GASTRINOMA

Eric Feliberti, MD, FACS, Associate Professor, Surgical Oncology, Eastern Virginia Medical School, Norfolk, VA
Marybeth S. Hughes, MD, FACS, Associate Professor, Chief, Division of Surgical Oncology Eastern Virginia Medical School, Norfolk, VA
Roger R. Perry, MD, FACS, Robert L Payne, Jr. Professor of Surgery, Division of Surgical Oncology, Eastern Virginia Medical School, Norfolk, VA
Aaron I. Vinik, MD, PhD, Murray Waitzer Endowed Chair for Diabetes Research
Professor of Medicine/Pathology/Neurobiology, Director of Research and Neuroendocrine Unit
Division of Endocrine and Metabolic Disorders, Eastern Virginia Medical School, Norfolk, VA
vinikai@evms.edu

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ABSTRACT

Gastrinomas may be benign sporadic, malignant metastatic, and part of MEN-I. They occur in the pancreas, duodenum, jejunum, lymph nodes, mesentery, gallbladder, and ovary. Patients with peptic ulcer disease should have a screening gastrin and if elevated (> 150 pg/ml) undergo a secretin stimulation test (2ug/kg with a rise in gastrin of > 100 pg/ml) to distinguish hypergastrinemia from other causes such as atrophic gastritis, G cell hyperplasia, hypercalcemia, hyperparathyroidism, pernicious anemia and MEN-1. Diagnosis is certain if the gastric acid output is > 15mmol/h, ph is <3. CT, MRI and somatostatin receptor scintigraphy yield the best results for localization. Small tumors require portal venous sampling enhanced by secretin or calcium stimulation for localization. 68Ga-DOTATATE PET, detects 75-85%, 68Ga-DOTANOC PET has a sensitivity of 93.5%. Treatment goals are control of acid hypersecretion with PPIs, resection of the tumor and managing the metastatic disease. MEN-1 requires identification of the tumor producing the gastrin and attention to the pituitary and parathyroid tumors which contribute to the mortality. For malignant metastatic disease the survival can be increased with liver directed therapies, debulking surgery, use of radiofrequency ablation and chemo and bland embolization. Progression free survival (PFS) is increased using somatostatin analog therapy. Peptide receptor radioligand therapy (PRRT) prolongs PFS and enhances quality of life. Second line therapy includes MTOR and Tyrosine kinase inhibitors. Chemotherapy achieves responses in >50%.

INCIDENCE

The gastrinoma syndrome, or Zollinger-Ellison syndrome, has traditionally been associated with a severe, fulminant ulcer diathesis, often with multiple ulcers, and ulcers in unusual locations such as the post-bulbar region of the duodenum and proximal jejunum. However, with increasing recognition of this syndrome, as well as the availability of a radioimmunoassay for serum gastrin, most patients with gastrinoma now present with either milder forms of peptic ulcer disease, or

with secretory diarrhea. The syndrome can exist in multiple forms, including benign sporadic, malignant metastatic, and as part of the MEN-I syndrome. Approximately 66% of gastrinomas are sporadic (2). Sporadic tumors are reported to be malignant in approximately 40-85% of cases. Sporadic gastrinomas occur primarily in the gastrinoma triangle, defined as the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially (1). Although they can occur in the pancreas, the duodenum has been shown to be the most common site of gastrinomas, based on the pioneering work of Debas and colleagues (3), Thompson and colleagues(4), and others. Duodenal wall gastrinomas have been identified in 43-77% of patients (4-6). These duodenal wall tumors are frequently small and multiple. Sporadic tumors occurring in the pancreas tend to be solitary. Primary tumors may also occur in a variety of ectopic sites, including the body of the stomach, jejunum, peripancreatic lymph nodes, splenic hilum, root of the mesentery, omentum, liver, gallbladder, common bile duct, and the ovary (2); (7-13). A recent immunohistochemical study in 20 autopsy patients suggests that primary lymph node gastrinomas are due to entrapment of neuroendocrine cells during development (14). Overall, about 5.6% of patients have a primary gastrinoma located in an ectopic site (15). Another study suggests that up to 10% of sporadic gastrinomas are lymph node primaries (16). Solitary tumors in ectopic sites are less likely to be malignant than solitary tumors in pancreatic sites (13). Although traditionally surgical cure rates have been less than 50%, the increasing recognition of the duodenal wall as the most common location of gastrinoma has resulted in an increasing number of surgical cures.

