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Surgical strategies for nonfunctioning neuroendocrine pancreatic tumors and for other pancreatic neoplasms associated with multiple endocrine neoplasia type 1

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Abstract

The most important step in the management of nonfunctioning neuroendocrine pancreatic tumors (NEPTs) is the determination of the primary tumor location and the tumor extent. In patients with localized, nonmetastatic disease, complete surgical resection of the primary tumor is the treatment of choice. For locally advanced, unresectable tumors, the surgical indication remains problematic. It is difficult to indicate palliative pancreatic resection due to the potential morbidity associated with debulking procedures and high recurrence rates. In patients with clinically nonfunctioning NEPTs in multiple endocrine neoplasia type 1 (MEN-1), the role of surgery is controversial. Based on the characteristic multifocality of the tumors, some have suggested that surgery should be limited to those larger than 2 cm in size (primary tumor size appears to correlate with metastatic potential). For insulinoma MEN-1 patients, it seems that subtotal distal pancreatectomy, preserving the spleen, combined with enucleation of any tumors identified in the pancreatic head, should be the standard operation. The role of surgery for MEN-1 Zollinger-Ellison syndrome (ZES) patients is debatable.

Keywords: Nonfunctioning neuroendocrine pancreatic tumors; Insulinoma; Gastrinoma; MEN-1

Neuroendocrine pancreatic tumors (NEPTs) are rare neoplasms with an annual incidence of 1 in 100,000 and represent 1% to 2% of all pancreatic neoplasms. These tumors show no significant gender predilection and occur at all ages, with a peak incidence between 30 and 60 years. NEPTs are described in relation to the hormone responsible for the clinical syndrome. Tumors that cause such syndromes are classified as functional, while those without obvious hypersecretion are classified as nonfunctional. Nevertheless, nonfunctional tumors secrete various peptides and proteins, including chromogranins, plasma levels of which can be used as tumor markers.

Most NEPTs are sporadic, but a minority of patients with NEPTs have one of the inherited disorders producing tumors at many sites: multiple endocrine neoplasia type 1 (MEN-1), Von Hippel-Lindau disease, neurofibromatosis, and tuberous sclerosis. Sporadic NEPTs are usually solitary tumors, in contrast to tumors in patients with MEN-1 in whom NEPTs are characteristically multifocal.

The usual histological pattern of malignant neoplasms (nuclear pleomorphism, mitotic activity, and infiltration into the surrounding tissue) is often unreliable. Only the presence of gross local invasion and/or metastasis is definitive in determining malignancy. Metastasis is most commonly found in the liver, less frequently in regional lymph nodes, and dissemination to other distant sites is unusual [1]. Overt malignancy has been found in 5% to 10% of patients with insulinoma; in contrast, malignant features have been reported in approximately 60% of patients with gastrinomas, in 60% of patients with somatostatinomas, and in 50% to 90% of those with vipomas. Although the development of metastatic disease in patients with MEN-1–related NEPTs is uncommon before age 30, metastatic neuroendocrine carcinoma is the major cause of disease-related mortality in MEN-1 [1].

Surgical Treatment

The most important step in the management of NEPTs is the determination of the primary tumor location and the

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tumor extent. This information is essential both for patients whose disease is amenable to surgical resection, and for the clinical management of patients with advanced disease. Surgery remains the only curative modality currently available for resectable NEPTs. The surgical management varies with tumor type, location, and size; because of their biologic heterogeneity, there is no standard surgical approach to the management of NEPTs, creating unique challenges for surgeons. In addition, patients with NEPTs associated with MEN-1 need a different surgical approach than that required for patients with sporadic NEPTs. NEPTs are identified in 30% to 80% of patients with MEN-1. Insulinomas, gastrinomas, and nonfunctioning NEPTs are the most common NEPTs in patients with MEN-1 [2].

Nonfunctioning Endocrine Tumors

Nonfunctional NEPTs are located most commonly (~60%) in the pancreatic head but can be found anywhere within the pancreas. The diagnosis is often delayed (>5 years) and tumors become clinically apparent when already inoperable and/or metastatic. Most nonfunctioning NEPTs are associated with increased serum levels of pancreatic polypeptides (PP) and therefore are referred to as PPomas. Nonfunctioning and PPomas do not appear to differ in presentation or biologic behavior.

