated with palliative intent. Exploration revealed no evidence of extrahepatic disease. Multiple subcentimeter nodules were found throughout all segments of the liver in addition to the significant left lateral segment lesion. A large right hepatic tumor extending into segment 4 of the liver was also noted and would have required trisegmentectomy for removal. Given the extent of her disease, it was decided that a right trisegmentectomy would not be indicated. Cytoreduction of 75% of the tumor burden was achieved by a combination of a partial hepatic resection and several ablations (Fig 4B). The patient had regression of symptoms for 6 months following surgery with decreased requirements for somatostatin.

**Case 5**
A 41-year-old woman presented with severe diarrhea and electrolyte abnormalities in 2001. Upon further
workup she was found to have a functioning pancreatic neuroendocrine cancer in the head of her pancreas with extensive bilobar hepatic metastases (Fig 5A). Evaluation for functionality revealed increased serum motilin and pancreatic polypeptide levels. Initial treatment, which was performed at another institution, consisted of cytoreductive therapy with incomplete enucleation of a 5-cm mass in the head of the pancreas and removal of enlarged periportal lymph nodes. None of the liver metastases could be resected as a result of extensive bulky disease. Subsequently, the patient was started on octreotide LAR with regression of her symptoms. In 2002, she was noted to have progression of her liver disease and was treated with sequential bilobar hepatic artery embolization and chemotherapy.

While on cytotoxic chemotherapy, the mass in the head of the pancreas and one of the indicator lesions in her liver increased in size. In 2004, the patient was referred to Rotterdam, Holland, for an experimental protocol using peptide receptor radionuclide therapy. She received four treatments of lutetium-177 linked to octreotide ([177Lu-DOTA⁰,Tyr³]octreotide) with significant tumor regression and normalization of her biologic markers (Fig 5B). After reviewing her most recent radiographic studies, she was thought to be a good candidate for cytoreductive therapy. This included a pancreaticoduodenectomy with ultrasound-assisted RFA of five liver metastases. Debulking consisted of removal or destruction of greater than 90% of her tumor burden (Fig 5C). Postoperatively the patient had a small pancreatic leak that resolved nonoperatively. Three months following cytoreductive therapy, she remains symptom-free with use of low-dose octreotide LAR.

**Case 6**

A 73-year-old woman presented with symptomatic flushing and diarrhea in 2003. Initial workup revealed a well-differentiated carcinoid tumor within the terminal ileum, a synchronous adenocarcinoma of the ascending colon, and bilobar metastatic carcinoid disease of the liver (Fig 6A). At the time of diagnosis, she underwent an uneventful right hemicolectomy at another institution. Over the next 6 months, her symptoms of flushing and diarrhea worsened. CT and somatostatin receptor scintigraphy confirmed the findings of several large right hepatic lobe lesions and a smaller lesion in the left lobe. With her disease being confined to the liver, it was felt that she would benefit from cytoreductive surgery. Intraoperatively, two large lesions measuring 5 cm and 7 cm were found in the right lobe and were treated with right hepatectomy. A third lesion measuring 3 cm was noted in segment 2 of the liver and was ablated. All lesions were confirmed by pathology to be metastatic carcinoid cancer and margins of resection were free of disease. At 6 months of follow-up, she remains symptom-free and has no evidence of recurrence on repeat radiographic studies (Fig 6B).

**Case 7**

A 61-year-old man presented with intermittent diarrhea for 1 year. In mid 2004, a CT scan of the abdomen and somatostatin receptor scintigraphy revealed a large right-sided intra-abdominal mass and multiple liver densities consistent with metastatic disease (Fig 7A). A right hemicolectomy was performed at the initial operation, and the final pathology revealed a well-differentiated carcinoid cancer. Postoperatively, the patient underwent hepatic artery embolization for treatment of the liver disease. He was subsequently referred
for cytoreductive therapy. At the time of exploration, the patient had multiple bilobar lesions that were amenable to RFA and limited wedge resection. A cholecystectomy was also performed (Fig 7B). The patient is 2 months postsurgery and currently under surveillance for recurrence.

