Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)

AUTHOR: Emily Bergsland, MD
SECTION EDITOR: Mark Feldman, MD, MACP, AGAF, FACG
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **May 31, 2022.**

INTRODUCTION

Patients with Zollinger-Ellison syndrome (ZES) have gastrin-secreting tumors and the associated clinical consequences. This disorder can occur sporadically, or as a manifestation of multiple endocrine neoplasia type 1 (MEN 1). Medical therapy is the current standard of care for most patients with ZES as part of the MEN 1 syndrome. By contrast, many patients with sporadic ZES are candidates for surgical therapy. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Multiple endocrine neoplasia type 1: Management" and 'Surgery' below.)

Prior to the development of effective acid suppression therapy, the major morbidity and mortality of ZES were related to complications of fulminant peptic ulcer disease; total gastrectomy was the only effective measure to protect patients from these problems [1].

The development of H2 antagonists and the more powerful proton pump inhibitors has resulted in a significant decrease in morbidity and mortality from ulcer disease and has obviated the need for gastrectomy [2]. Of 212 patients with ZES studied prospectively for a mean of 13.8 years, a ZES-related cause of death could be identified in only one-half of the 31 percent who died. All of the ZES-related deaths were due to tumor spread; none were due to hypersecretory complications [3].

This topic review will discuss the two current goals of therapy in ZES [4]:

- Control of the complications resulting from autonomous release of gastrin
- Control of the tumor itself

MEDICAL MANAGEMENT

The goal of medical management in Zollinger-Ellison syndrome (ZES) is to limit the clinical manifestations and complications of peptic ulcer disease. Because peptic symptoms in patients with ZES are often a poor marker of acid secretion, formal acid secretory studies have been advocated to guide the dosage of acid suppressants, with the goal of reducing gastric acid secretion to below 10 mEq/h prior to the next dose [5]. However, such studies are often not available even in major medical centers, and it has become customary among many gastroenterologists to initiate and maintain proton pump inhibitors at high dosage, using symptoms alone as a signal to increase the dose. To the author's knowledge, there have been few if any episodes of major peptic diathesis associated with this approach.

Proton pump inhibitors — Proton pump inhibitors (eg, omeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, and esomeprazole) effectively block acid secretion by irreversibly binding to and inhibiting the hydrogen/potassium ATPase that resides on the luminal surface of the parietal cell. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders".)

Their effects last for more than 24 hours; as a result, many patients can be treated with a once a day regimen [5].

Patients with ZES should be started on a high dose of a PPI (eg, omeprazole 40 mg twice daily, pantoprazole 80 mg twice daily) [4,6,7]. PPIs have been generally safe, even when used in high doses. Some patients require an early upward titration of these doses; however, once control of acid output has been achieved, a gradual dose reduction is usually possible [8]. In a study of 37 patients who had received high-dose omeprazole for almost two years, nearly 50 percent were able to titrate the maintenance dose down to 20 mg daily [9]. Overall, 95 percent of patients without MEN 1, severe gastroesophageal reflux, or previous partial gastrectomy had safe reductions in their medication dose. PPIs are generally well tolerated and can control hypergastrinemia in ZES for >10 years (although some patients experience low vitamin B12 levels) [10,11]. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects'.)

When PPIs are unable to control gastric acid secretion, somatostatin analogs such as octreotide and lanreotide can inhibit secretion of gastrin [12,13]. However, due to the unpredictability of

the response and requirement for parenteral administration, they are not first-line agents for symptomatic patients with hypergastrinemia.

SURGERY

Patients with a sporadic gastrinoma who do not have evidence of metastatic spread of disease should be offered exploratory laparotomy and resection with curative intent, even in the event of negative imaging studies in approximately 17 percent of patients [1,4,14,15]. This recommendation stems from the fact that 60 to 90 percent of gastrinomas are malignant and, in addition to eliminating (or at least decreasing) the need for antisecretory medical therapy, successful resection of sporadic gastrinomas protects against the possibility of eventual morbidity and death from metastatic spread of the tumor (see below). In the hands of an experienced surgeon, up to 50 percent of these patients will be cured [14,16]. Lymphadenectomy exceeding more than 10 lymph nodes at the time of surgery has been shown to achieve a higher biochemical cure as compared with selective or no lymphadenectomy [17,18]. The number of positive lymph nodes (or lymph node ratio) appears to have prognostic significance in gastrinoma and other panNETs. Recognizing the potential for cure in patients undergoing complete tumor removal (particularly with modern imaging tools and our ability to control acid hypersecretion throughout the perioperative period), the merits (and risks) of surgery need to be considered in the context of the life expectancy and co-morbidities of each patient [10].