Knowledge of the morphologic features of the nonfunctioning tumor provides the information needed to ensure correct treatment. Several treatment strategies have been proposed:

1. In patients with localized, nonmetastatic disease, complete surgical resection of the primary tumor is the treatment of choice; the median survival was reported at 7.1 years [3]. Phan et al [4] have reported the 5-year survival rate following resection approximates 50%. However, only 48% of the patients with localized, nonmetastatic disease who underwent resection of the primary tumor were alive and without evidence of recurrent disease at a median follow-up time of 2.7 years (range, 1 to 8 years) from diagnosis [3]. The authors [3] emphasize that it is inappropriate to assume that complete resection of the primary tumor in the absence of metastatic disease corresponds to long-term cure.
2. In patients with locally advanced, unresectable tumors, the surgical indication remains problematic. The median survival for these patients is approximately 5 years without surgery [5]. It is difficult to indicate palliative pancreatic resection due to the potential morbidity associated with debulking procedures and high recurrence rates. In Bartsch's series [6], the price for such an aggressive approach was an overall complication rate of 44% and mortality of 16.6%. In patients with biliary and gastric outlet obstruction, palliative surgery (surgical bypass) should be recommended.
3. In patients with metastatic disease, resection of the primary tumor should be based on the presence of clinical symptoms and the location of the tumor [5]. In the absence of a symptomatic primary tumor, distal pancreatectomy in the presence of unresectable extrapancreatic metastatic disease is probably not indicated. However, patients with large tumors in the pancreatic head who have low-volume hepatic metastases are potentially at risk for gastrointestinal hemorrhage or biliary and gastric outlet obstruction; pancreaticoduodenectomy may provide relief from local tumor-related symptoms. In selected patients with localized liver metastasis, a combined resection of the primary tumor and liver metastasis should be attempted [7–9]. The 5-year survival rate for patients who were cleared of pancreatic and liver disease was 65% in a recent series [10]. However, tumor recurrences occurred in three quarters of patients who underwent resection with curative intent, and most of these recurrences were detected within 2 years. In an attempt to identify which patients are most likely to benefit from aggressive surgical resection of metastatic neuroendocrine tumors, Chamberlain et al [11] developed a prognostic scoring system based on functional status of the primary tumor, presence of extrahepatic metastasis, extent of liver replacement with tumor, and the presence of bilobar hepatic metastasis. The presence of any two of these factors was associated with lower rates of both complete resectability and survival. When hepatic resection is not possible or other treatment options have failed, recent data indicate that in otherwise healthy patients under the age of 50 years, hepatic transplantation may prolong symptom-free survival with acceptable operative morbidity [12].
4. In patients with clinically nonfunctioning NEPTs in MEN-1, the role of surgery is controversial. Based on the characteristic multifocality of the tumors, some have suggested that surgery should be limited to those larger than 2 cm (primary tumor size appears to correlate with metastatic potential) [5]. Bartsch et al [9] have reported that no distant metastasis has yet been described in nonfunctioning NEPTs less than 10 mm in size. Thompson [13] advocates an aggressive surgical approach to distal subtotal pancreatectomy, enucleation of any identified lesions in the pancreatic head or uncinate process, and regional lymphadenectomy, although cure is rarely achieved since 73% of patients developed new nonfunctioning NEPTs during follow-up [14]. However, the goal of Thompson's procedure is to delay the need for total pancreatectomy, despite the majority of patients developing metachronous neoplasms in the remaining pancreas, and therefore requiring completion of the total pancreatectomy because of the resulting long-term complications of insulin-dependent diabetes, especially in young patients.

Others believe that tumor size is not a reliable predictor of malignant behavior, and an aggressive surgical approach is indicated if peptide levels increase in the absence of radiographic evidence of a pancreatic neoplasm [15].

Insulinomas

Insulinomas represent up to 70% to 80% of clinically symptomatic NEPTs and occur in all age groups. Most are

solitary lesions, but 10% are multiple. Most insulinomas are sporadic in origin with only 7.6% associated with MEN-1. Sporadic insulinomas and insulinomas in patients with MEN-1 may arise at different times [16]. Insulinomas occur more often in MEN-1 patients who are younger than 40 years and may arise in individuals before the age of 20 years. In non–MEN-1 patients, insulinomas generally occur in those older than 40 years. Insulinomas may be the first manifestation of MEN-1 in 10% of patients, and approximately 4% of patients presenting with insulinomas will have MEN-1. By 1991, Demeure et al [17] had collected and reviewed data on 60 patients in the English literature. These authors suggested that patients with insulinomas associated with MEN-1 need a different surgical approach than that required for patients with sporadic insulinomas.

Most insulinomas are benign; only 10% have any evidence of malignancy. The lesions are small with a diameter of less than 2 cm in 90% of patients, and less than 1.3 cm in 50% of patients. They are distributed equally within the head, body, and tail of the pancreas. Therefore, an insulinoma may be occult and difficult to localize both before and during surgery. Notwithstanding recent refinements in imaging techniques for patients with insulinoma, preoperative diagnostic studies still have the same limitations when assessing the number and exact location of the tumors. Endoscopic ultrasound (EUS) is the most sensitive modality for detecting insulinomas, with preoperative detection rates of 86% to 93%. In recent years, spiral computed tomography (CT) scanning has become more successful in localizing insulinoma and may also provide additional information regarding suspected malignancy [18,19]. The combination of biphasic thin-section helical CT and EUS resulted in an overall diagnostic sensitivity of 100%.