**Review of the Literature**

**Adjuncts to Surgical Resection**

The goal of cytoreductive therapy is the complete resection or removal of at least 90% of tumor burden. Patients presenting with limited disease should be considered for early surgical resection. Those with advanced disease and large tumor burden are candidates for adjuvant therapies, with the ultimate goal being surgical intervention. As illustrated in our case studies, multimodal therapy including hepatic artery embolization, chemotherapy, and RFA are commonly required to convert unresectable hepatic metastases into surgically resectable disease.

**Hepatic Artery Embolization and Chemoembolization**

Hepatic artery embolization with or without the addition of chemotherapy has been used to treat both primary and metastatic lesions of the liver. Because liver tumors derive more than 80% of their blood supply from the hepatic artery and normal liver parenchyma is supported mostly by the portal vein, selective occlusion of the hepatic artery results in tumor ischemia. However, this effect has proven to be temporary, as hepatic tumors have the remarkable capability of developing collateral vessels.

Embolization of the hepatic artery is beneficial for many patients with metastatic neuroendocrine cancers. It is helpful in palliating symptoms and has
become a useful adjunct in reducing bulky disease in preparation for surgical resection.\textsuperscript{23-25} Patients with bilobar disease are acceptable candidates, and sequential embolizations can be performed. Hepatic arterial occlusion can also be repeated as indicated and tolerated by the patient. Patients with greater than 80% liver involvement or portal vein occlusion are not candidates for occlusive therapy secondary to inadequate liver reserve.

Hepatic artery occlusion can be performed either surgically or percutaneously. However, surgical ligation is rarely performed today since interventionalists continue to refine their abilities to selectively target vessels supplying the tumor, resulting in less morbidity. After an angio gram of the liver is performed and portal vein patency is established, selected branches of the hepatic artery are chosen for occlusion based on the blood supply to the tumor. Embolizations can be performed using polyvinyl alcohol, gelatin sponge particles, or microspheres. Complications of hepatic artery occlusion include vomiting, abdominal pain, fever, and elevated liver transaminases.\textsuperscript{23,26,27} One series reported severe complications of hepatic necrosis, gallbladder perforation, abscess formation, and development of hepatorenal syndrome in 12% of patients.\textsuperscript{27} Our own experience reported by Strosberg et al\textsuperscript{28} elsewhere in this issue had less morbidity.

Hepatic artery occlusion provides symptomatic relief to patients with functioning neuroendocrine cancers, but duration of response is short and repeated embolizations are often required to maintain regression of symptoms. In several series, occlusion alone resulted in an objective tumor response in 50% to 60% of patients.\textsuperscript{23,27,29} Complete tumor regressions were rare, and median duration of effect was 4 to 12 months.\textsuperscript{23,27} Patients with carcinoid tumors were reported to have a 5-year survival rate of 60% from the time of embolization compared to those with pancreatic endocrine cancers, whose median survival was only 20 months.\textsuperscript{23} Similar survival benefits were confirmed by Moertel et al.\textsuperscript{27} Interestingly, they showed an 80% objective response and mean duration of symptom regression of 18 months when systemic chemotherapy was added after the embolization. This suggests that subsequent chemotherapy following hepatic arterial occlusion may improve the rate and duration of regression. Concurrent chemotherapy and embolization (chemoembolization) has also been effective in relieving symptoms in 60% to 100% of patients, with objective tumor responses of 40% to 86%.\textsuperscript{20,30,31} Combinations of chemotherapeutic agents including mitomycin, cisplatin, epirubicin, doxorubicin, and streptozocin have been used. Thus, hepatic arterial embolization or chemoembolization is an effective temporizing measure for those with unresectable liver disease, but complications can be significant.

