

Is total gastrectomy still a viable option in the management of patients with the Zollinger-Ellison syndrome?

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It is generally held that landmarks in the evolution of the medical treatment of the Zollinger-Ellison syndrome (ZES) have also had a profound effect on the surgical approach to peptic ulcer disease. After 1955 when Zollinger and Ellison¹ initially described the syndrome, total gastrectomy remained the treatment of choice until a new generation of antisecretory agents were introduced over 30 years ago.^{2,3}

The introduction of histamine receptor 2 antagonists (H₂RAs) in 1974, and the development of proton pump inhibitors (PPIs) in 1980, are quite rightly considered to be landmarks in the medical treatment of acid hypersecretory states. However, it soon became evident that the administration of H₂RAs was not without problems. There were troublesome side-effects and 25% of patients developed complications because of inadequate control.³ However, the early 1980s heralded a new era that differed fundamentally from the H₂RA approach when the introduction of PPIs revolutionised the management of peptic ulcer disease. With the advent of PPIs, gastric hypersecretion could be controlled in almost every case. In the early 1990s gastric surgery was considered to be an unresolved issue in ZES cases.⁴ However, based on numerous studies showing that acid hypersecretion can be controlled in ZES patients for long periods, Norton and Jensen⁵ currently hold that total gastrectomy is not indicated for hypersecretory control.

The following clinical presentation describes a patient with peptic ulceration of the duodenum and a stenosed oesophagus as a result of a peri-pancreatic gastrinoma. As the patient enjoys excellent quality of life 13 years after total gastrectomy for ZES, this provided the impetus to reconsider the advantages of total removal of the target organ as an alternative to lifelong medical treatment of the lethal hypersecretory effects of residual gastrin-producing tumour tissue.

Clinical presentation

A 60-year-old man presented with a history of repeated operations over a period of 14 years for the complications of recalcitrant peptic ulceration. These included an omentopexy for a perforated duodenal ulcer (1979), vagotomy and gastroenterostomy for bleeding (1982), gastrectomy for recurrent duodenal ulceration (1993), and closure of a perforation of a large proximal gastric ulcer (1993). The final operation (1993) included a cervical oesophagostomy and a feeding jejunostomy for stenosis of the oesophagus which extended from a small gastric remnant to the arch of the aorta.

The patient was emaciated and extremely depressed. The serum immunoreactive gastrin levels were raised (444 ng/l, normal range 0 - 100 ng/l). Computed tomography (CT) scan showed a 4 x 3 cm tumour in the head of the pancreas.

In view of the patient's uncompromising attitude that the proposed operation would be his final submission to any form of surgery, it was decided to remove the source of the secretagogue as well as the target organ before fashioning the neo-oesophagus. This decision was arrived at on account of the well-documented finding that gastrinomas are often multiple and malignant.^{1,2,5}

Operative procedure

The operation was performed in January 1994 and included a total gastrectomy, removal of a peri-pancreatic gastrinoma, as well as a colonic interposition to restore oesophago-intestinal continuity (Figs 1 - 3).

The first step was to remove the gastric remnant. The stenosed oesophagus was left *in situ*.

After Kocherisation of the duodenum, a tumour was found on the posterior aspect of the head of the pancreas. This was removed together with several peri-pancreatic lymph nodes.

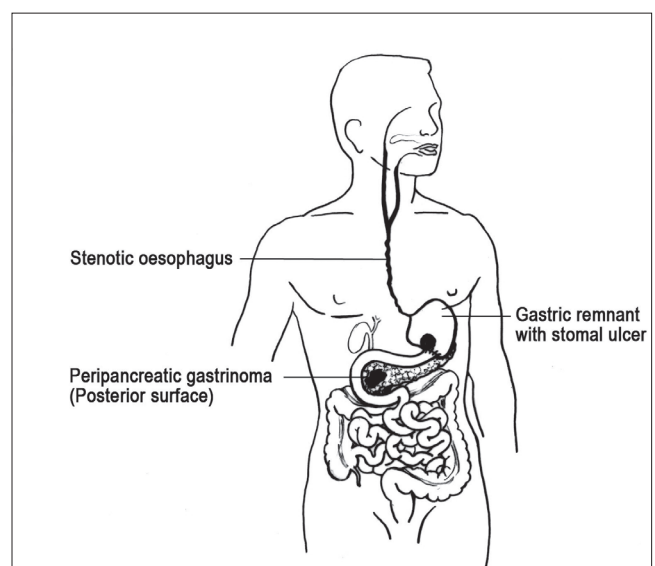


Fig. 1. Preoperative findings – extensive oesophageal stenosis, gastric remnant with stomal ulcer, peripancreatic gastrinoma.