GASTRINOMAS IN MEN-1

About 33% of gastrinomas are associated with the MEN-I syndrome (17-22). Gastrinomas in MEN-I patients present a variety of unique problems. The tumors are usually multiple, and often small and undetectable (17) (18) (20) (23) (24). Most cases are discovered at a younger age than in sporadic cases. Although these tumors are less frequently (7-12%) malignant, the frequency of malignancy may truly be considerably higher than this. Because of the multiplicity of the tumors and their small size, it is generally quite difficult to find the specific tumor(s) that is/are secreting gastrin. Thus, the likelihood of surgical cure in MEN-I patients is considerably less than in sporadic patients, unless a specific site or sites responsible for the hypergastrinemia has been identified preoperatively.

CLINICAL COURSE

Patients with gastrinoma can present with a number of symptoms and signs related to gastric acid hypersecretion. The majority of patients with sporadic gastrinoma present with abdominal pain related to peptic ulcer disease. Most ulcers are found in the first portion of the duodenum, while 25% are found in the more distal portions of the duodenum or jejunum (25). Peptic ulcers related to gastrinomas are more likely to be refractory to standard medical therapy and to recur. In addition, patients with gastrinoma can present with diarrhea from the volume of gastric acid secretions produced, weight loss and gastrointestinal bleeding.

Gastrinoma can metastasize to a variety of locations, including the lymph nodes and liver. The presence of gastrinoma in peripancreatic lymph nodes is not evidence of incurability (11) (12) (24-27), if the nodes can be completely resected at the time of surgery for the primary tumor.

The search for better prognostic markers continues. In a study of 27 gastrinomas, 12 (44%) had chromosome 1q loss of heterozygosity (LOH). Such LOH was associated with aggressive tumor growth and development of liver metastases (28)(. Other than the initial presence of distant metastases, or the development of disease progression on long-term follow-up, it has been difficult to establish whether a particular gastrinoma is malignant. A recent study examined 21 consecutive patients with neuroendocrine pancreatic tumors. Of the different biological markers examined, increased levels of topoisomerase II alpha had a 88% sensitivity, and 100% specificity for predicting malignancy (29).

DIAGNOSIS

Prior to the development of the radioimmunoassay for serum gastrin, 80% of gastrinoma patients presented with a severe ulcer diathesis, bleeding, obstruction, or perforation. Two thirds of patients had at least one operation. Currently, only 20% of patients present with severe ulcer complications, and only one third have had prior surgery (30). H. pylori infection is not a risk factor for peptic ulceration in patients with gastrinoma (31). In a study of 84 gastrinoma patients, the prevalence of H. pylori exposure was only 23%, 10% with active infection (31), less than the general population. The possibility of gastrinoma should be considered in all patients with peptic ulcer disease, and those with unexplained secretory diarrhea. All such patients should undergo measurement of fasting serum gastrin levels. An aggressive testing policy has been shown to be cost effective.

Diagnosis of gastrinoma syndrome depends on the demonstration of: 1) elevated serum gastrin levels; 2) a positive secretin stimulation test; and 3) gastric acid hypersecretion. Hypergastrinemia in the absence of increased acid production is not due to gastrinoma. It is vital to stop H2 blockers, proton pump inhibitors, and octreotide at least 24 hours before performing these tests for gastrinoma. (Assay is available at Inter Science Institute-800-255-2873).

NCCN guidelines suggest that gastrin levels should be measured while fasting and off proton pump inhibitors for 1 week (32). It should be noted that most clinical chemistry laboratories have switched to commercial kits. However, the accuracy of many of these kits has been brought into question. A recent study of 40 patients suspected or known to have ZES found that 7 of 12 tested commercial kits inaccurately measured plasma concentrations of gastrin, with 4 kits finding false low concentrations and 3 kits finding false high concentrations. This can result in misdiagnosis or delay in diagnosis of patients with gastrinoma (33).

Serum gastrin levels are usually greater than 150 pg/ml in patients with the gastrinoma syndrome. The exception is a small fraction of patients who secrete a biologically active variant not recognized by the antiserum used for the assay (34). A careful history and physical is

required, as gastrin levels may be elevated for a variety of other reasons (table 1). Measurement of gastric pH is also useful, because in the absence of anti-secretory drugs, a pH of 3.0 or higher excludes Zollinger-Ellison Syndrome.