The likelihood for surgical cure is especially high for extrapancreatic gastrinomas (eg, those in the duodenum or peripancreatic lymph nodes). In contrast, laparotomy is not routinely recommended for patients with Zollinger-Ellison syndrome (ZES) as part of MEN 1 since the multifocal nature of the tumors in this disorder almost uniformly precludes cure of gastrin hypersecretion [4,16]. (See "Multiple endocrine neoplasia type 1: Management".) However, because a minority of MEN-1 tumors can have aggressive growth patterns, some recommend imaging techniques or even surgical exploration to identify those exceeding 2 cm with the intent of resecting them. Of note, while not routine, some groups have taken a more aggressive approach in MEN1 patients with gastrinomas, pursuing surgical resection based on localization with the selective arterial secretagogue injection test to achieve a biochemical cure [19].

Eighty percent of curable gastrinomas lie within the gastrinoma triangle comprised of the head of the pancreas and the duodenal sweep. Sporadic gastrinomas are often solitary and >2 cm and located in the pancreas; tumors arising in the setting of MEN 1 most commonly arise in the duodenum and are typically small (<2 cm) and multiple [20]. The combination of preoperative localization techniques makes it possible for the experienced surgeon to identify over 90

percent of sporadic gastrinomas [4,21]. Intraoperative transduodenal illumination and duodenotomy are of particular value in detecting very small gastrinomas arising in the wall of the duodenum [15,22]. Enucleation is preferred when feasible, but local resection is often required for pancreatic head lesions and a distal pancreatectomy may be necessary for large tail lesions [10]. Whipple resections are not routine in ZES, but are reserved for pancreatic head or duodenal lesions that cannot be removed by enucleation. In such cases, the potential benefits, including improved lymph node retrieval, need to be weighed against the risks of complications from the Whipple procedure. In the unlikely event that a sporadic gastrinoma cannot be identified at surgery, we suggest deferring a Whipple's procedure in favor of closure, with the intent of serial imaging every six months to try to localize the neoplasm [23]. Laparoscopic surgery is controversial in ZES compared with other panNETs, owing to the need for more extensive exploration and lymphadenectomy in sporadic tumors. A minimally invasive approach may be reasonable, however, in the setting of a pancreatic tail gastrinoma occurring in the setting of MEN1 [10]. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms".)

Gastric secretion may not return to the normal range following gastrinoma resection because of a residual excess of gastric parietal cells, a consequence of the trophic effect of chronically elevated gastrin levels. Up to 40 percent of patients will require prolonged antisecretory therapy to control hyperacidity following curative resection, and such patients need continued monitoring for acid hypersecretion [24,25]. Of 50 patients who underwent curative resection for ZES, gastric hypersecretion was observed for a mean of eight years in 62 percent of patients and was judged to be extreme in 28 percent despite normal blood gastrin levels [26].

A parietal cell (proximal gastric) vagotomy performed at the time of tumor resection has been advocated to reduce (and in some cases obviate) the need for postoperative medical therapy, particularly when complete resection of the gastrinoma tissue cannot be accomplished [24,27]. However, it is currently uncommonly performed because of the efficacy of proton pump inhibitors. Furthermore, relatively few surgeons currently perform this procedure.

The reduction in mortality associated with surgical therapy for patients without metastatic disease was illustrated in a prospective study of 124 patients with gastrinoma presumed to be free of metastasis by imaging studies [28]. Only 3 percent of the 98 patients who underwent resection developed liver metastases during a mean follow-up period of 6.3 years [28]. By contrast, 23 percent of 26 patients treated medically developed metastatic disease over a slightly longer follow-up period (8.7 years). Two deaths due to metastatic gastrinoma occurred in the medically treated group compared with no disease-specific deaths in the operative group.

Reoperation for recurrence — Although surgery decreases the incidence of hepatic metastases and improves survival, long-term biochemical cure is achieved in less than 30 percent. Reoperation may be of benefit in those with recurrent ZES in whom the tumor can be identified and localized. In one study, for example, 17 patients with recurrent disease that was unequivocally imaged underwent 18 reoperations [29]. Five patients were disease free after operation, with a median follow-up of 28 months. There were no deaths in the cured group; two patients in the group with persistent disease died during a median follow-up of 34 months [30].