\section*{Radiofrequency Ablation}

Conventional partial hepectomy is rarely possible since approximately 90% of metastases are multifocal and bilateral.\textsuperscript{32} Thus, RFA has emerged as an important alternative treatment modality for patients with hepatic metastases from neuroendocrine cancers. This technique uses an electrode that is introduced into the tumor under ultrasonic guidance, producing coagulation necrosis. A generation of high-frequency alternating current results in ionic agitation that is converted to heat, inducing cellular death. A 1-cm margin of normal liver parenchyma surrounding the tumor is also ablated to decrease local recurrence rates. Initial CT scans will demonstrate a cystic density lesion larger than the original tumor; this will decrease in size over time (Figs 1A-C and Figs 4A-B).\textsuperscript{33} RFA can be performed laparoscopically, percutaneously, or as part of an open surgical procedure. Patients previously thought to be nonsurgical candidates secondary to bilobar disease can now be considered for combination therapy with surgical resection and ablation.\textsuperscript{34}

RFA is an effective and safe means of reducing symptoms in patients with liver metastases of neuroendocrine origin. Symptomatic relief occurs in 95% of patients, with significant or complete control in 80%, for a mean duration of 10 months (6 to 24 months).\textsuperscript{34,36} Multiple ablations in a single setting can be performed with low morbidity (<5%).\textsuperscript{33,34} Complications following RFA include intrahepatic abscess, fever, pain, biliary fistulae, and perihepatic abscesses.\textsuperscript{35} Recurrence rates are reported as 2.2% to 6% per lesion.\textsuperscript{33,34,37,38} Most recurrences occurred in lesions greater than 5 cm.\textsuperscript{33,34} New third-generation probes reaching 7 cm hold promise for the future. Berber et al\textsuperscript{34} reported on 34 patients undergoing laparoscopic RFA for neuroendocrine liver metastases. Mean survival from diagnosis was 5.5 years, and 73% of patients were alive at a mean follow-up of 1.6 years following RFA. Data regarding duration of symptomatic regression and impact on overall survival are still maturing. Future reports may better delineate the role of RFA on the treatment of metastatic neuroendocrine disease.

\section*{Chemotherapy}

Systemically administered chemotherapeutic agents are minimally effective in reducing symptoms and slowing disease progression for any significant period of time. This is in part due to decreased kinetic activity of these tumors and a high degree of tumor differentiation. Furthermore, neuroendocrine cancers have considerable differences in chemosensitivity. Streptozocin-based therapies in combination with doxorubicin or 5-fluorouracil result in regression rates of 36% to 69% in patients with metastatic disease from islet cell cancers.\textsuperscript{7,8} However, duration of regression is short and toxicity is significant. A report by Moertel et al\textsuperscript{39} in
1991 shows a response rate of 67% in patients with anaplastic neuroendocrine cancers using a combination of cisplatin and etoposide. Conversely, carcinoid tumors have had a poor response to chemotherapy in clinical trials with regression in less than 30% of patients.9-10 Systemic administration of interferon-α (IFN-α) was introduced by Oberg and Eriksson40 in 1982. Initial experience demonstrated a biochemical response rate of 50% in carcinoid tumors with tumor reduction in 15% of patients. A recent review by Oberg41 of 13 series (383 patients) supports these findings, with a biochemical response rate of 44% and tumor response rate of 11% reported.

Somatostatin analogs such as octreotide and lanreotide provide symptomatic improvement in 70% of patients with neuroendocrine cancers.4,42-44 Biochemical response rates of 30% to 70% are reported; however, objective tumor shrinkage occurred in less than 10% of cases.4,43,44 In a recent nonrandomized study, the long-acting somatostatin analog, octreotide LAR, was investigated in the adjuvant setting following hepatic cytoreduction.45 The median symptom-free interval was 60 months with octreotide LAR compared to 16 months in patients treated with alternative adjuvant therapies. The 3-year overall survival rate was significantly improved with octreotide LAR (100% vs 37%). Overall, somatostatin analogs are well tolerated with few side effects. The most significant side effect is cholelithiasis and biliary dyskinesia, with risk approaching 50%.46 Although somatostatin analogs are effective in relieving symptoms, drug resistance can develop in patients with carcinoid tumors after 12 months of treatment and in islet cell cancers after 3 to 4 months of therapy.47