Table 1. Causes of Hypergastrinemia

With increased acid	With decreased acid
MEN-1 = Multiple endocrine neoplasia type 1; ZE = Zollinger-Ellison	
Gastrinoma	Atrophic gastritis
G-cell hyperfunction	Pernicious anemia
Gastric outlet obstruction	Vagotomy
Short bowel syndrome	Gastric carcinoma
With increased acid	With decreased acid
Retained antrum	Renal disease
Hypercalcemia	Rheumatoid arthritis
Hyperparathyroidism	Vitiligo
MEN-1	Diabetic pseudo ZE syndrome

Establishment of the presence of gastric acid hypersecretion should include measurements of volume as well as basal and pentagastrin-stimulated acid secretion. The diagnosis is confirmed if: a) the volume of gastric secretion is large, typically greater than 10 liters per 24 hours; b) the basal acid output is over 15 mmol/h. Values in the 10-15 range are borderline, and less than 10 mmol/h exclude diagnosis of Zollinger-Ellison Syndrome. In patients who have previously undergone vagotomy, basal acid output in gastrinoma is over 3 mmol/h; c) the ratio of basal acid output to maximal pentagastrin stimulated acid output is greater than 0.6.

The most accurate and sensitive test remains the Secretin Stimulation test for gastrin secretion. No new test has emerged with a greater sensitivity or specificity. Secretin, 2 mcg/kg is given intravenously, and blood samples for gastrin are drawn at 2, 5, 10, 20, and 30 minutes. A rise of more than 100 pg/ml is strongly suggestive of Zollinger-Ellison Syndrome. False positive results are rare, and are usually found in hypochlorhydric states (35).

Mention must be made of the G-cell (gastrin cell) hyperplasia syndrome, which can be sometimes confused with the gastrinoma syndrome. Patients with G-cell hyperplasia typically have an equivocal response to secretin stimulation, and an exaggerated response to food ingestion, thus distinguishing them from patients with gastrinoma (24).

The possibly of gastrinoma should be considered in all patients with Multiple Endocrine Neoplasia type I, since 50-60% of such patients will develop gastrinoma. Patients with hyperparathyroidism should also be screened for gastrinoma, since up to 38% of patients will be found to have gastrinoma (19) (36) (37).

LOCALIZATION

Tumor localization is important in gastrinoma patients, as it may have a direct bearing on patient management. A variety of non-invasive and invasive techniques have been used, with varying levels of success (see table 2). Non-invasive techniques include ultrasound, CT scan, MRI, and most recently somatostatin receptor scintigraphy. Transabdominal ultrasound (2) and CT (38) have proven to be of limited value, as these tumors are frequently small and below the resolution of the techniques. In addition, the density of these tumors is similar to that of surrounding pancreatic tissue, making them difficult to detect. MRI has not been shown to be superior to the previous techniques (39) (40). Perhaps the greatest value of CT scan is that it identifies most patients with liver metastases.

Some have advocated endoscopic ultrasound. In experienced hands, localization rates of 80-100% in patients with pancreatic gastrinomas have been reported (41) (42). However, the ability to detect small lesions less than 5 millimeters in size, or occult duodenal lesions, is uncertain. The pancreatic head is examined with the scanner positioned in the duodenum, and the body and tail of the pancreas are studied with the scanner in the stomach. Some have used a special saline filled balloon at the tip of the instrument with installation of approximately 400 cc of saline into the stomach to provide an interface between the ultrasonic unit and the stomach wall (41) (42).

Table 2. Methods of Tumor Localization in Gastrinoma

								PTHVS
Factor	Ultrasound	Infusional CT	Computed Tomography	SRS	Selective angiography	Secretin angiography	Local	Regional
Sensitivity	21	40	31	71	60, 29	89	35	94
Specificity	92	100	66	86	100, 100	100	89	97
Positive predictive value	80	100	83	85	100, 100	---	---	94
Negative predictive value	44	50	15	52	60, 100	---	89	---

PTHVS = percutaneous transhepatic portal, pancreatic, and hepatic venous gastrin sampling. Data from Norton and colleagues, \(43) (44), as well as Vinik and colleagues, (39) (40) {Dunnick, 1980 13028 /id