RADIATION THERAPY FOR NONSURGICAL CANDIDATES

Experience with external beam radiotherapy (RT) in the management of gastrinomas is limited. Although pancreatic neuroendocrine tumors were previously considered to represent a radioresistant neoplasm, data from published case reports and small case series suggest that RT can produce high rates of symptomatic palliation and freedom from local progression in patients who are not candidates for surgical resection [31-37].

THERAPY OF METASTATIC DISEASE

The liver is the major metastatic site for gastrinomas, as it is with other islet cell tumors. The second most common site is bone (7 percent of patients in one series), almost all of which occur in patients who also have liver metastases [38]. The axial skeleton (spine or sacrum) is the primary site of bone metastasis, but other sites can be involved [38]. Historically, somatostatin receptor scintigraphy and MRI have been thought to be the best imaging modalities to detect these lesions; the former being preferred because extra-axial lesions can occur. Because of its greater sensitivity, 68-Ga DOTATATE PET/CT may be preferable to conventional somatostatin receptor scintigraphy, if available [39,40].

Metastatic gastrinoma is now the most common cause of morbidity and mortality in patients with Zollinger-Ellison syndrome (ZES). Unfortunately, current treatment modalities are of limited benefit. A general algorithmic approach to therapy for patients with metastatic disease is outlined in the figure (algorithm 1).

Somatostatin analogs — Somatostatin analogs like octreotide and lanreotide are highly effective in controlling the symptoms associated with hormone hypersecretion in other pancreatic islet cell tumors that express somatostatin receptors such as glucagonomas and VIPomas, as well as carcinoid tumors; its efficacy is less predictable for gastrinomas [41-43]. Octreotide can reduce gastrin levels, and may slow tumor growth, but objective evidence of

antitumor activity is rare [43-46]. As an example, in a report of 15 patients treated with octreotide for malignant gastrinoma and progressive hepatic metastases, seven had stabilization of tumor growth, and one an objective decrease in tumor size [46]. The median duration of benefit was 25 months. In the United States, octreotide is approved for control of hormone-mediated symptoms in patients with neuroendocrine tumors.

Lanreotide appears to have similar clinical efficacy as octreotide, and is also available in a long-acting depot form (Lanreotide-SR) [41,47]. It is approved for use in the United States based on the results of the randomized phase III CLARINET study showing a statistically significant improvement in progression-free survival in patients with nonfunctional gastroenteropancreatic neuroendocrine tumors treated with lanreotide compared to those treated with placebo [48]. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Benefits'.)

Liver-directed therapy

Resection — Hepatic resection is indicated for the treatment of metastatic liver disease in the absence of diffuse bilobar involvement, compromised liver function, or extensive extrahepatic metastases (eg, pulmonary, peritoneal). Although the majority of cases will not be cured by surgery, prolonged survival is often possible, given the slow-growing nature of these tumors [49,50].

In general, resection should be considered only for patients with a limited number of hepatic metastases and is most successful when undertaken with curative intent. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Surgical resection'.)

Hepatic artery embolization — Liver metastases derive most of their blood supply from the hepatic artery, whereas healthy hepatocytes derive approximately 70 percent of their blood supply from the portal vein. This provides the rationale for therapeutic embolization of the hepatic artery, with the goal of inducing necrosis of the metastases with minimal damage to normal liver parenchyma.

Hepatic arterial embolization with or without selective hepatic artery infusion of chemotherapy is frequently applied as a palliative technique in patients with symptomatic hepatic metastases who are not candidates for surgical resection [51-54]. Response rates, as measured by a decrease in hormonal secretion or by radiographic regression, are generally over 50 percent. Randomized trials have not yet been performed, thus it is not known with certainty if one type of embolization is preferable to another. Radioembolization with selective internal radiation

therapy using Yttrium microspheres is also used, although prospective studies comparing one type of embolization with another have not been completed [54]. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Hepatic arterial embolization'.)

RFA and cryoablation — Other approaches to the treatment of hepatic-predominant disease include radiofrequency ablation (RFA) and cryoablation, either alone or in conjunction with surgical debulking [55-57]. These procedures, which can be performed using percutaneous or laparoscopic approaches, appear to be less morbid than either hepatic resection or hepatic artery embolization. However, both techniques are applicable only to smaller lesions, and their long-term efficacy is uncertain. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Ablation'.)