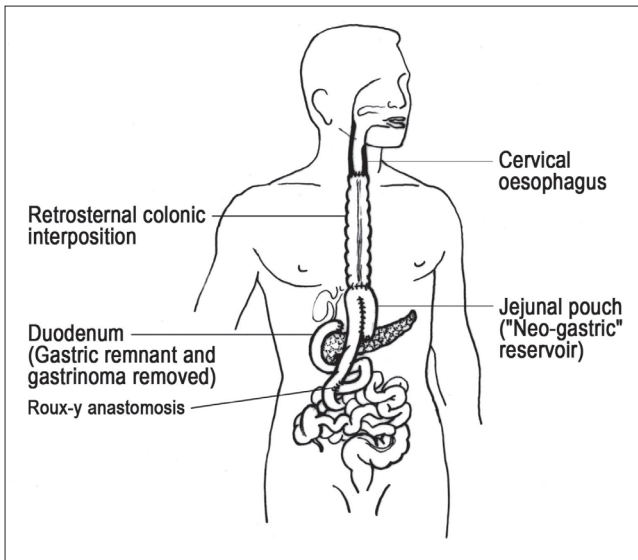


Fig. 2. Completed colonic bypass (via retrosternal tunnel).

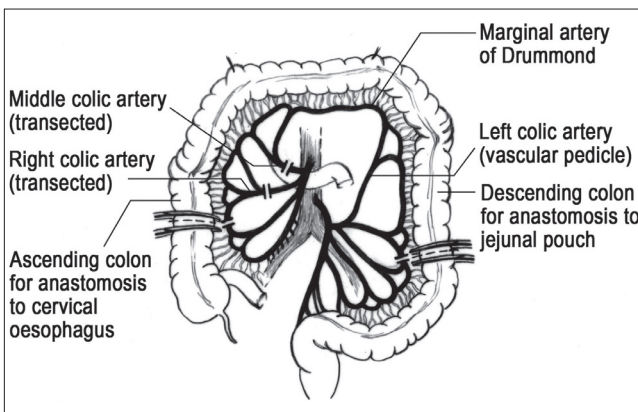


Fig. 3. Preparation of isoperistaltic loop (right transverse and left colon).

The well-circumscribed tumour, which measured 4 x 3.5 x 3 cm, showed the histological features of a gastrinoma which stained heavily for gastrin. In one peri-pancreatic lymph node there was evidence of direct infiltration by tumour tissue. There was a stomal ulcer in the gastrectomy specimen which measured 2.5 x 1 cm.

A segment of colon which included the ascending colon (without the caecum), the transverse colon and the descending colon up to the sigmoid (which was nourished by the left colic artery) was brought up as an isoperistaltic loop, via a retrosternal tunnel for anastomosis to the cervical oesophagus (Fig. 3). The distal colon was anastomosed to a jejunal pouch which serves as a 'neo-gastric' reservoir (Fig. 2).

Apart from an incisional hernia which was duly repaired 6 months later, the postoperative course was uneventful. Interestingly, the serum gastrin level dropped to normal levels (35 ng/l after the operation and 26.5 ng/l 3 years later), which raises the question whether the tumour was possibly an 'ectopic' or primary lymph node gastrinoma where simple excision is often associated with a favourable outcome.^{6,7}

At the latest follow-up, 12 years and 9 months after the operation, the patient maintains that he enjoys excellent quality of life. He has 2 light meals during the day and a

large meal every evening. At the age of 72 he is still a keen gardener. He also travels extensively with a caravan. Apart from his monthly vitamin B₁₂ injection, he requires no further medication.