The development of somatostatin receptor scintigraphy has been an important advance in the imaging of pancreatic neuroendocrine tumors, and specifically gastrinoma. Somatostatin receptor scintigraphy should be obtained in all patients with a diagnosis of gastrinoma. The results with this technique approach those obtained with more invasive localization methods (see table 2). A recent study of 146 patients by Gibril and colleagues from the National Institutes of Health using 111 Indium-pentetreotide revealed a sensitivity of 71%, specificity of 86%, and a

positive predictive value of 85%, higher than any other non-invasive modality {Gibril, 1999 10247 /id}. Somatostatin receptor scintigraphy altered management in 47% of patients overall. Like most imaging modalities, somatostatin receptor scintigraphy tends to miss small duodenal tumors less than 1cm in diameter (45). False positives do occur in about 10% of patients, thus the clinical context must be considered and the results interpreted carefully. Newer radiolabeled tracers have been developed that have a higher affinity to somatostatin receptors. One test using these newer tracers, 68Ga-DOTATATE PET, was able to detect 168 of the 226 lesions (74.3%) that were identified with cross-sectional imaging and identified significantly more lesions than 111In-DTPA-octreotide scintigraphy (45). More recently, 68Ga-DOTANOC PET has shown promising results with higher detection rates of neuroendocrine tumors. In a prospective study of 18 patients with neuroendocrine tumors, 68Ga-DOTANOC PET was found to have an improved lesion-based sensitivity 93.5%, compared with 85.5% for 68Ga-DOTATATE PET (46) (47). Our current approach is to combine somatostatin receptor scintigraphy, along with either CT scan or MRI, to provide anatomic information and to help exclude liver metastases. this is consistent with current NCCN guidelines, where measurement of gastrin levels, and multiphasic CT or MRI are recommended. Somatostatin receptor scintigraphy , EUS, and Chromogranin A measurements are done “as appropriate” (32).

With the advent of somatostatin receptor scintigraphy, there is currently less need for the use of invasive techniques. The invasive techniques are highly accurate, however they involve discomfort, considerable expense, and require the expertise of an experienced angiographer. Selective visceral angiography has been shown to be useful for localizing tumors in patients with gastrinoma, as well as identify occult metastatic disease (3). The addition of intra-arterial injection of secretin to selective angiography greatly improves the accuracy of the technique (39). This requires the insertion of a catheter in a hepatic vein and a peripheral vein to sample gastrin levels. When secretin is injected into a vessel that supplies the gastrinoma, the hepatic vein levels of gastrin greatly exceed the peripheral levels. It may also increase the number of patients who show a tumor blush on angiography. This technique may be more accurate than percutaneous transhepatic venous sampling (PTHVS) alone (39).

Percutaneous transhepatic venous sampling (PTHVS) is a highly accurate technique, however it is both costly and time consuming (34). This technique has been shown to be of value in those with a primary gastrinoma not detected by conventional imaging methods (40,48-51). It has clearly been shown that PTHVS is a useful method to regionalize a tumor. However, the success of this technique is highly operator dependent, and requires a detailed understanding of the variable venous anatomy present in the region (24) (50) (51). A variety of technical issues, including placement of cannulae to avoid vessel obstruction, and streaming of portal blood flow, can affect the results of the study. Because of potentially rapid changes in the secretory rate of gastrinomas, it is important to simultaneously measure gastrin in pancreatic veins and central arteries, to determine gradients.

For the first time, a staging system has been developed for pancreatic and neuroendocrine tumors by the American Joint Committee on Cancer (AJCC). (AJCC 7th edition). This staging system has been derived from that for exocrine pancreatic carcinomas. A recent study of 425

patients with pancreatic NETS, comparing histopathologic grade, the ENETS classification, and AJCC classification, found that both the AJCC classification and ENETS classification were highly prognostic for survival (52).

TREATMENT

The goals of treatment of gastrinoma include: 1) management of the gastric acid hypersecretion; 2) resection of what are commonly malignant tumors with the risk of distant spread, and 3.) management of metastatic disease.

Treatment has undergone significant changes since the syndrome was originally described in 1955 (13). Most patients underwent emergency surgery for complications such as massive hemorrhage or perforation. Total gastrectomy became the standard operation for patients with gastrinoma (2) (11) (12) (17). Although this operation was effective in controlling the end result of acid hypersecretion, many patients went on to suffer morbidity and mortality from the tumor itself (2).

