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Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger–Ellison syndrome, hypoglycaemia or both

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Abstract. Thompson NW (University of Michigan, Ann Arbor, MI, USA). Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger–Ellison syndrome, hypoglycaemia or both (Minisymposium: MEN & VHL). *J Intern Med* 1998; **243:** 495–500.

The management of multiple endocrine neoplasia type 1 (MEN-1) pancreatic-duodenal disease, particularly when the Zollinger–Ellison syndrome (ZES) is the presenting manifestation, has remained controversial. The management of hypoglycaemia and other syndromes as well as large tumours detected by imaging is less controversial, although standardized surgical techniques have not been generally adapted. The rationale for an aggressive operative management plan for ZES and other syndromes is based on the facts that neuroendocrine tumours of both the pancreas and the duodenum have malignant potential and that the functional manifestations can be controlled with appropriate surgical procedures based on current concepts of the MEN-1 disease. Of the ten concepts presented, the one critical to the surgical treatment of ZES is that a duodenotomy is essential in detecting the source of hypergastrinaemia in most MEN-1 patients. The complete operation is multifaceted and includes peripancreatic lymph node dissection (ZES), enucleation of any head or uncinate tumours and a distal pancreatectomy. Our results in 40 MEN-1 patients with functional syndromes treated with these procedures are encouraging. Ten patients with hypoglycaemia (four with concomitant ZES) have been 'cured' with follow-up as long as 18 years. Sixty-eight per cent of 34 patients with ZES have remained eugastrinaemic during follow-up as long as 19 years. One patient developed a solitary liver metastasis that was excised a year ago without other evidence of recurrence. There has been no operative mortality and three subsequent deaths were due to unrelated disease.

Keywords: duodenotomy, gastrinomas, insulinomas, MEN-1, Zollinger–Ellison syndrome.

Introduction

Clinical manifestations of neuroendocrine disease of the pancreas and/or the duodenum develop in approximately 70% of patients with multiple endocrine neoplasia type 1 (MEN-1) [1–3]. Virtually all patients develop a diffuse endocrine dysplasia of the pancreas consisting of islet cell hyperplasia, microadenomatosis and nesidioblastosis [4, 5]. Symptomatic MEN-1 patients develop benign or malignant neoplasms in addition to these microscopic findings, some of which are functional, causing a specific hormonal syndrome [3, 6]. The morbidity and mortality from MEN-1 pancreatic disease is the result of the functional activity of a variety of tumours and/or their malignant behaviour. The management of MEN-1 pancreatic disease, particularly when the Zollinger–Ellison syndrome (ZES) is the presenting manifestation, has remained controversial [3, 7–18]. Many groups have advocated a nonoperative approach and utilize a proton pump inhibitor to control the effects of hypergastrinaemia [17]. The management of hypoglycaemia and other syndromes as well as large imaged tumours is less controversial and surgical treatment is universally advocated, although a standardized technique has not been generally adapted. The rationale for our aggressive operative management of ZES and other syndromes is based on the facts that neuroendocrine tumours of both the pancreas and the duodenum have malignant potential and that the functional manifestations can actually be eliminated with an appropriate procedure [7, 9–11].

Current concepts

The operative management of neuroendocrine disease in MEN-1 patients has been directly influenced by important findings during the past two decades. Application of this new knowledge, obtained from both the basic and the clinical sciences, has increased the likelihood of successful operations in treating both MEN-1 ZES and hypoglycaemia. Ten concepts have evolved that are emphasized as the basis of our surgical approach.

1 *Islet cell dysplasia (hyperplasia and nesidioblastosis), common to all MEN-1 patients, is not the cause of a functional syndrome such as ZES.* Immunohistochemical studies have identified that discrete tumours of the pancreas or duodenum or both are invariably found in patients with syndromes and that the islet cell hyperplasia and nesidioblastotic cells fail to stain for the hormone involved in the syndrome [4].

2 *Most neuroendocrine tumours of the pancreas less than 3 cm in diameter are not associated with liver metastases [14].* As a result, earlier detection and excision of tumours less than 3 cm in diameter favours the possibility of a curative rather than a palliative procedure. Furthermore, small tumours are nearly always encapsulated and not locally invasive. They can usually be enucleated without subsequent local recurrence.

