Surgery for Gastroenteropancreatic Neuroendocrine Tumors (GEPNETS)

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The only therapy with the potential for complete cure of patients with gastroenteropancreatic neuroendocrine tumors (GEPNETS) is complete surgical excision.1 Surgical treatment for all patients with abdominal neuroendocrine tumors falls into four major categories: (1) resection of the primary tumor and its regional (nodal) draining basin with curative or palliative intent; (2) resection of regional or distant metastatic disease with cytoreductive intent; (3) resection of disease for palliation without cytoreductive intent (bleeding, obstruction, or perforation); and (4) resection for treatment of lesions associated with multiple endocrine neoplasia (MEN) syndromes.2 These categories often overlap in clinical practice. Because of the usually slow and indolent nature of this disease, patients with GEPNETS may require surgical therapy in more than one or all of these categories during their lifetime. Multimodality treatment options in addition to standard surgical excision now include such things as radiofrequency ablation, chemoembolization, yttrium 90 microsphere embolization, 131-iodine MIBG therapy, numerous clinical trials, and other forms of systemic therapy.2 Because of the availability of multiple treatment options, the sequencing of these therapies and the relationship and timing of operations to these therapies becomes important. These types of management decisions are often best made in specialized centers that have experience with the use of these modalities, their risks and benefits, and the limitations they may impose on subsequent therapies. The maximum benefits of a well-planned longitudinal treatment plan can be exploited with input from multispecialty team

KEYWORDS

- Carcinoid
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- Midgut carcinoid
- MEN
- Asymptomatic primary
members whose focus is primarily the diagnosis and management of patients with neuroendocrine tumors. Several such centers that can offer expert advice counseling and treatment options currently exist around the country.\(^2\)

Surgical options per se are often dictated by the tumor’s site of origin, degree of tumor burden, and overall health or debility of the individual patient. This article considers different options based on the type of tumor and site of origin.

**GASTRIC CARCINOIDs**

Gastric carcinoids are generally thought of as belonging to one of three types. Type I gastric carcinoids arise from the enterochromaffin-like cells of the stomach lining. They develop in response to elevated gastrin levels, such as encountered in patients with autoimmune gastritis and achlorhydria. These patients typically have an elevated gastric pH. Type II gastric carcinoids arise in 23% to 29% of patients with MEN-1 syndrome, hypergastrinemia secondary to the Zollinger-Ellison syndrome gastrinoma.\(^3,4\) Sporadic gastrinomas give rise to Type II gastric carcinoid in only 1% to 3% of cases.\(^3,4\) Gastric pH is usually low. Type III or sporadic gastric carcinoids arise spontaneously in the presence of normal gastric pH and normal gastrinemia.

In Type I, the performance of a gastric pH at the time of endoscopy assists the clinician in determining the type of carcinoid present. A high gastric pH with elevated gastrin levels indicates a Type I tumor. These are usually multiple and small. Endoscopic ultrasound (EUS) helps to determine the thickness and size of the lesions. Transendoscopic excision of a few (<6) small tumors with periodic surveillance is an acceptable form of therapy.\(^5\) Pathologic examination for degree of differentiation, presence of lymphovascular invasion, and completeness of excision helps the surgeon decide if a more aggressive resection is required. Patients who have frequent recurrences or numerous tumors caused by the persistence of elevated gastrin levels should be considered for antrectomy, because this maneuver removes the source of gastrin and is curative in approximately 80% of cases.\(^2\) Residual tumors in the body and cardia of the stomach often resolve after antrectomy. Tumors larger than 3 cm have a higher malignant potential and metastatic rate\(^3,6\) and should be completely excised. These tumors, although often multiple and small, have a potential for hemorrhage and should be removed if feasible. The metastatic rate for gastric carcinoids Type I is approximately 10% to 30%, even though most of the tumors are small in the 1- to 2-cm range.\(^5\) This indicates that close surveillance is required, because the potential for metastasis and lethality exits. Recalcitrant and recurrent lesions should lead one to consider a more aggressive therapy than endoscopic excision alone. Transmural invasion by the tumor seen on EUS is an indication for surgical resection and should not be attempted endoscopically. Frequent repeat endoscopy is usually indicated for both Types I and II in an ongoing surveillance program.\(^5\)