The development of potent antisecretory drugs has changed the management of patients with Gastrinoma (17) (53) (54) (55). In most patients gastric acid hypersecretion can be controlled with long-term omeprazole or other proton pump inhibitors and surgery for the control of gastric acid hypersecretion is no longer required. An initial prospective study of 40 patients with gastrinoma found that omeprazole reduces basal acid output and maximal acid output with once daily dosing and resolved peptic symptoms in 23 of 29 patients who had symptoms while on histamine H2-receptor antagonist therapy (17) (53) (54) (55). Because current antisecretory agents are so effective, surgery for the control of gastric acid hypersecretion is no longer required. A subsequent study of 212 patients from the National Institute of Health at a mean follow-up of nearly 14 years showed that none of the patients suffered an acid related death (56). Overall, 31% of patients died, one half due to the gastrinoma itself. The major morbidity of gastrinoma has shifted from peptic diathesis to metastatic disease (56).

Patients on long-term omeprazole can develop gastric carcinoid tumors. In addition, significant decreases in serum vitamin B12 have been observed (2) (57). Thus vitamin B12 levels should be monitored in these patients.

SURGERY

Thus, the current role of surgery is to identify and remove the responsible tumor or tumors, to prevent tumor progression and ultimately death. In early surgical series, the cure rate was relatively modest, ranging from 15-30% (12) (20) (37) (58) (59) (60) (61). Those with extra-pancreatic tumors were noted to have a cure rate as high as 50% with surgical excision (2) (11) (12) (62). With improvements in preoperative imaging studies, the increasing recognition of the duodenum as a site for gastrinoma, and an aggressive surgical approach, the number of positive explorations has increased in one group from 64% to over 90%, primarily through the

identification and resection of duodenal wall gastrinomas (6) (63). Even after successful resection, many patients do recur with long-term follow-up. In a study of 151 patients by Norton and colleagues, in patients with sporadic gastrinoma the 10 year disease free survival was 34%, and the disease specific survival was 95% (63).

Surgery for gastrinoma includes meticulous technique and a thorough exploration. The lesser sac is widely opened, and the entire pancreas is mobilized throughout its length. This allows for careful bimanual palpation of the gland. Although many of the lesions are palpable, some are quite deeply located in the gland, and may not feel dissimilar to the adjacent normal pancreatic parenchyma. Intraoperative ultrasound has been shown by a number of investigators to be useful, and should be performed in any patient undergoing exploration for gastrinoma. Intraoperative ultrasound is useful in identifying difficult to palpate and non-palpable lesions. It is also may detect signs suggestive of malignancy, as well as the relationship of the tumor to the main pancreatic duct and major blood vessels (64) (65). Intraoperative ultrasound is not particularly useful in identifying duodenal wall gastrinomas, however. Intraoperative endoscopy with transillumination of the duodenum is capable of locating duodenal wall gastrinomas (66). However it is not useful in identifying the more than 50% of duodenal wall gastrinomas located along the medial wall. The most accurate method of detecting duodenal wall gastrinomas remains duodenotomy with careful palpation, a technique employed by experienced teams during surgical exploration for gastrinoma (4) (6). Duodenotomy has been shown to increase the gastrinoma detection rate to 98% compared to 76% without duodenotomy, as well as the short term cure rate (65% vs. 44%), and long term cure rate (52% vs. 26%) (67). Because primary duodenal gastrinomas are associated with lymph node metastases in 60% of patients, a more aggressive lymphadenectomy has been recommended (68).

Major vascular involvement is not a contraindication to attempt at resection. A recent study of 273 patients showed 46 (17%) had evidence of major vascular involvement on pre-operative imaging. Forty-two of these 46 patients underwent successful resection (69).

Despite improvement of surgical techniques, and despite higher identification rates of gastrinoma at the initial operation, many or most patients with gastrinoma will suffer from persistent or recurrent disease in long term follow up. In a study of 151 patients with sporadic gastrinoma the 10-year disease free survival was 34% (56). The time to recurrence is 181 months in those patients treated with radical resection (63). Similarly, a study utilizing the US population SEER database found that patients with gastrinomas have a median survival of 10.2 years (67). The management of such patients with recurrent or persistent ZES remains controversial. However, it has been shown that excellent long term survival and biochemical cure can be obtained in selected patients who undergo re-operation for ZES (68).

The use of endoscopic and/or laparoscopic approaches for the management of neuroendocrine tumors including gastrinomas has been recorded in small numbers of patients (70) (71) (72) (73). However, the role for such an approach in gastrinoma patients appears to be limited for a variety of technical issues including the multiciplicity of lesions, the small size of duodenal tumors, the frequent presence of lymph node metastases, and the presence of critical structures

in the usual gastrinoma location in the pancreatic head region. These difficulties tend to favor an open surgical approach (67).