Discussion

Based on the well-documented finding that gastrinomas are often multiple and metastatic, curative resection is often difficult to achieve.^{1,2,5,8} Furthermore, patients with severe peptic ulcer disease, acid reflux oesophagitis or recalcitrant diarrhoea may have very small tumours that are not identifiable on CT scan or with magnetic resonance imaging. However, with new localisation techniques, notably the selective arterial secretagogue injection (SASI) test for the localisation of gastrinoma as described by Imamura *et al.*⁹ in 1987, and somatostatin receptor scintigraphy (SRS) as suggested by Krenning *et al.*¹⁰ in 1994, as well as intra-operative localisation methods such as intra-operative ultrasonography, duodenoscopy and secretin tests, there has been a marked improvement in the success rate of curative surgery in patients with gastro-pancreatic endocrine tumours.⁸

Despite these highly sophisticated techniques, it would seem that liver metastases may occur irrespective of the size of the tumour.⁸ Although the incidence of hepatic metastases has been reported to be greater than 60% in cases of pancreatic gastrinoma, the majority appear to exhibit an indolent growth pattern. For this reason genetic testing which may become available shortly, could be of significant value for the early identification of the more aggressive tumours.¹¹ However, it should be underscored that curative resection of gastrinomas based on accurate localisation techniques is not always available in rural Africa.

According to Norton *et al.*¹² the role of surgical exploration for gastrinoma resection has remained controversial since 1955 when the ZES syndrome was first described. Whereas the initial debate revolved around the issue of whether patients should be treated by total gastrectomy or attempted tumour removal, with or without gastric resection, the controversy has now changed to whether these patients should be treated medically or whether removal of the gastrinoma should be considered in all ZES patients with potentially resectable disease.¹² Their results showed that routine surgical exploration increased disease-related survival.¹² However the main thrust of this review is whether total gastrectomy should be considered in indigent patients with unresectable disease.

Indications for total gastrectomy

Although total gastrectomy is now rarely performed in First-World countries, it would seem that this procedure may be considered for ZES patients who develop aggressive gastric carcinoids,⁵ for the small number of patients in whom gastric hypersecretion cannot be controlled on medical treatment, or in non-compliant patients, especially those from a rural environment who cannot or will not take their medication for financial or logistical reasons.⁶

It has been shown that long-term PPI therapy poses major fiscal and compliance problems particularly in population groups that cannot afford expensive drug therapy.⁶ Based on his own work, Radebold⁶ concludes that total gastrectomy remains a viable, if not preferred option for indigent patients who live in remote rural areas.

We have also found that patients on PPI therapy may be deluded into the dangerous misconception that a dramatic remission implies a permanent cure.

Quality of life after total gastrectomy for ZES

In the case of total gastrectomy for cancer,¹³ it should be underscored that the high rate of crippling sequelae has not been reported where the operation was done for gastric hypersecretion.⁶ Thompson *et al.*¹⁴ found that gastrectomy is safe and dependable in the treatment of hypersecretory problems in ZES patients.

Rattner¹⁵ is of the view that total gastrectomy should be reserved for patients who cannot be controlled with medical therapy. The operation is extremely well tolerated in patients with ZES and can be performed with a 0 - 5% mortality rate.¹⁵

Radebold⁶ reported excellent function with few side-effects in the ZES patients from rural areas who did not have reliable supplies of PPIs. This has also been our experience with the patient under discussion who enjoys an excellent quality of life almost 13 years after a total gastrectomy and a colonic interposition for recalcitrant oesophageal reflux. One of the patients described in Zollinger and Ellison's original report¹ went on to have 2 children and was working almost 30 years after undergoing total gastrectomy. Approximately 50% of their patients survived 10 years or more.

It is of particular interest that in their most recent article entitled 'Surgery increases survival in patients with gastrinoma' Norton *et al.*¹² from Stanford University point out that 55% of their patients refused to undergo surgery after discussion with the referring physician. These patients were then placed on lifelong oral antisecretory drugs. One of these patients died as a result of acid-related causes when his acid hypersecretion was inadequately controlled while admitted to an outside hospital for pneumonia, resulting in upper gastrointestinal bleeding and leading to death. Our own experience (as also shown in the case report under discussion) is that uncontrolled gastric hypersecretion is a highly lethal disease. It is therefore quite evident that in the case of ZES patients in developing countries where PPIs are not available, total gastrectomy is the only viable alternative for those who do not qualify for curative resection.⁶

Conclusion

The present case seems to lend support to the concept that total gastrectomy with excision of gross tumour may offer a viable if not preferred option to ensure acceptable long-term quality of life in ZES patients faced with the lethal effects of uncontrolled hypersecretion, in non-compliant patients, or in those in remote rural areas who are unable to take their medication because of severe financial constraints or inaccessible supplies of PPI.

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