Liver transplantation — The number of patients with liver-isolated metastatic disease in whom orthotopic liver transplantation (OLT) has been attempted is small, and follow-up data are insufficient to judge whether complete cure has truly been achieved. The limited availability of donor organs in many regions has restricted investigation of this procedure.

Until more data become available, most clinicians consider that liver transplantation is an investigational approach for metastatic islet cell tumors, including gastrinoma. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Liver transplantation'.)

Chemotherapy and novel treatment approaches — Experience with systemic chemotherapy for metastatic gastrinoma is limited. The traditional regimen of choice has been streptozocin and doxorubicin. Although objective response rates as high as 69 percent were initially reported for metastatic neuroendocrine tumors, [58] with decreases in endocrine hyperfunction, the true radiologic response rate is probably between 10 and 40 percent [59,60]. Uncertainty as to efficacy, as well as the toxicity of this regimen, which can include nausea, prolonged myelosuppression, and renal failure, has prevented its widespread acceptance as a standard first-line therapy for patients with metastatic neuroendocrine tumors, including gastrinoma.

Antitumor activity has also been shown for regimens containing the orally active alkylating agent temozolomide. A retrospective review of 143 patients treated with capecitabine plus temozolomide reported that 54 percent of patients experienced a radiographic response to therapy [61]. Response to chemotherapy was not influenced by O(6)-methylguanine DNA methyltransferase expression, proliferative activity, or ALT pathway activation. More recently, the results from a prospective randomized study (ECOG2211) of capecitabine plus

temozolomide compared with temozolomide alone in pancreatic neuroendocrine tumors revealed similar response rates in both arms (approximately 30 percent), but the median progression-free survival was longer in the combination arm (22.7 months versus 14.4 months, HR 0.58, p=0.023) [62]. As a result of this study, use of capecitabine plus temozolomide has become routine for advanced panNET. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Cytotoxic chemotherapy'.)

The modest efficacy of conventional cytotoxic chemotherapy has prompted the development of novel therapeutic approaches for patients with advanced pancreatic neuroendocrine tumors. These include molecularly targeted therapy with inhibitors of the mechanistic target of rapamycin (mTOR), small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors, and lutetium Lu177 dotatate peptide receptor radioligand therapy [63-67]. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Molecularly targeted therapy' and "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Peptide receptor radioligand therapy'.)

PROGNOSIS

Mortality from gastrinomas largely depends upon whether the tumor is benign or malignant, and the extent of disease involvement. In an illustrative series, 185 patients with Zollinger-Ellison syndrome (ZES) were followed prospectively for a mean of 12.5 years [68]. The following results were noted:

- Liver metastases were found in 24 percent of patients at the time of diagnosis; the majority of these patients had a primary pancreatic neoplasm, and 67 percent had primary tumors that were greater than 3 cm in size.
- Patients with liver metastases had a 10-year survival of only 30 percent compared with a 15-year survival of 83 percent in those without liver metastases.
- Patients with lymph node metastases had the same mortality as those who were free of visceral metastases.
- Patients with MEN 1 had a significantly lower rate of metastasis at the time of initial diagnosis (6 percent); their high overall survival rate (100 percent at 20 years) reflected this fact.

The level of fasting serum gastrin (FSG) at the time of initial diagnosis may provide an indication of disease extent and estimated prognosis in patients with sporadic ZES. In a follow-up report of 239 patients with ZES, the level of preoperative FSG correlated with tumor size and presence of lymph nodes and liver metastases (as found at exploration), as well as primary site (pancreas tumors associated with highest levels of FSG) [69]. The five-year survival rates for patients with mild (0 to 499 pg/mL), moderate (500 to 1000 pg/mL), or severe elevations (>1000 pg/mL) of FSG were 94, 92, and 86 percent, respectively. The corresponding 10-year survival rates were 86, 87, and 73 percent.

POSTTREATMENT SURVEILLANCE

There is limited evidence from which to make recommendations for follow-up after resection of a gastrinoma. Guidelines from the National Comprehensive Cancer Network based upon expert consensus include the following recommendations for follow-up after resection of pancreatic neuroendocrine tumor [70]:

- 3 to 12 months postresection – History and physical examination, serum gastrin, and abdominal multiphasic computed tomography or magnetic resonance imaging and chest CT (+/- contrast) as clinically indicated.
- Long-term – History and physical examination with tumor markers every 6 to 12 months for a maximum of ten years. Imaging studies with abdominal multiphasic computed tomography or magnetic resonance imaging and chest CT (+/- contrast) as clinically indicated.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Well-differentiated gastroenteropancreatic neuroendocrine tumors".)