Not surprisingly, the laparoscopic approach to gastrinoma is associated with a higher conversion rate to an open procedure. The use of endoscopic techniques would also appear to be fairly limited, for similar reasons. There have been occasional reports of patients who underwent endoscopic removal of gastrinoma. Duodenal gastrinomas tend to occur in a submucosal location, making removal or banding of these lesions more difficult. Also, since up to 60% of gastrinomas can be associated with lymph node metastases, endoscopic treatment of the duodenal gastrinoma alone would result in incomplete removal of disease (74).

The treatment of the patient with MEN-I and gastrinoma remains controversial (17) (21) (75). Few data are available on patients with MEN-I syndrome and gastrinomas who have undergone careful preoperative evaluation followed by possible palliative or curative surgery. Therefore, a definitive statement about optimal management in these patients cannot be made at the present time, and treatment should be individualized. If a clear-cut source of the hypergastrinemia can be identified using functional and anatomic studies, then surgical exploration, with enucleation or resection, should be strongly considered. Such an approach may offer excellent palliation, if not cure. Other groups take an even more aggressive posture (See MEN-1 Section). The malignant potential of these lesions should also be taken into account. Patients with tumors more than 3cm in size should be considered for resection, even in the absence of clear-cut function. The relatively low incidence of malignancy in gastrinoma patients with MEN-I compared to those without MEN-I does not mean that a more cavalier approach can be taken in these patients. Traditionally gastrinoma in patients with MEN-I has been associated with a better prognosis than in patients with sporadic gastrinoma. However, a recent European study of 758 symptomatic MEN-I patients showed that most deaths were related to MEN-I.Thymic tumors, duodenal pancreatic tumors and gastrinoma increased the risk of death compared to non-affected patients with a hazard ratio of 1.89 (76).

In addition to the indications for resection in MEN-I patients with gastrinoma, the extent of the resection in MEN-I also remains controversial. A multi-national European group of 27 patients suggest that partial pancreatectomy is superior to enucleation resulting in a higher rate of biochemical cure (77). However another group which studied 20 patients suggests that is not the extent of the pancreatic resection, but rather a formal duodenal evaluation and anatomic regional lymphadenectomy which are the important factors for achieving biochemical cure and long term eugastrinemia (78).

SURGERY FOR ADVANCED DISEASE

Because of the poor outcome of patients with advanced and metastatic gastrinomas, and the overall disappointing results with systemic therapy, a number of groups have advocated a very aggressive management approach Several single institutional studies have reported on hepatic resection for curative treatment of metastatic neuroendocrine tumors (75) (76) (77) (78,79). In these studies adjunct measures including radiofrequency ablation were utilized in addition to

resection to treat all lesions for cure and concomitant resection of the primary tumor was also feasible. The long-term results were notable with reported 5- year survival rates ranging from 61% to 82% and median survival of 96 to 115 months, with a perioperative mortality of 0 to 1.2%. Few patients were cured, though, with a recurrence rate as high as 84%. These studies are, however, are from single institutions and selection criteria were non-random and unclear. A multi-institutional cohort study of 339 patients with neuroendocrine hepatic metastases from 8 hepatobiliary centers reported a median survival of 125 months with an associated disease recurrence of 94% at 5 years (80). Patients with hormonally functional tumors who had R0/R1 resection benefited the most from surgery.

Several groups have compared outcomes of an aggressive surgical approach to other treatment modalities. A study of 60 patients with neuroendocrine liver metastases compared patients with medical ("non-aggressive") treatment, resection/ablation, and chemoembolization +/- resection/ablation (76). Median survival increased significantly from 20 months to greater than 96 months and 50 months respectively, and 5-year survival from 25% to 72% and 50%, respectively, favoring a role for surgical therapy. A multi-institutional study of 753 patients with neuroendocrine hepatic metastases compared surgical therapy to intra-arterial therapy (81). The surgical cohort had less hormonally active tumors (28% vs. 48%) and had less hepatic tumor involvement (liver tumor burden >25%: 52% vs 76%). Median and 5-year survival of patients treated with surgery was significantly prolonged to 123 months and 74% compared to 34 months and 30%, respectively, for IAT. A propensity analysis found that surgery was associated with superior outcomes in patients with a low (<25 percent) hepatic disease burden, and in those who were symptomatic and with >25 percent hepatic tumor involvement. On the contrary, one study from a European center found no difference in outcome in patients with neuroendocrine liver metastases treated with surgery/RFA versus nonoperative therapy with a 5 year disease specific survival of 74% and 78% (82).

