
Surgical treatment and prognosis of gastrinoma

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Zollinger–Ellison syndrome (ZES) is a clinical syndrome with severe peptic ulcer disease and diarrhea caused by gastric acid hypersecretion secondary to a neuroendocrine tumour that secretes excessive amounts of the hormone gastrin (gastrinoma). Gastrinomas occur in a familial and a sporadic form. Patients with gastrinoma in the familial setting of Multiple Endocrine Neoplasia type I (MEN-I) are seldom, if ever, cured of Zollinger–Ellison syndrome by the current non-Whipple operations to remove duodenal and pancreatic gastrinoma. Surgery is currently used in these patients to deal with the malignant nature of pancreatic or duodenal neuroendocrine tumours. Malignant potential is best determined by tumour size. Tumours that are greater than 2 cm in size should be excised. In the sporadic setting, cure occurs in a significant proportion of patients (50%) by surgical resection of gastrinoma. Duodenotomy has improved both the tumour detection rate and the cure rate and should be routinely done. Whipple pancreaticoduodenectomy results in the highest probability of cure in both sporadic and MEN-I gastrinoma patients as it removes the entire gastrinoma triangle. However, the excellent long-term survival of these patients with lesser operations and the increased operative mortality and long-term morbidity of Whipple make its current role unclear until further studies are done.

Key words: gastrinoma; Zollinger–Ellison syndrome; multiple endocrine neoplasia type I; sporadic; surgery; cure; duodenotomy; whipple pancreaticoduodenectomy.

Zollinger–Ellison syndrome (ZES) is a clinical syndrome of severe peptic ulcer disease and diarrhea caused by a gastrin-producing tumour (gastrinoma). Gastrinomas were originally described as pancreatic neuroendocrine tumours and now it is realized that they are most commonly within the wall of the duodenum. Initially surgery for Zollinger–Ellison syndrome was designed to control the severe peptic ulcer disease. Total gastrectomy was required because lesser procedures resulted in recurrent symptoms. During these initial operations in patients with ZES frequently tumour was not identified which further supported the use of total gastrectomy. However, since proton pump inhibitors have been utilized to control the acid hypersecretion in all patients with ZES without failure or complications, total gastrectomy is no longer

indicated and surgery now focuses on removal of the gastrinoma for potential cure of ZES. Cure is described as normal fasting serum level of gastrin, negative secretin test, and no tumour on imaging studies including computed tomography (CT) and somatostatin receptor scintigraphy (SRS). Recently studies have shown that duodenal gastrinomas are much more common than pancreatic tumours. Most of the tumours that had been missed at previous operations are now found in the wall of the duodenum. At surgery methods have focused on finding small tumours in the duodenum. As more tumours are found, the cure rate has increased. However, cure rate is also dependent on whether or not ZES occurs in a sporadic form or a familial form (Multiple Endocrine Neoplasia type I, MEN-I). Gastrinoma is the most common functional pancreatic neuroendocrine tumour in MEN-I. This paper focuses on the surgical cure rate in MEN-I and sporadic patients with ZES, the role of pancreatic surgery in MEN-I patients, and the role of Whipple pancreaticoduodenectomy in ZES.

SURGICAL CURE RATE IN MEN-I GASTRINOMA

Since 1990 it is appreciated that the majority of gastrinomas in patients with MEN-I and ZES arise in the duodenum.¹⁻⁴ Prior to 1990 this lack of knowledge of the location of the primary gastrinoma may have contributed to the low cure rate^{1,5-10} and the controversy about routine surgical exploration for cure.¹ However, more recent studies with intense exploration of the duodenum including duodenotomy have demonstrated that without pancreaticoduodenectomy the surgical cure rate in MEN-I patients with gastrinoma is still very low 0-10 and 25% when all reported series are clumped together (Table I).¹¹⁻¹⁵

Some investigators^{3,16,17} have reported cures. However, these studies are flawed because they did not include a negative secretin test and normal fasting gastrin levels measured postoperatively. Further, in most of these studies the follow-up was short. Late recurrences can occur and have been reported.^{18,19} It has been shown that the secretin test is the most sensitive method to detect recurrence.¹⁸ It will diagnose recurrent or persistent gastrinoma before tumours are seen on imaging examinations. Since gastrinomas in MEN-I are usually in the gastrinoma triangle that includes the head of the pancreas and the duodenum, some advocate the use of more radical procedures like Whipple pancreaticoduodenectomy for cure or improved survival. This approach is more controversial and will be discussed in detail, subsequently.