3 *Nearly all neuroendocrine tumours of the pancreatic head or uncinate can be detected by endoscopic ultrasound (EUS), intraoperative ultrasound (IUS), or direct palpation and enucleated.* Lymph node metastases associated with neuroendocrine tumours of the head or uncinate are rare. A pancreatico-duodenectomy is not an obligatory procedure in obtaining a good result.

4 *Most, but not all, MEN-1 ZES patients have one or more duodenal neuroendocrine tumours (gastrinomas) that are the cause of hypergastrinaemia [2, 19–26].* Failure to search for, detect and excise these often small tumours will invariably result in persistent hypergastrinaemia. Furthermore, despite their small size, duodenal tumours, in contrast to pancreatic islet cell tumours, frequently metastasize to the peripancreatic and periduodenal lymph nodes. However, they are associated with liver metastasis in fewer than 10% of cases and then only after a long period without surgical intervention.

5 *A distal pancreatectomy should be done in any MEN-1 patient with either a hormonal syndrome or a neuroendocrine tumour, regardless of its location in the pancreas and/or the duodenum [7, 8, 14].* In our experience, all MEN-1 ZES patients have had concomitant neuroendocrine tumours in the neck, body or tail. These are rarely the cause of gastrin hypersecretion. Their excision reduces the chances for another syndrome (hypoglycaemia) and the potential expression of malignancy and subsequent metastatic disease.

6 *A duodenotomy should be performed in any MEN-1 patient with an elevated serum gastrin and a positive secretin stimulation test, regardless of whether any tumour is palpable in the duodenum at exploration [4, 7, 19].* The majority of duodenal gastrinoma are within the first and second portions of the duodenum but it is not unusual to find one in the third portion as

well. Rarely the location may be in the fourth portion or even the proximal jejunum. Small tumours are best detected by direct visualization and palpation of the mucosal surface after an extensive duodenotomy.

7 *A peripancreatic lymph node dissection is required in any MEN-1 patient with a duodenal neuroendocrine tumour or a pancreatic tumour 3 cm in diameter or larger*. Approximately 50% of patients with duodenal gastrinomas will have at least one metastatic node. Many of these nodes are of normal size and their involvement cannot be judged by palpation alone. Small pancreatic neuroendocrine tumours are much less likely to metastasize to lymph nodes. However, tumours larger than 3 cm in diameter occasionally metastasize to lymphatics rather than the liver, therefore there is a need to excise regional nodes. This requires a splenectomy for any large tumour involving the distal half of the pancreas.

8 *Localization studies are of little value in most MEN-1 ZES patients except for ruling out liver metastases (CT and octreotide scan), identifying adrenal cortical tumours (CT scan), and small neuroendocrine tumours in the pancreatic head or uncinate process (EUS) [8].*

9 *Adrenal cortical tumours larger than 4 cm in diameter or functioning should be excised at the time of pancreatic exploration*. Although most adrenal cortical tumours in MEN-1 patients are benign and nonfunctioning, they are occasionally the cause of Cushing's syndrome and larger ones may be malignant.

10 *Parathyroidectomy can be safely performed during the same anaesthesia if hyperparathyroidism has not been previously treated [7]*. Either a subtotal parathyroidectomy, leaving a viable 60 mg remnant, or a total parathyroidectomy and autotransplant are the procedures of preference [27–32]. Both should be accompanied by a cervical thymectomy [7].

Our surgical approach, developed over the past 20 years, is based on the premise that MEN-1 patients with neuroendocrine disease of the pancreas or duodenum can be cured of their syndrome or nonfunctional tumours, provided that the tumour has not metastasized to the liver and that the operation is extensive enough to excise all sites of disease. An aggressive surgical approach is indicated because the incidence of malignancy is similar to that in patients with sporadic islet cell tumours. Liver metastases are less common than in sporadic ZES at the time of diagnosis, possibly because of the younger age of patients. The frequency of duodenal primary tumours in MEN-1 ZES patients is also a factor. These tumours appear to have a less aggressive biological behaviour than those that arise in the pancreas even though lymphatic metastases may occur from very small tumours.

Based on the previously noted concepts, the following operation has evolved for any MEN-1 patient with a functional syndrome or an imaged tumour.