The role of liver transplantation in these patients remains controversial. An analysis of the UNOS database showed that of 87,280 liver transplantations performed, 150 were done for patients with liver metastasis from neuroendocrine tumors. This group included 11 (7.3%) with gastrinoma. Overall survival rates were similar to those who underwent transplantation for hepatocellular carcinoma, thus the study concluded that excellent results can be obtained in a highly selected patients with liver metastasis from neuroendrocrine tumors (83).

Thus, the literature would suggest that there appears to be some benefit to an aggressive approach in selected patients with advanced and metastatic gastrinoma. However, the selection criteria are unclear, most of the studies are small and non-randomized, and it is a bit difficult to determine if there is a survival benefit.

SYSTEMIC CHEMOTHERAPY

There is little experience with the use of adjuvant chemotherapy following surgical resection. The small number of patients treated, the relatively indolent nature of these tumors, and the short follow-up times are insufficient to recommend adjuvant chemotherapy outside of clinical trials.

However, it may be appropriate to consider adjuvant chemotherapy in selected patients felt to be at high risk of subsequent recurrence, understanding that there is little data to show benefit with this approach.

The activity of chemotherapy in patients with metastatic gastrinomas is difficult to determine since most published series have studied chemotherapy for all histologic types of pancreatic endocrine tumors grouped together. In addition, the growth rate of metastatic gastrinoma varies markedly (84), further complicating assessment of response to therapy. Systemic therapy for metastatic disease depends on the extent of disease and the presence of any symptoms. Due to the relative indolent growth that can be seen in neuroendocrine tumors, individuals with low volume disease and who are asymptomatic can be observed and take part in a surveillance strategy. Those with symptoms are typically treated with somatostatin analogs as first line therapy to manage symptoms and control tumor growth. Octreotide has been the most commonly used somatostatin analog and has been found to decrease baseline gastrin levels by 76% and decrease basal acid output and peak acid output by 68% in patients with gastrinoma (84) (85). In addition to having an effect on gastric acid hypersecretion, somatostatin analogs have been shown in a number of prospective trials to have an effect on tumor growth. These trials have included non-functional and functional neuroendocrine tumors with only a minor number of patients with gastrinoma. Both octreotide (30 mg monthly) and lanreotide (120mg monthly) have been found in prospective trials to prolong progression-free survival compared to placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors (86) (87). A small study of 15 patients with progressive hepatic metastases from gastrinoma showed a partial response rate of 6% (one patient), and stabilization in 47% with long acting octreotide (88) (89) (90).

Second line therapy available for patients with neuroendocrine tumors refractory to somatostatin therapy includes mTOR inhibitors. Everolimus used alone or in combination has been studied in a series of prospective trials in patients with metastatic gastroentero pancreatic neuroendocrine tumors (91) Yao 2011 (92) Pavel 2011 (93) (94). Monotherapy with everolimus (10 mg daily) has been shown to increase progression-free survival to 11 months compared to 3-4 months, while combination therapy with octreotide LAR showed a borderline significant prolongation of progression-free survival from 11 months to 16 months.

Other systemic therapy options for patients with metastatic gastrinoma include tyrosine kinase inhibitors, newer somatostatin analogs and cytotoxic chemotherapy. The tyrosine kinase inhibitor sunitinib (37.5 mg daily) was compared with placebo in a phase III trial of 171 patients with progressing pancreatic NET, of which 19 had gastrinoma (95). Median progression-free survival (PFS) was significantly longer with sunitinib (11.4 versus 5.5 months). Pasireotide (60 mg monthly), a somatostatin analog with a higher affinity to the somatostatin receptor 5, has been shown in patients refractory to first-generation somatostatin analogues to prolong progression-free survival over octreotide from 6.8 months to 11.8 months, but is associated with higher adverse events of hyperglycemia, fatigue and nausea (96). Systemic therapy with cytotoxic agents have included streptozotocin and temozolomide. Streptozotocin has been the most active single agent in patients with metastatic gastrinoma, with objective response rates

reported in up to 50% of patients (97). There is no evidence that the addition of 5-FU with or without doxorubicin improves the outcome compared to streptozotocin alone (98) (99). Differences in the doses used, the schedules of administration, and the criteria used to assess tumor responses, make firm management recommendations difficult. A more recent study in 79 patients from Britain studied the combination 5-FU, cis-platinum, and streptozocin for metastatic or locally advanced neuroendocrine tumors of a variety of sites. The overall response rate was 33% (38% for pancreatic primary sites, and 25% for non-pancreatic primary sites), stable disease 51%, and progression in 16%. Thus, overall results are not superior to streptozocin alone (100). More recently, temozolomide with capecitabine has been studied as first line therapy in patients with metastatic well to moderately differentiated pancreatic neuroendocrine tumors. This combination showed an objective response rate of 70% and an associated progression-free survival of 18 months (101).