SUMMARY AND RECOMMENDATIONS

- Medical therapy is the current standard of care for most patients with Zollinger-Ellison syndrome (ZES) as part of the MEN 1 syndrome. (See "Multiple endocrine neoplasia type 1: Management".) By contrast, we recommend that (in addition to medical therapy) patients with a sporadic gastrinoma and without evidence of metastatic spread of disease be

treated with exploratory laparotomy and resection with curative intent (**Grade 1B**). In addition to eliminating or at least decreasing the need for antisecretory medical therapy, successful resection of sporadic gastrinomas reduces the risk of eventual morbidity and death from metastatic spread of the tumor. (See 'Medical management' above.)

- The goal of medical management in ZES is to limit the clinical manifestations and complications of peptic ulcer disease. We recommend that patients with ZES should be started on a high dose proton pump inhibitor (eg, omeprazole 40 mg twice daily) (**Grade 1B**). Subsequent lowering of dosage without recurrence of symptoms is usually achievable. (See 'Medical management' above.)

- Mortality from gastrinomas depends largely upon whether the tumor is benign or malignant, and the extent of disease involvement. Metastatic gastrinoma is the most common cause of morbidity and mortality in patients with ZES. Unfortunately, the current modalities for treatment of metastatic disease are not curative. (See 'Prognosis' above.)

- For patients with limited, resectable liver-isolated metastatic gastrinoma, we recommend surgical resection of the hepatic metastases along with the primary tumor (**Grade 1B**). Although the majority of cases will not be cured by surgery, given the slow-growing nature of the tumor, extended survival is sometimes possible. (See 'Resection' above.)

- Other treatment options for patients with unresectable hepatic-predominant metastatic disease include bland embolization, chemoembolization, selective internal radiation therapy (radioembolization), RFA, and cryoablation. (See 'Liver-directed therapy' above.)

- The efficacy of somatostatin analogs for patients with symptomatic metastatic gastrinoma is unpredictable, but some patients with somatostatin receptor-positive tumors may benefit. (See 'Somatostatin analogs' above.)

- Other systemic therapy approaches (chemotherapy, molecularly targeted agents, and peptide receptor radioligand therapy) to control symptoms and tumor growth are discussed in detail elsewhere. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion".)

ACKNOWLEDGMENT

The UpToDate editorial staff thank Dr. Stephen E. Goldfinger, MD, for his contributions as author to prior versions of this topic review.

REFERENCES

1. Meko JB, Norton JA. Management of patients with Zollinger-Ellison syndrome. Annu Rev Med 1995; 46:395.
2. Quatrini M, Castoldi L, Rossi G, et al. A follow-up study of patients with Zollinger-Ellison syndrome in the period 1966-2002: effects of surgical and medical treatments on long-term survival. J Clin Gastroenterol 2005; 39:376.
3. Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. J Clin Oncol 1999; 17:615.
4. Jensen RT, Fraker DL. Zollinger-Ellison syndrome. Advances in treatment of gastric hypersecretion and the gastrinoma. JAMA 1994; 271:1429.
5. Metz DC, Pisegna JR, Fishbeyn VA, et al. Control of gastric acid hypersecretion in the management of patients with Zollinger-Ellison syndrome. World J Surg 1993; 17:468.
6. Hirschowitz BI, Simmons J, Mohnen J. Clinical outcome using lansoprazole in acid hypersecretors with and without Zollinger-Ellison syndrome: a 13-year prospective study. Clin Gastroenterol Hepatol 2005; 3:39.
7. Metz DC, Comer GM, Soffer E, et al. Three-year oral pantoprazole administration is effective for patients with Zollinger-Ellison syndrome and other hypersecretory conditions. Aliment Pharmacol Ther 2006; 23:437.
8. Maton PN, Vinayek R, Frucht H, et al. Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. Gastroenterology 1989; 97:827.
9. Metz DC, Pisegna JR, Fishbeyn VA, et al. Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high. Gastroenterology 1992; 103:1498.
10. Norton JA, Foster DS, Ito T, Jensen RT. Gastrinomas: Medical or Surgical Treatment. Endocrinol Metab Clin North Am 2018; 47:577.
11. Venkat PG, Longstreth GF. Gastroesophageal Reflux Disease and the Zollinger-Ellison Syndrome. Am J Gastroenterol 2022; 117:1012.
12. Aerts M, Reynaert H. Disease Control on Lanreotide Autogel® 120 mg in a Patient with Metastatic Gastrinoma: A Case Report. Case Rep Gastroenterol 2017; 11:616.
13. Daniels LM, Khalili M, Morano WF, et al. Case report: optimal tumor cytoreduction and octreotide with durable disease control in a patient with MEN-1 and Zollinger-Ellison