Table I. Cure rates for gastrinoma dependent on operation and setting.

Group	Reference	N	# Cure-rate (%)
MEN-I/ZES without duodenectomy	21	242	31 (25)
Whipple	21	82	56 (68)
Standard-operation sporadic	11	123	49 (40)
Standard-operation MEN-I	32	81	0 (0)
Duodenotomy plus lymph node sampling	29	94	47 (50)

SURGICAL CURE RATE IN SPORADIC GASTRINOMA

There has been disagreement on the cure rate in patients with sporadic gastrinoma who undergo surgical resection of tumour.¹ Most studies had small numbers of patients and follow-up was short and incomplete.^{1,20} In 1999 we published a prospective study that involved 123 sporadic gastrinoma patients who had surgical resection of tumour and were assessed for 8 ± 4 years postoperatively. Ninety-three percent of patients had gastrinoma found, including each of the last 81 consecutive cases. The immediate postoperative cure rate was 60, 40% at 5 years, and 34% at 10 years.¹¹ These results, coupled with no operative mortality and low morbidity (< 15%) with surgery,¹² strongly supported routine surgical exploration and excision of gastrinoma. The surgery was both safe and produced long-term cures in some patients.²¹ We believe that these results establish this operation as the surgery of choice for sporadic patients with ZES (Table 1).

SURGERY IN PATIENTS WITH GASTRINOMA AND MEN-I

Since with the current surgical approach, cure of ZES in patients with MEN-I is either zero or seldom (Table 1). Whether routine surgical exploration should be performed in a patient with ZES and MEN-I is controversial. Surgery may reduce the malignant spread of tumour and increase survival,^{11,17,22-30} however, that has not been convincingly demonstrated. Nevertheless, some recommend routine surgical exploration to decrease the probability of malignant spread.^{17,31} The proposed operation includes distal pancreatectomy-splenectomy, intra-operative ultrasound and enucleation of tumours in the pancreatic head, duodenotomy and excision of duodenal wall tumours, and systematic removal of lymph nodes around the pancreas, along the celiac trunk and hepatic ligament.¹⁷ In contrast, other groups recommend that surgical exploration be reserved for patients with an imageable tumour 2–3 cm.¹¹ Further, there is disagreement about which surgical procedure should be performed, especially the role of distal pancreatectomy.²²

This lack of consensus has occurred for a number of reasons. First, a controlled study has not been done to determine the exact timing and role of surgery. Second, these patients have excellent long-term survival without surgery and, even with metastatic disease, they have a 15-year survival of 52%.³² Therefore, even long-term studies are unlikely to resolve current treatment strategies. Finally, the history of patients with MEN-I/ZES in the current era of medical management of the acid hypersecretion and satisfactory treatment of the parathyroid and pituitary disease is largely unknown.³³ Even when patients die of metastatic neuroendocrine tumours,³⁴⁻³⁷ it is unclear if it is the gastrinoma, another neuroendocrine tumour, or even a thymic,³⁸ or gastric carcinoid.³⁹ However, recent results suggest that progression of the gastrinoma and/or other neuroendocrine tumours is probably the most important determinant of long-term survival.^{35,40} These findings support the role for surgery in select patients with a potentially malignant neuroendocrine tumour. Size is the most important determinant of a malignant tumour, as approximately 25–40% of pancreatic neuroendocrine tumours greater than 4 cm can have liver metastases. Secondly, a recent study indicated that 23% of the pancreatic neuroendocrine tumours in MEN-I patients had aggressive growth and hepatic metastases.⁴¹ Further, one third of patients with aggressive tumours die from tumour, which was much greater than

patients with non-aggressive tumours. These observations suggest that surgery is indicated in MEN-1 patients with large identifiable tumours. Third, when these patients were explored with imageable tumours of 2–3 cm, the majority (50–70%) had lymph node involvement, but not liver metastases.¹¹ This observation has led us to propose that surgery is performed when tumours are 2–3 cm in size to avoid the poorer outcome associated with even larger tumours.^{11,42} Fourth, in a recent study of 81 patients³² with MEN-1/ZES, the 15-year survival was 100% in 25 patients with no surgical exploration with small pancreatic neuroendocrine tumours <2.5 cm, 100% in 17 patients with a single tumour <6 cm removed surgically, and 89% in 31 patients with ≥ 2 tumours or one tumour >6 cm with surgical resection. Further, distal pancreatectomy was not routinely performed suggesting that it may not be necessary unless the imageable tumour is in the body or tail.³²