Type III (spontaneous) gastric carcinoids are found in the presence of normal gastrin and normal pH. These tumors have a higher mitotic rate and a higher propensity to metastasize early. They behave more like adenocarcinoma of the stomach, tend to be greater than 2 cm in size at the time of diagnosis, and should not be observed. They should be excised along standard oncologic surgical principles for gastric cancer with total or subtotal gastrectomy and lymph node dissection.\(^5,6\)

**PANCREATIC NEUROENDOCRINE TUMORS**

The most common pancreatic islet cell neuroendocrine tumor is the insulinoma,\(^7,8\) which secretes insulin or, less commonly, proinsulin leading to hypoglycemia. Most
insulinomas are benign (90%) and solitary (90%). They are more commonly small, less than 2 cm, and single. Approximately 10% of insulinomas are malignant.7,8 Long-term survival is good (88% at 10 years)7 with the exception of patients with MEN-1. Insulinomas in these patients have a tendency to recur or metastasize. The only known cure for insulinoma is complete surgical excision. Cure rates approach 100% for non-MEN patients, depending on the stage at presentation and adequacy of resection.2 Improved outcomes and higher cure rates have been consistently reported at dedicated tertiary centers.9 Once the diagnosis is confirmed, the difficulty arises, as with most small pancreatic islet cell tumors, in localizing the lesion preoperatively. For pancreatic head and body tumors, contrast-enhanced EUS with tattooing or marking of the lesion facilitates surgical excision and seems to be a more sensitive method than CT scanning, MRI, or transabdominal ultrasound.7,10–12

The weakness of endoscopic EUS lies in the inability to obtain good visualization of the distal body and tail of the pancreas. Detection rates in this region range from 37% to 60% versus 83% to 100% detection for proximal pancreatic tumors.2,13 Transhepatic selective portal venous sampling and selective arterial calcium stimulation has been shown to be highly effective in localizing tumors to a given region of the pancreas when EUS is nondiagnostic and aids the surgeon in focusing exploration to a particular portion of the pancreas.2 An additional useful tool is intraoperative ultrasound (IOUS) coupled with careful bimanual palpation of the entire gland when preoperative attempts at localization are not precise. By combining IUS with preoperative portal venous sampling and selective arterial calcium injection, detection rates approach 95%.14 Radical blind pancreatic resection has been replaced with pancreas-sparing enucleation, avoiding ductal and vascular structures with the use of IUS. In selective cases, insulinoma enucleation can be accomplished laparoscopically in experienced hands.2,5

RARE FUNCTIONING PANCREATIC NETS

Gastrinomas, non-MEN-1 (VIPomas), glucagonomas, carcinoid tumors, somatostatino- mas, ACTHomas, calcitonin-secreting tumors, and other peptide-secreting tumors are much less common than insulinomas. Unlike insulinomas, however, these tumors are most often malignant, presenting with metastatic disease at the time of diagnosis. Lymph node and liver metastases are also common and attempts at R0 curative resections are recommended whenever possible.2,5 Palliative cytoreduction for hormonal and symptom control is a secondary but worthwhile goal and plays a major role in patient management. Staged resections, radiofrequency ablation, and other cytoreductive therapies may all play a role in the surgical strategy and should be performed in specialized centers as part of an overall treatment regimen.2,5 Surgical debulking can facilitate radionuclide therapy or chemotherapy for symptom control. Staged resections, bilateral adrenalectomies for Cushing syndrome, and liver transplantation in the absence of extrahepatic disease have all been used.5