syndrome-over a decade of follow-up. World J Surg Oncol 2019; 17:213.

14. Norton JA, Fraker DL, Alexander HR, et al. Surgery increases survival in patients with gastrinoma. Ann Surg 2006; 244:410.
15. Norton JA, Fraker DL, Alexander HR, Jensen RT. Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. Ann Surg 2012; 256:509.
16. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999; 341:635.
17. Bartsch DK, Waldmann J, Fendrich V, et al. Impact of lymphadenectomy on survival after surgery for sporadic gastrinoma. Br J Surg 2012; 99:1234.
18. Giovinazzo F, Butturini G, Monsellato D, et al. Lymph nodes metastasis and recurrences justify an aggressive treatment of gastrinoma. Updates Surg 2013; 65:19.
19. Imamura M, Komoto I, Ota S, et al. Biochemically curative surgery for gastrinoma in multiple endocrine neoplasia type 1 patients. World J Gastroenterol 2011; 17:1343.
20. Epelboym I, Mazeh H. Zollinger-Ellison syndrome: classical considerations and current controversies. Oncologist 2014; 19:44.
21. Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol 2005; 19:799.
22. Norton JA, Doppman JL, Jensen RT. Curative resection in Zollinger-Ellison syndrome. Results of a 10-year prospective study. Ann Surg 1992; 215:8.
23. Máthé Z, Tagkalos E, Paul A, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation 2011; 91:575.
24. Jensen RT. Should the 1996 citation for Zollinger-Ellison syndrome read: "Acid-reducing surgery in, aggressive resection out"? Am J Gastroenterol 1996; 91:1067.
25. Pisegna JR, Norton JA, Slimak GG, et al. Effects of curative gastrinoma resection on gastric secretory function and antisecretory drug requirement in the Zollinger-Ellison syndrome. Gastroenterology 1992; 102:767.
26. Ojeaburu JV, Ito T, Crafa P, et al. Mechanism of acid hypersecretion post curative gastrinoma resection. Dig Dis Sci 2011; 56:139.
27. McArthur KE, Richardson CT, Barnett CC, et al. Laparotomy and proximal gastric vagotomy in Zollinger-Ellison syndrome: results of a 16-year prospective study. Am J Gastroenterol 1996; 91:1104.
28. Fraker DL, Norton JA, Alexander HR, et al. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann Surg 1994; 220:320.

29. Jaskowiak NT, Fraker DL, Alexander HR, et al. Is reoperation for gastrinoma excision indicated in Zollinger-Ellison syndrome? Surgery 1996; 120:1055.
30. Grobmyer SR, Vogel SB, McGuigan JE, et al. Reoperative surgery in sporadic Zollinger-Ellison Syndrome: longterm results. J Am Coll Surg 2009; 208:718.
31. Contessa JN, Griffith KA, Wolff E, et al. Radiotherapy for pancreatic neuroendocrine tumors. Int J Radiat Oncol Biol Phys 2009; 75:1196.
32. Strosberg J, Hoffe S, Gardner N, et al. Effective treatment of locally advanced endocrine tumors of the pancreas with chemoradiotherapy. Neuroendocrinology 2007; 85:216.
33. Tennvall J, Ljungberg O, Ahrén B, et al. Radiotherapy for unresectable endocrine pancreatic carcinomas. Eur J Surg Oncol 1992; 18:73.
34. Torrisi JR, Treat J, Zeman R, Dritschilo A. Radiotherapy in the management of pancreatic islet cell tumors. Cancer 1987; 60:1226.
35. Gery B, Roussel A, Valla A. Usefulness of radiotherapy in the treatment of advanced gastrinomas. Radiother Oncol 1993; 27:259.
36. Lee J, Choi J, Choi C, Seong J. Role of radiotherapy for pancreatobiliary neuroendocrine tumors. Radiat Oncol J 2013; 31:125.
37. Saif MW, Ove R, Ng J, Russo S. Radiotherapy in the management of pancreatic neuroendocrine tumors (PNET): experience at three institutions. Anticancer Res 2013; 33:2175.
38. Gibril F, Doppman JL, Reynolds JC, et al. Bone metastases in patients with gastrinomas: a prospective study of bone scanning, somatostatin receptor scanning, and magnetic resonance image in their detection, frequency, location, and effect of their detection on management. J Clin Oncol 1998; 16:1040.
39. Deppen SA, Liu E, Blume JD, et al. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. J Nucl Med 2016; 57:708.
40. Sadowski SM, Neychev V, Millo C, et al. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. J Clin Oncol 2016; 34:588.
41. Tomassetti P, Migliori M, Gullo L. Slow-release lanreotide treatment in endocrine gastrointestinal tumors. Am J Gastroenterol 1998; 93:1468.
42. Eriksson B, Renstrup J, Imam H, Oberg K. High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. Ann Oncol 1997; 8:1041.