1 A subtotal parathyroidectomy and cervical thymectomy, preserving a viable 60 mg remnant, is initially performed in those patients with concurrent hyperparathyroidism.

2 A distal pancreatectomy to the level of the superior mesenteric vein, preserving the spleen when appropriate or feasible, is routinely performed.

3 Enucleation of any tumours in the pancreatic head or uncinate process is performed after identification by EUS, palpation or IUS.

4 A duodenotomy and excision of any tumours in the first through the fourth portion of the duodenum is performed in any MEN-1 ZES patient as determined by elevated gastrin levels and a positive secretin stimulation test.

5 A peripancreatic lymph node dissection, including nodes in the porta hepatis and along the common hepatic artery, is performed. This is done routinely only in those patients with duodenal neuroendocrine tumours.

6 Large tumours in the body or tail should be treated by distal pancreatectomy and splenectomy in continuity with the lymph nodes to the level of the coeliac axis.

Results

Since 1978, 40 MEN-1 patients with functioning pancreatico-duodenal tumours without liver metastases have undergone these procedures. Thirty-four patients with MEN-1 had ZES, six had hypoglycaemia and four had concomitant syndromes. All patients with hypoglycaemia had one or more insulinomas found in the neck, body or tail, and all but one patient had two or more tumours that stained positive for insulin. One patient, a young man with normal gastrin levels, had multiple insulinomas in the body and tail as well as a 7 cm insulinoma arising from the neck of his pancreas. The latter tumour was determined to be malignant as it was associated with an insulin-staining metastatic node near the superior mesenteric vein. He has had no evidence of recur-

Table 1 MEN-1 ZES: location of gastrinomas

Location	No.	(%)
Duodenal gastrinomas	30/34	(88)
Multiple duodenal gastrinomas	20/34	(59)
Malignant duodenal gastrinomas	12/30	(40)
Pancreatic gastrinomas	12/34	(35)
Duodenal and pancreatic gastrinomas	8/34	(24)
Pancreatic gastrinomas (only)	4/34	(12)
Palpable NE tumour body or tail	34/34	(100)

Table 2 MEN-1 ZES: malignancy

	No.	(%)
Duodenal gastrinomas	12/30	(40)
Pancreatic NE tumours	1/34	(3)
Liver metastasis[a]	1/34	(3)
ECL gastric tumours	2/34	(6)

Table 3 MEN-1 ZES: survival and deaths

Survival	
5 years	97%
10 years	94%
15 years	94%
Deaths	
34-year wf	3 years – Pulmonary embolism
64-year wm	13 years – Adenocarcinoma stomach
60-year wf	16 years – Myocardial infarction

Table 4 MEN-1 ZES: Results of surgical treatment

	No.	(%)
Normal basal gastrin[a]	23/34	(68)
Negative secretin test	9/27	(33)

[a]Longest follow-up 19 years.

rence during 6 years of follow-up. All patients with hypoglycaemia have been rendered euglycaemic and asymptomatic during follow-up periods as long as 18 years.

Thirty-four patients with MEN-1 and ZES as determined by preoperative elevated serum gastrin levels and positive secretin tests underwent pancreatic duodenal procedures. There were 19 females and 15 males with a mean age of 39.4 years. All 34 patients had one or more parathyroid explorations which in 13 were concomitant with their abdominal explorations. Thirty-three of 34 patients were normocalcaemic on follow-up studies (1997). Gastrinomas were excised in all cases as determined by immunohistochemical staining. Their locations are shown in Table 1. Most patients (88%) had duodenal gastrinomas with or without concomitant gastrinomas in the head or the uncinate process (2490). Only one patient, who had an 8 cm gastrinoma in the body of the pancreas, had no other concomitant gastrinomas in either the duodenum or the head of the pancreas. That patient survived for 16 years with normal gastrin levels and negative secretin tests before succumbing to a myocardial infarction. Malignancy as determined by lymph node metastases occurred in 43% with all except two lymph node metastases resulting from duodenal primary tumours. One of the exceptions was a patient who had a 2 cm somatostatinoma in the body of the pancreas and one peripancreatic malignant lymph node staining positive for somatostatin. This patient has survived 14 years with no evidence of subsequent recurrence (Table 2). The other exception was the patient with a 7 cm insulinoma in the neck of the pancreas and a single node metastasis. Only one patient has developed a liver metastasis. This was detected on routine follow-up 6 years after a distal pancreatectomy and excision of four large ($>$ 1 cm) duodenal gastrinomas. This patient also had several very large peripancreatic lymph node metastases, including one 6 cm in diameter. The liver metastasis was detected by follow-up screening with an octreotide scan for persistent hypergastrinaemia. It was wedged excised a year ago at which time no other disease was detected. There has been no hormonal evidence of a recurrence since and a follow-up octreotide scan at 1 year was negative. The 5, 10 and 15-year mortality is noted in Table 3. There was no operative mortality nor has any patient subsequently died of MEN-1-related disease. Three patients have died from unrelated diseases; one at 3 years from a pulmonary embolus, one at 13 years from adenocarcinoma arising at the cardio-oesophageal junction and a third at 16 years from a myocardial infarction. Two-thirds of these patients have remained eugastrinaemic (Table 4). Although only one-third have negative secretin stimulation tests, some of these eugastrinaemic patients have remained asymptomatic and without any drug therapy for periods of up to 18 years.