MULTIPLE ENDOCRINE NEOPLASIA TYPE I

Duodenal and pancreatic NETs in MEN-1 syndrome can present as functioning or nonfunctioning. Fifty-five percent are nonfunctioning.4,5 The two most common functional pancreatic NETs in MEN-1 are gastrinomas (Zollinger-Ellison syndrome) and insulinomas. Both gastrinomas and insulinomas are often multiple. Gastrinomas are often submucosal, occurring in the duodenum or situated in the head of the pancreas. EUS with tattooing is helpful in the preoperative localization for these tumors. The only cure for these tumors is surgical and approximately 50% of the lesions are benign. Duodenal tumors are found by duodenotomy and palpation and can be locally excised
if small. Larger lesions of the duodenum and pancreas, especially those greater than 2 cm, require a more extensive resection and lymph node dissection because malignant potential is greater. An R0 resection is preferred, but recurrences are likely. Total pancreatectomy is controversial and is not routinely recommended.\textsuperscript{5,15} Liver resection for metastatic disease after Whipple resection carries an increased risk of liver abscess and biliary sepsis, but may be required to control hormonal secretion. Debulking may aid in palliation and improve survival.\textsuperscript{3–5} The nonfunctioning pancreatic neuroendocrine tumors are usually malignant. Well-differentiated nonfunctional tumors are more difficult to diagnose at an earlier stage, but palliative, non-R0 resections provide benefit by decreasing local regional complications (pain, bleeding, and obstruction). Only R0 resections have demonstrated survival benefit in non–MEN-1 patients. For MEN-1 patients, lesions larger than 2 cm again have a higher malignancy rate and nonfunctional pancreatic NETs cause up to 20\% of MEN-1–related deaths.\textsuperscript{16} The surgical strategy ranges from enucleation to aggressive resection (subtotal pancreatectomy) as prophylaxis against tumor recurrence. Recurrent lesions can be re-resected in otherwise healthy patients.\textsuperscript{16} Hepatic debulking for metastatic disease should include cholecystectomy to avoid the potential complication of cholecystitis from long-term octreotide therapy and the complication of biliary necrosis from chemoembolization or yttrium 90 microsphere embolization. A 90\% hepatic debulking can lead to 47\% to 65\% 5-year survival\textsuperscript{16,17} versus a 30\% to 40\% 5-year survival for unresected patients.

POORLY DIFFERENTIATED NONFUNCTIONING NETS OF THE FOREGUT (STOMACH, DUODENUM, PANCREAS)

Patients with these rare tumors are candidates for surgery only if R0 resection can be achieved or if their tumor demonstrates responsiveness to systemic therapies. These tumors tend to be fast-growing with high mitotic index and therapy for nonresectable tumors is primarily medical. Partial debulking in surgery for metastatic disease is associated with poorer outcomes\textsuperscript{15,18} and generally not recommended.

MIDGUT CARCINOIDS OF THE JEJUNOILEUM

The only known cure for midgut carcinoids is surgical. Many patients are diagnosed at the time of an operation for some other reason or as a result of an evaluation for chronic gastrointestinal blood loss, obstruction, or as a result of evaluation for metastatic disease.\textsuperscript{6} The findings of a gut-based neuroendocrine tumor should be followed by an in-depth search for additional primary tumors, because these tumors are often small and multiple. They can only be detected by close inspection and palpation in many cases. Laparoscopic resections have the potential for being inadequate because the ability to evaluate the entire small bowel in a tactile manner is negated and carries the risk of incomplete resection. I have encountered several patients in this category and have found as many as 70 tumors along a length of bowel after prior laparoscopic resection for carcinoma.\textsuperscript{2,19} The extent of surgical resection should proceed along sound oncologic principles with excision of the draining nodal basin. Resection of the mesenteric lymph nodes encasing the mesenteric vessels should be undertaken by experienced surgeons familiar with the technique of debulking these metastases to prevent the disastrous complication of intestinal ischemia or infarction, either as a result of tumor progression or as a result of surgical misadventure.\textsuperscript{2,9,20} Approximately 50\% of the patients referred to our center with bulky mesenteric vascular encasement were declared unresectable or were operated elsewhere and could be successfully decompressed.
LYMPHATIC MAPPING

The ileocecal valve can be spared in up to 40% of patients with terminal ileal tumors by using a technique of intraoperative lymphatic mapping. The technique used is similar to that for sentinel node mapping with lymphazurin blue or methylene blue dye. If the lymphatic drainage of the subserosal lymphatics from the tumor closest to the ileocecal valve crosses the ileocecal valve onto the cecum, it is advised to resect the colon and associated draining lymphatic nodal basin along with the distal small bowel. Every effort should be made to save the ileocecal valve in syndromic patients, because they are already challenged with diarrhea as a result of their tumor secretions and may already be at risk for having shortened gut. If the subserosal lymphatics do not cross the ileocecal valve, one can often spare the ileocecal valve and still do an adequate lymph node resection.

Lymphatic mapping may also explain the relationship between the primary tumor and multiple small bowel primary tumors. I have found longitudinal lymphatic spread to extend beyond 20 cm from an individual tumor along the intestinal wall, often in the presence of bulky mesenteric nodal metastases and proximal lymphatic obstruction. This may explain why multiple primary carcinoid tumors in the small bowel have been shown to be of monoclonal origin, perhaps caused by the longitudinal lymphatic intramural spread of drop metastases when central lymphatic drainage roots are occluded by tumor and the desmoplastic reaction. These drop metastases may also explain the phenomenon of local recurrence at or near the previous resection margin. Subserosal lymphatics that are mapped by the blue dye may represent the true resection margin rather than an arbitrary 5-cm margin from the tumor border.