43. Guarnotta V, Martini C, Davì MV, et al. The Zollinger-Ellison syndrome: is there a role for somatostatin analogues in the treatment of the gastrinoma? Endocrine 2018; 60:15.
44. Saijo F, Naito H, Funayama Y, et al. Octreotide in control of multiple liver metastases from gastrinoma. J Gastroenterol 2003; 38:905.
45. Shojamanesh H, Gibril F, Louie A, et al. Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. Cancer 2002; 94:331.
46. Burgess JR, Greenaway TM, Parameswaran V, Shepherd JJ. Octreotide improves biochemical, radiologic, and symptomatic indices of gastroenteropancreatic neoplasia in patients with multiple endocrine neoplasia type 1 (MEN-1). Implications for an integrated model of MEN-1 tumorigenesis. Cancer 1999; 86:2154.
47. Gaztambide S, Vazquez JA. Short- and long-term effect of a long-acting somatostatin analogue, lanreotide (SR-L) on metastatic gastrinoma. J Endocrinol Invest 1999; 22:144.
48. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014; 371:224.
49. Zhang XF, Beal EW, Weiss M, et al. Timing of disease occurrence and hepatic resection on long-term outcome of patients with neuroendocrine liver metastasis. J Surg Oncol 2018; 117:171.
50. Spolverato G, Bagante F, Aldrighetti L, et al. Neuroendocrine Liver Metastasis: Prognostic Implications of Primary Tumor Site on Patients Undergoing Curative Intent Liver Surgery. J Gastrointest Surg 2017; 21:2039.
51. Chen JX, Rose S, White SB, et al. Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival. Cardiovasc Intervent Radiol 2017; 40:69.
52. Pericleous M, Caplin ME, Tsochatzis E, et al. Hepatic artery embolization in advanced neuroendocrine tumors: Efficacy and long-term outcomes. Asia Pac J Clin Oncol 2016; 12:61.
53. Havens SJ, Hruby PM, Margalit E. Listeria monocytogenes panophthalmitis: a novel strain follows a virulent course. Retin Cases Brief Rep 2013; 7:409.
54. de Mestier L, Zappa M, Hentic O, et al. Liver transarterial embolizations in metastatic neuroendocrine tumors. Rev Endocr Metab Disord 2017; 18:459.
55. Deol ZK, Frezza E, DeJong S, Pickleman J. Solitary hepatic gastrinoma treated with laparoscopic radiofrequency ablation. JSLS 2003; 7:285.

56. Fairweather M, Swanson R, Wang J, et al. Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database. Ann Surg Oncol 2017; 24:2319.
57. Grandhi MS, Lafaro KJ, Pawlik TM. Role of Locoregional and Systemic Approaches for the Treatment of Patients with Metastatic Neuroendocrine Tumors. J Gastrointest Surg 2015; 19:2273.
58. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980; 303:1189.
59. Prakash L, Bhosale P, Cloyd J, et al. Role of Fluorouracil, Doxorubicin, and Streptozocin Therapy in the Preoperative Treatment of Localized Pancreatic Neuroendocrine Tumors. J Gastrointest Surg 2017; 21:155.
60. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22:4762.
61. Cives M, Ghayouri M, Morse B, et al. Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. Endocr Relat Cancer 2016; 23:759.
62. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). Journal of Clinical Oncology 2018; 36:4004.
63. Leimer M, Kurtaran A, Smith-Jones P, et al. Response to treatment with yttrium 90-DOTA-lanreotide of a patient with metastatic gastrinoma. J Nucl Med 1998; 39:2090.
64. Grozinsky-Glasberg S, Barak D, Fraenkel M, et al. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. Cancer 2011; 117:1377.
65. Brabander T, Van der Zwan WA, Teunissen JJ, et al. Long-term efficacy, survival and safety of [177Lu-DOTA0,Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res 2017.
66. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:514.
67. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:501.

68. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. Gastroenterology 1995; 108:1637.

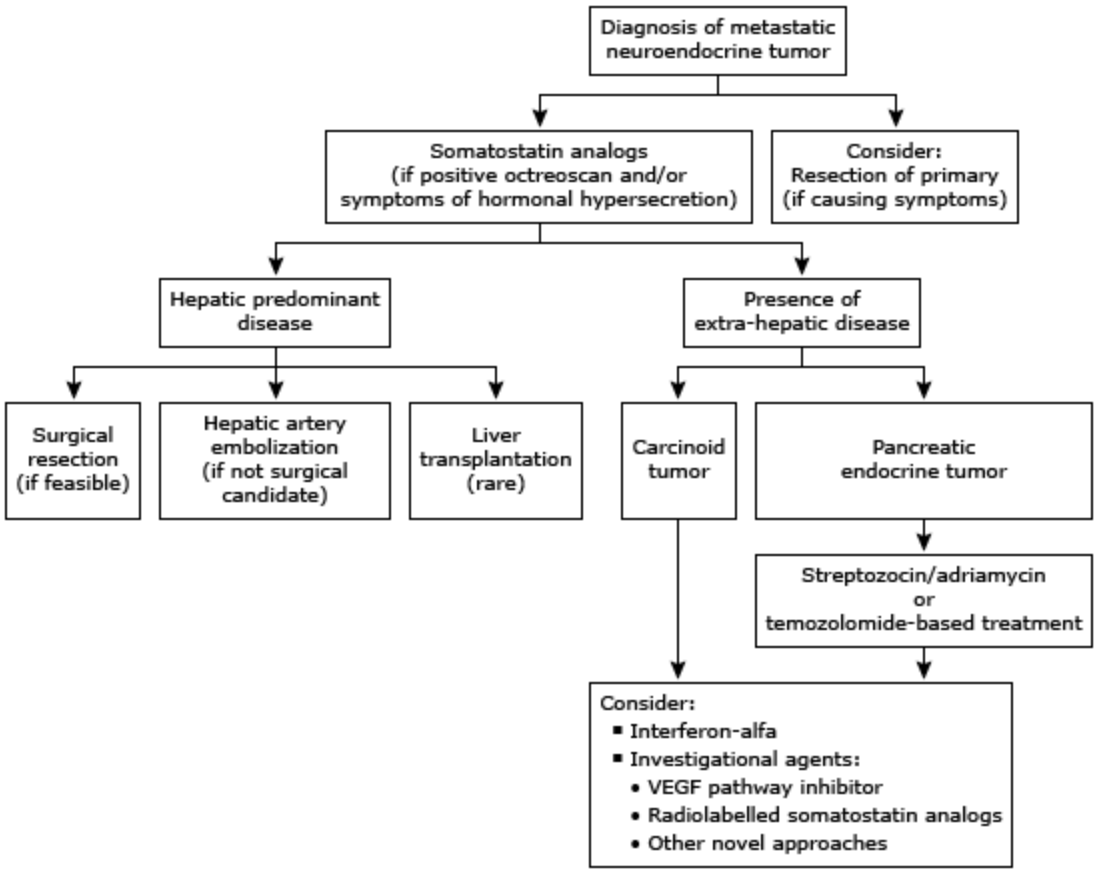
69. Berger AC, Gibril F, Venzon DJ, et al. Prognostic value of initial fasting serum gastrin levels in patients with Zollinger-Ellison syndrome. J Clin Oncol 2001; 19:3051.

70. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/default.aspx (Accessed on May 22, 2020).

Topic 2584 Version 24.0

GRAPHICS

Algorithm for treatment of metastatic neuroendocrine tumors



VEGF: vascular endothelial growth factor.

Graphic 79461 Version 4.0

Contributor Disclosures

Emily Bergsland, MD Grant/Research/Clinical Trial Support: Merck [Carcinoid/pNET]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→