Peptide receptor radionuclide therapy (PRRT) is an innovative treatment modality for locally advanced or metastatic neuroendocrine cancers. PRRT uses radio-labeled somatostatin analogs to target cancers with prominent somatostatin receptors. Three radio-labeled somatostatin analogs have been studied: [90Y-DOTA⁰,Tyr³]octreotide, [177Lu-DOTA⁰,Tyr³]octreotide, and [111In-DTPA⁰]octreotide. Kwekkeboom et al48 recently reviewed the findings of several phase I and phase II trials using these compounds. The ability to achieve a complete or partial clinical response differed between therapies. Treatment with [177Lu-DOTA⁰,Tyr³]octreotide, which has a higher affinity for the subtype 2 somatostatin receptor, resulted in a complete or partial clinical response in 30% of patients, a 10% to 30% response rate was achieved with [90Y-DOTA⁰,Tyr³], and a less than 10% clinical response was noted with [111In-DTPA⁰]octreotide. Side effects were mild and few, and symptomatic improvement was reported in nearly all of the patients treated. Duration of the therapeutic response was more than 2 years. As illustrated in several of our own case studies (cases 1, 4, and 5), significant responses can convert extensive disease into disease that is amenable to cytoreductive surgery. Hence, PRRT is a promising new concept in the treatment of advanced disease of neuroendocrine origin.

**Hepatic Resection**

The goal of cytoreductive surgery is the removal or in situ destruction of tumor in order to reduce clinical symptoms, improve quality of life, and prolong survival. For neuroendocrine cancers this is achieved through either complete resection or reduction of at least 90% of the tumor burden.11,12 As a component of multimodality therapy, surgical resection of metastases is often combined with at least one of the above adjuvant therapies, with improved responsiveness.49 The primary cancer, if localized, is resected if technically feasible, either at an initial operation or at the time of metastasectomy. Concurrent resection of the primary cancer with hepatic metastases is safe for selected patients with no additional morbidity.15,16,50

Patients are carefully selected for cytoreductive surgery. An initial helical CT or magnetic resonance imaging (MRI) is performed to evaluate the extent of liver involvement and potential extrahepatic disease.

### Hepatic Resection for Metastatic Gastrointestinal Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Author</th>
<th>Carcinoid</th>
<th>Noncarcinoid</th>
<th>Symptomatic Response (%)</th>
<th>Operative Mortality (%)</th>
<th>Operative Morbidity (%)</th>
<th>Overall Survival (%)</th>
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<td>96</td>
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<td>10</td>
<td>–</td>
<td>0</td>
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<td>10</td>
<td>–</td>
<td>0</td>
<td>13</td>
<td>47 at 5 yrs</td>
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<tr>
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<td>8</td>
<td>50</td>
<td>0</td>
<td>–</td>
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<td>13</td>
<td>88</td>
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* Included both hepatic arterial embolization procedure-related mortality and 30-day operative mortality.
The addition of somatostatin receptor scintigraphy increases detection rates for primary cancers to 68% and liver metastases to 96%, and it is routinely performed at our institute. Based on these studies, tumors are assessed for resectability and liver reserve is estimated. Bilobar disease is not a contraindication to cytoreductive surgery. Surgical resection combined with RFA has been shown to be an effective and safe means of cytoreduction in patients with multicentric or bilobar disease. Additionally, each case is assessed on an individual basis with respect to the patient’s comorbidities and risk/benefit ratio for surgery.

Cytoreductive surgery for neuroendocrine disease increases survival and improves quality of life. The survival rate for unresected metastatic disease at 5 years is reported as 30% to 40%. In contrast, patients undergoing surgical resection are experiencing 5-year survival rates of 47% to 82% (Table). Differences in survival may reflect the completeness of resection. Nave et al showed a significant difference in 5-year survival rates for those undergoing R0 and R2 resections: 86% and 26%, respectively. This is in contrast to the findings of Sarmiento et al who found no difference in survival. In a later review, however, they reported a significant difference in recurrence rates based on extent of resection. Those patients undergoing R0 resection recurred at a median of 30 months compared with 16 months in those undergoing palliative resection. No difference in survival was found based on functionality or between carcinoid tumors and islet cell carcinomas. Therefore, surgery may play an important role in improving survival for nonfunctioning tumors as well, since survival for patients with nonfunctioning islet cell cancers and metastatic disease is rarely beyond 24 months.