ASYMPTOMATIC PRIMARY TUMOR

An asymptomatic primary tumor is usually not asymptomatic forever and is not a contraindication for operation, even in the presence of distant metastases. On the contrary, by the time the primary tumor in the gut becomes symptomatic, the patient may become a higher risk for surgery as when emergency operations for bleeding, obstruction, or intestinal ischemia are performed in an overall debilitated patient secondary to a chronic carcinoid syndrome and malnutrition. I have found as many as 33% of patients who were referred for progressive carcinoid syndrome with worsening abdominal pain, distention, and episodic diarrhea were actually suffering from occult intestinal obstruction caused by their “unknown primary” in the small bowel. An additional subgroup of patients were suffering from intestinal ischemia caused by progressive desmoplastic reaction, fibrosis, and vascular encasement from bulky mesenteric nodal disease. It was often difficult to sort out their symptomatology from obstruction ischemia versus poorly controlled syndrome.

A delay in resection of an intestinal primary may make later attempts at resection more difficult, if not impossible. Patients with an “unknown primary” and liver and mesenteric metastases had a small bowel tumor found at operation in 50% to 70% of cases. At the time of operation, cholecystectomy is recommended, because many of these patients are on long-term octreotide therapy. Both functioning and nonfunctioning tumors and their metastases can sometimes be found at operation by gamma probe radioguided surgery after injection of 111In-labeled octreotide or 123I-MIBG. I have found this technique of radioguided surgery useful in evaluating the liver, ovaries, pelvis, retroperitoneum, and nodal basins of the head and neck, upper mediastinum, and pelvis. I have also found that waiting 7 days after injection of 111In octreotide facilitated results by allowing the background radiation levels to decay low enough so as not to overwhelm the handheld gamma probe.
APPENDICЕAL AND COLONIC CARCINOIDS

Most appendiceal carcinoids are cured by appendectomy if (1) the tumor is less than 1 cm and located at the tip, (2) the base of resection is not involved by tumor, (3) there is no invasion of the mesoappendix, (3) there is no lymphovascular invasion, and (4) the mitotic index is low. Careful pathologic examination of the specimen is required. If tumor is present at the base, lymphovascular or mesoappendicidal invasion is present, or the mitotic index is high, right hemicolectomy and formal node resection should be undertaken. Cecal and colonic carcinoids behave more like adenocarcinomas and aggressive surgical resection is required with en bloc removal of associated lymph node draining basin. These tumors are often metastatic at the time of diagnosis. A rare variant adenocarcinoid, also called “goblet cell” carcinoma, behaves very aggressively with mucin production and a propensity to metastasize, similar to that for adenocarcinoma. Lymphatic mapping may assist in completeness of regional lymphadenectomy. The mortality for colonic carcinoids and appendiceal carcinoids is directly related to tumor size and the presence or absence of metastases. Tumors larger than 2.5 cm should be considered malignant.

RECTAL CARCINOIDS

Resection of the primary tumor and associated regional lymph nodes is the only curative therapy for rectal and hindgut carcinoids typically associated with the descending colon. Local excision or endoscopic excision of small rectal carcinoids is justified if transrectal ultrasound shows no invasion of the muscularis propria and no pathologic lymph nodes. Pathologic examination should show no lymphovascular invasion and a well-differentiated tumor. Patients treated with local excision require periodic surveillance and repeat EUS. Patients with lymphovascular invasion, invasion through the muscularis propria, or lymph node metastases require low anterior resection and total mesorectal excision. Malignancy is greater when lesions are greater than 2.5 cm or when unfavorable pathology, such as a poorly differentiated lesion, is encountered.