LIVER DIRECTED THERAPY

Liver directed therapies including chemoembolization, radioembolization, bland embolization, and percutaneous radiofrequency ablation continue to play a role in the management of neuroendrocrine tumors metastatic to the liver, including metastatic gastrinomas. Indeed, with the multiple therapies available, it is recommended that a multi-disciplinary treatment team be involved in management decisions. Radioembolization with Yttrium-90 has also shown to be effective, and may be even better tolerated than chemoembolization (102). The early results of radioembolization with resin 90 Y-microspheres in liver metastases from a variety of neuroendocrine tumors has been encouraging, with early responses noted to be 22.7% stable, partial response 60.5%, complete response 2.7%, and progressive disease in 4.9%. In general transarterial chemoembolization (TACE) has been shown to be a relatively safe procedure, with improvements in symptom control, time to progression, and survival (103). In one of the largest reports of 81 patients undergoing embolization or chemoembolization for carcinoid tumor, the median response duration was 17 months, and progression-free survival (PFS) rates at one, two, and three years were 75, 35, and 11 percent (104). Radioembolization may have advantages over chemoembolization because it causes fewer side-effects and requires fewer treatments. Based on current European Neuroendocrine Tumor Society Consensus Guidelines, radioembolization can be substituted in patients with either liver-only disease or those with limited extrahepatic metastases.

An elegant option to treat metastatic neuroendocrine tumors is peptide receptor radioligand therapy, taking advantage of the high affinity of somatostatin analogs to deliver radiation. A study of 16 patients with disseminated neuroendocrine tumors examined the efficacy of high activity (111) In-pentetreotide. There was minimal toxicity, and at six months there were two complete responses, and three partial responses. Disease progression was 30% at six months, and 69% at eighteen months (105). Other small studies have shown similar results. A study of 14 patients with disseminated neuroendrocrine tumors, who were treated, with indium in-111 octreotide therapy resulted in stable disease in 50 % of the patients, partial response in 14%, and disease progression in 36%, including the 1 gastrinoma patient (106). Peptide receptor radioligand therapy (PRRT) was studied in 11 gastrinoma patients with progressive disease.

Symptomatic improvement was noted in all patients with complete response in 1, partial response in 5, and stabilization in 5 (107). A quality of life study in 13 such patients, also including 1 with gastrinoma, showed marked improvements in quality of life (108). The response rate to peptide receptor radioligand therapy may be predicted by Ga – DOTATOC study pretreatment (104). A prospective trial using peptide receptor radioligand therapy randomized patients with midgut NET that had progressed on first line somatostatin therapy to lutetium 177-Dotatate 7.4 GBq q 8 weeks plus best supportive care including octreotide versus octreotide alone (109). Preliminary results have been published reporting a progression-free survival at 20 month of 65.2% compared to 10.8% in control group with a response rate of 18% vs 3%. For further information on this topic, readers are encouraged to review the ENETS consensus guidelines (110).

FOLLOW-UP

Follow up of patients with gastrinoma has traditionally depended upon use of biochemical studies such as fasting serum gastrin levels, and imaging studies such as computed tomography and somatostatin receptor scintigraphy. A study of 72 consecutive gastrinoma patients revealed that serum chromogrannin A and gastrin are not sufficiently sensitive to replace serial imaging studies to detect changes in tumor burden (111). The specificity varied from 53% to 99% for chromogranin A and from 49% to 93% for gastrin, depending on whether the tumor size had increased, decreased or no change. An annual surveillance strategy utilizing CT or MRI of the abdomen, octreoscan, fasting serum gastrin, secretin stimulation gastrin level and gastric acid output has been used by Norton et colleagues (112). Per recently published NCCN guidelines (32) a follow up strategy has been recommended for neuroendocrine tumors. In general, at 3 to 12 month intervals post-resection, the guidelines recommend history and physical examination, and “consider” appropriate markers as indicated, as well as multi-phasic CT or MRI. At more than 1 year post-resection a similar strategy is recommended every 6 to 12 months thereafter.

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