Symptomatic relief from disabling endocrinopathies is initially achieved in 80% to 90% of patients, with a mean duration of 16 to 26 months. Dura-

ing of response is related to the completeness of resection and normalization of hormonal markers. Unfortunately, the majority of patients develop recurrent disease within 5 years of surgical resection.

Cytoreductive surgery is safe in patients with metastatic neuroendocrine disease. Improvements in anesthesia, surgical technique, and perioperative care have resulted in mortality rates of less than 4% for major hepatic resections. Cytoreductive surgery for neuroendocrine metastases, like that for colorectal surgery, is commonly performed at high-volume centers, with perioperative mortality rates of 0% to 3%.

Patients with carcinoid tumors are treated preoperatively with somatostatin therapy at doses of 150 to 500 μg subcutaneously and 100 μg/hr by intravenous administration during the procedure. The administration of somatostatin is aimed at preventing the hemodynamic instability associated with carcinoid crisis, which manifests in 10% of cases. Cholecystectomy is routinely performed to eliminate complications associated with chronic somatostatin analog therapy and potential hepatic artery embolization. Perioperative morbidity rates of 14% to 30% are reported for neuroendocrine cytoreductive surgery. Reports are inclusive of gastrointestinal complications from concomitant resection of the primary tumors. Bile leaks, intrahepatic and perihepatic abscesses, and bleeding are the most common complications following hepatic resection.

Discussion

Of all the potential treatment options for metastatic neuroendocrine disease, surgical resection is the only therapy proven to impact long-term survival. Therefore, the goal of cytoreductive therapy should be surgical resection. Unfortunately, less than 20% of patients present with surgically manageable disease. Most present with extensive bilobar disease or bulky tumor requiring alternative therapy; these are the majority of patients seen at our institute.

Patients with advanced disease can be managed initially with chemotherapy and/or hepatic artery embolization. As illustrated in several case studies, response of liver metastases can be significant. Patients should be re-evaluated, however, with each intervention for potential surgical candidacy. Complacency with the initial response should not prevent resection of surgically resectable disease; as recurrence and disease progression are inevitable.

Now commonly accepted in the use of colorectal hepatic metastases, RFA has become a useful tool in cytoreductive surgery. Patients who were once not considered for surgical resection secondary to bilobar disease are now able to benefit from surgical resection with concomitant RFA. Although symptomatic regression with low morbidity (<5%) is predictable with combination therapy, data regarding impact on overall survival are still maturing.

The extent of hepatic disease and the overall health of the patient are the main factors determining the algorithmic approach to the management of neuroendocrine metastases (Fig 8). Surgical resection should be considered in all healthy patients with operable disease. Emphasis should be placed on early resection regardless of tumor functionality or symptoms. Patients with bulky or bilobar disease should be treated initially with chemotherapy and/or hepatic artery embolization. Patients in whom traditional therapies are unsuccessful should be considered for clinical trials. Reassessment of tumor burden is essential to the timing of surgical resection. Restaging studies including somatostatin receptor scintigraphy and CT or MRI are essential prior to undergoing surgical resection to assess for extrahepatic dis-
Cytoreductive surgery results in the regression of symptoms in 90% of patients with functioning neuroendocrine cancers, and it improves overall survival. Thus, aggressive surgical resection is an important component of the multimodality treatment plan for neuroendocrine hepatic metastases. As surgical resection is possible in a minority of cases, the importance of adjuvant therapies such as chemotherapy, embolization, and RFA cannot be overemphasized in increasing the chance for resectability. Such aggressive palliative procedures should be performed only by experienced surgeons at high-volume centers in order to minimize perioperative morbidity and mortality. The challenge for cytoreductive therapy in the future is curative resection, emphasizing early detection of metastases with aggressive surgical resection and the formulation of innovative treatment therapies.

**References**