HEPATIC METASTASES

Liver resection for metastatic GEPNETs can be for curative or palliative intent. The most common cause of death in carcinoid patients is liver failure, followed by bowel obstruction or ischemia. Tumor burden, hormonal control, and overall physiologic state of the patient and the presence or absence of options for adjunctive therapies and the ability to control the primary tumor, along with anatomic considerations, all play a role in the surgical strategy for liver resection. Cytoreductive ablative therapies, in addition to surgical resection, can offer improved survival and quality of life exceeding that of nonoperated patients (70%–90% vs 50% at 5 years) in selected series. Patients should not be deemed inoperable until they have been evaluated by an experienced center with a multispecialty team. Sometimes nonsurgical candidates can be rendered operable by adjunctive therapies, such as preoperative yttrium 90 microspheres, chemoembolization, 123I-MIBG therapy, chemotherapy, or other modalities. Conversely, surgical resection may sometimes render these modalities more effective. Proper sequencing of these therapies and operative management is best performed in dedicated tertiary centers.
LIVER TRANSPLANTATION

Liver transplantation for unresectable metastatic GEPNETS is the only acceptable indication for liver replacement for metastatic disease. The current recommendations regarding liver transplantation for patients with metastatic neuroendocrine tumors include the following inclusion criteria: (1) low mitotic index tumors (Ki67 ≤10%), (2) absence of extrahepatic disease, (3) the primary tumor should be drained by the portal venous system, (4) the patient should be stable for at least 6 months during the pretransplant waiting period, (5) generally less than 55 years old, (6) metastatic tumor burden to liver ratio is less than 50%; and (6) no unresectable extrahepatic disease. When these criteria (Milan criteria) are met, the 5-year survival rates exceed 75% and the recurrence rates are as low as 30%. Nonselective series of orthotopic liver transplantation have reported poorer outcomes with 45% survival at 5 years and recurrence rates approaching 75%. Clearly, recipient selection and tumor biology play a role in overall success rates and disease-free survival. In this era of organ shortage, proper recipient selection plays an increasing role in the appropriate use of a scarce resource. Some centers are pursuing the option of living donor liver transplantation to circumvent the scarce donor organ problem. There are additional unanswered questions regarding liver transplantation for metastatic GEPNETS: (1) which tumor type carries the best prognosis for disease-free survival and long-term survival, (2) what is the best immunosuppressive regimen to follow that would minimize the risk of tumor recurrence, and (3) how can the complication rate be reduced with simultaneous en bloc primary tumor resection with multivisceral liver transplantation. Morbidity and mortality are increased when liver transplantation is combined with more aggressive and extensive resections. It is now known that quality of life is definitely increased for syndromic patients who have hypersecretion syndromes after orthotopic liver transplantation.

CARCINOID CRISIS

The prevention of carcinoid crisis and other hypersecretion syndromes can be mitigated by use of continuous-infusion octreotide. It is best used in the preoperative, intraoperative, and postoperative setting and is recommended for any syndromic patient, such as the carcinoid syndrome, undergoing a major surgical procedure. Carcinoid crises can be precipitated by any surgical procedure, but especially during manipulation of the liver when bulky tumor burden is present. Carcinoid crisis can also be caused by physiologic or emotional stress, or even relatively minor procedures, such as biopsy, endoscopy, or bronchoscopy. I currently use a 250- to 500-μg bolus of octreotide followed by a 250- to 500-μg per hour continuous infusion, which is tapered over 4 to 48 hours, depending on the magnitude of the procedure. Epinephrine and other vasopressors worsen rather than correct the hypotension of carcinoid crisis, unless the patient is covered with high-dose octreotide before administration of vasopressor substances. Vasopressors, such as epinephrine, can cause degranulation of the amines containing the tumor cells and can lead to vasomotor collapse. Vasopressors have been used successfully during cardiac valvular procedures in carcinoid syndrome patients under octreotide infusion coverage. Other hypersecretion syndromes may also be ameliorated by continuous octreotide infusion during surgical extirpations. Acute exacerbations of carcinoid crises can be treated with additional 500- to 1000-μg boluses until stabilization occurs. Careful preoperative planning with the anesthesiologist and surgical team is required for successful operations in patients with carcinoid syndrome. Often the operation must be halted until the patient stabilizes, additional octreotide is administered, and blood pressure improves. The operation can then resume under increased octreotide coverage.
SUMMARY

Overall, with the advent of newer and more complex treatment options for patients with GEPNETS, a well thought out treatment plan, sequencing, and explanation of options is best performed in an experienced tertiary center with dedicated multispecialty teams for the care of patients with these rare tumors. The treatment plan can often be performed at home in conjunction with the patient’s local physician, except when specialized skills or equipment are required.

REFERENCES