In summary, at present there are no reliable clinical, laboratory or tumoural markers that predict the aggressiveness of the pancreatic neuroendocrine tumour in an individual patient with ZES and MEN-1. The most important predictor of survival is the development of liver metastases. Lymph node metastases do not appear to adversely affect survival.^{22,43} Studies have demonstrated that in pancreatic neuroendocrine tumours and carcinoids, primary tumour size is highly predictive of liver metastases.^{22,24,27} Therefore, at present, because patients with ZES/MEN-1 are not cured, those with tumours ≤ 2 cm have a 100% 15-year survival and those with larger tumours have an increased probability of developing liver metastases, we continue to recommend surgical exploration only for MEN-1/ZES patients with an imageable tumour ≥ 2 cm and not to perform a routine distal pancreatectomy. Additional studies are needed to clearly define whether a more aggressive approach is indicated.

ROLE OF WHIPPLE PANCREATODUODENECTOMY

Most experts do not recommend Whipple pancreaticoduodenectomy for the surgical management of gastrinoma.^{11–13,15,17,19,34,32,44} However, several small series have reported the use of Whipple resection in patients with ZES with or without MEN-1 (Table 1). In a high proportion of cases (68%), proximal pancreaticoduodenectomy has cured both sporadic and MEN-1 patients with ZES (Table 1). Whipple resection may provide a better chance of cure and improved survival especially in patients with MEN-1 who are seldom cured with lesser surgery (Table 1).^{45–48} In one series⁴⁶ of 12 patients with ZES, of whom three had MEN-1, 11 were reported to be cured by Whipple resection. However, despite the fact that serum gastrin levels remained normal during a 6-year follow-up, secretin tests were not done and early recurrences may have been missed.¹⁸ Whipple procedure is associated with a higher complication and death rate than simple excision or enucleation of pancreatic and duodenal tumours. Whipple may have long-term sequella like weight loss, diabetes and malabsorption. Further, Whipple resection may make re-operation technically more difficult. This is an issue in MEN-1 patients who may develop additional pancreatic neuroendocrine tumours. Finally, liver metastases occurring after Whipple procedure cannot be treated with chemo-embolization⁴⁷ because of an increased risk of ascending infection. Nevertheless, because of the dramatic increase in cure rate and the ability to totally remove the gastrinoma triangle, Whipple pancreaticoduodenectomy is clearly indicated in select patients with gastrinoma. We recommend its use be considered in both sporadic and MEN-1 patients with a large pancreatic head or duodenal tumour; multiple

localized lymph nodes; or if the patient is not cured after removal of a duodenal or pancreatic head gastrinoma by tumour enucleation as assessed by intra-operative secretin test.^{19,46–49}

At present, the more frequent use of Whipple resection cannot be routinely recommended until additional studies clarify critical issues. First, it should be unequivocally established that Whipple resection cures most patients with either sporadic or MEN-I gastrinoma. This requires meticulous follow-up with serial secretin tests. Second, the long-term side-effects of Whipple resection in these patients and their frequency need to be carefully assessed in a prospective study. This is an important point because these patients currently have an excellent quality and duration of life without Whipple resection. Finally, it will need to be established that a Whipple resection extends survival in patients with gastrinoma with and without MEN-I compared to those treated with lesser procedures. This may be impossible because currently the 10-year survival for patients with sporadic and MEN-I gastrinoma is 95%¹¹ and 86%,¹¹ respectively. Furthermore, in MEN-I patients survival may be determined not by gastrinoma but some other neuroendocrine tumour like thymic or gastric carcinoid,³⁸ or some other tumour.³⁸

In summary, patients with gastrinoma in the setting of MEN-I are seldom, if ever, cured of Zollinger–Ellison syndrome by the current non-Whipple operations to remove duodenal and pancreatic gastrinoma. Surgery is currently used in these patients to deal with the malignant nature of pancreatic or duodenal neuroendocrine tumours. Malignant potential is best determined by the imaging of a 2 cm neuroendocrine tumour. If this is the case, surgery should be performed to remove the imaged tumour and other defined by intraoperative methods. Cure does occur in a significant proportion of patients (50%) with sporadic gastrinoma. Duodenotomy has improved both the tumour detection rate and the cure rate and should be routinely done. Whipple pancreaticoduodenectomy results in the highest probability of cure in both sporadic and MEN-I gastrinoma patients as it removes the entire gastrinoma triangle. However, the excellent long-term survival of these patients with lesser operations and the increased operative mortality and long-term morbidity of Whipple make its current role in the management of these patients unclear until studies are done to clarify these issues.

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