Discussion

The management of ZES in association with MEN-1 remains controversial. This is the most frequent syndrome detected in MEN-1 patients with functional pancreatic-duodenal neuroendocrine manifestations. Our management is based on the facts that all gastrinomas, whether in the duodenum or the pancreas, have malignant potential or are malignant when detected and that surgical treatment can be successful in patients without liver metastases provided that the operative procedure performed addresses all facets of the disease. We believe that all patients without liver metastases should be explored with the intention of curing the disease, without performing either a Whipple procedure or a total pancreatectomy. A major reason for consistent failure in the surgical treatment of MEN-1 ZES in the past was the fact that duodenal primary tumours and their metastatic lymph nodes were not appreciated and were overlooked. Although concomitant pancreatic tumours arising in the tail, body, neck and even head of the pancreas often were detected and excised, it is now apparent that the vast majority of these were unrelated to the ZES. The procedure that we perform for MEN-1 ZES has been successful in the majority of patients and has initially lowered the serum gastrin in all patients. The causes of failure in the one-third of patients with persistent or recurrent disease have not been established in every patient even after long-term follow-up and even 'second look' procedures in a number of cases. Only one patient has developed a liver metastasis (octreotide scan). All patients with hypergastrinaemia have had periodic follow-up imaging with CT and octreotide scans and, during the past 4 years, EUS of the remaining pancreatic head. In addition to the liver metastasis excised at reoperation, several other patients have had additional metastatic lymph nodes detected and two small gastrinomas in the pancreatic head. Two patients have developed 'new' duodenal gastrinomas at 4 and 6-year intervals after their initial operations. The latter occurrences emphasized the need for a meticulous initial duodenal exploration and peripancreatic lymph node excision. Our experience suggests that the development of 'new' gastrinomas in either the head or the duodenum is relatively uncommon but does occur. However, recurrence of hypoglycaemia from the growth of new insulinomas in the remaining head or uncinate has not occurred in our experience. We have encountered several MEN-1 patients who were previously operated on elsewhere for hypoglycaemia who subsequently presented with ZES, one after 15 years and another after 22 years. Because of the potential for the development of additional neuroendocrine tumours, all MEN-1 patients require life-long annual follow-up and can never really be considered 'cured'. The fact that half of our eugastrinaemic patients have had positive secretin stimulation tests but have remained asymptomatic and without need for drug therapy for up to 18 years suggests that some patients may have small and undetectable tumours in either the duodenum or the head that may remain quiescent for an indefinite time. Clearly growth and progression of disease varies between patients and is not inevitable.

An alternative to the multifaceted procedure that we perform that is likely to result in a higher rate of eugastrinemia is a pancreatico-duodenectomy (Whipple procedure). If this operation were to be done, neuroendocrine tumours in the distal pancreas could be dealt with by enucleation. However, the price to be paid is an expected increase in morbidity and mortality although both have decreased appreciably in recent years. We will continue to perform the procedure described because of its low morbidity, lack of mortality and success rate in the majority of MEN-1 ZES patients. The fact that only one of our patients has developed a single liver metastasis that was possibly present but undetected at the time of his original procedure suggests that the long-term mortality from malignant pancreatico-duodenal neuroendocrine disease will be significantly decreased.

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