Surgical resection is the treatment of choice and offers the only chance of cure. The surgical strategy in patients with sporadic insulinoma should be restricted to removing the solitary tumor in about 90% of patients [16,18,19]. The use of enucleation or resection will depend on the localization of the tumor in the pancreas and the findings from intraoperative ultrasonography. The clear indications for tumor enucleation are tumors located at the periphery of the gland and tumors on the surface of the parenchyma totally or partially covered by a thin layer of pancreatic tissue. However, when the tumor is located in the distal part of the tail of the pancreas, it may be more convenient to remove that part of the gland containing the adenoma. Also, when the tumor is in close proximity to the Wirsung duct or lying on the splenic vein, resection is indicated to avoid pancreatic fistula or profuse bleeding. There is no question that tumors that are hard cause puckering of surrounding soft tissue and appear to be infiltrating, or they cause distal dilatation of the pancreatic duct and raise serious suspicions of malignancy, and resection rather than enucleation must be chosen. Overall cure rates of 75% to 98% are reported after surgery [16]. Recently, Grant [19] has reported the Mayo Clinic experience including 242 patients (216 primary and 31 reoperations on 233 sporadic and 14 MEN-1 patients). The tumors were enucleated in 59%, whereas distal pancreatic resection was necessary in 36% and only 8 patients (4%) required a Whipple procedure. Cure was achieved in 98% of patients.

With advances in laparoscopic techniques, both laparoscopic enucleation and resection of pancreatic insulinoma have been performed successfully. Using the criteria of Cushieri et al [20], the probable benefit of minimally invasive surgery over conventional open surgery depends on the ratio of access trauma to procedural trauma. Enucleation or limited pancreatic resection for solitary, small, benign insulinomas is better achieved using the laparoscopic approach in terms of parietal damage of the abdomen. The reported success for laparoscopic resection of insulinoma ranges from 60% to 100% [18,21–28]. We have recently reported the guidelines for the laparoscopic surgical strategies in the management of insulinomas [29]. It seems that the incidence of postoperative complications is similar for open surgery and laparoscopic surgery. However, the use of laparoscopic resection minimizes parietal damage, the hospital stay is relatively short, and an early return to previous activities was observed in most patients [18].

According to Gauger and Thompson [30], the surgical approach is based on the premise that patients with MEN-1 and neuroendocrine disease of the pancreas can potentially be cured of their syndrome or nonfunctioning tumors, provided the tumor has not metastasized to the liver and the operation is sufficiently extensive to excise all sites of disease. In most reports, enucleation or limited resection did not result in the development of recurrent hyperinsulinism for up to 15 years [31]. However, others reported recurrence rates of 40% at 10 years after enucleation. Enucleation alone of an insulinoma in patients with MEN-1 would likely lead to missed tumors and failed operations. More than 75% of patients with insulinoma and MEN-1 had multiple pancreatic tumors [32]. It seems that subtotal distal pancreatectomy, preserving the spleen, combined with enucleation of any tumors identified in the pancreatic head, should be the standard operation [30]. We believe that patients with MEN-1 insulinomas may benefit from the choice of the laparoscopic approach according to the principles developed during the past 20 years on use of the standard open approach. During the operation, intraoperative laparoscopic ultrasound (LapUS) may recognize other tumors not seen in preoperative localization studies. In addition, laparoscopic ultrasound identifies the demarcation between the normal pancreas and macroscopic disease pancreas and is useful for determining the optimal site of transaction [18,24].

Gastrinoma

Gastrinoma, as other NEPTs, may occur sporadically and as part of MEN-1. Gastrinomas are more common in men than in women; the mean age of diagnosis is 45 to 50 years and approximately 20% have MEN-1. Gastrinomas and nonfunctioning tumors are the most common malignant NEPTs. Approximately 65% to 90% of all gastrinomas found at surgery occur in the pancreatic head–duodenal region [33]. The surgical management is directed towards identification and resection of the primary tumor and regional metastasis to lymph nodes or liver to prevent malignant progression of disease.

The percentage of gastrinomas that behave in a benign or malignant fashion is not well established; malignancy is usually diagnosed by the presence of metastasis. Liver me-

tastasis occurred in 4% of gastrinomas smaller than 1 cm in diameter, in 28% of tumors 1.1 to 2.9 cm in diameter, and in 60% of tumors larger than 3 cm [33–36]. In addition to tumor size, tumor location appears to predict malignancy. Weber et al [37] have reported 90 patients who had pancreatic or duodenal gastrinomas. Lymph node metastasis occurred in 48% and 47%, respectively; however, only 5% of patients who had duodenal gastrinomas had liver metastasis compared with 52% of patients who had pancreatic gastrinomas. Surgical treatment results in an excellent prognosis and should be offered for good-risk candidates who have Zollinger-Ellison syndrome (ZES). However, the surgical approach is a challenge to surgeons; gastrinomas are frequently multiple and can be extrapancreatic. Surgical success depends on the ability to accurately identify not only the primary tumor but also the presence of metastatic disease.

Preoperative imaging modality will determine the surgical approach. CT scanning usually detects metastatic liver disease; however, its ability to detect primary tumors has been shown to be directly related to tumor size. Somatostatin receptor scintigraphy is one of the most sensitive methods for localizing primary disease (60%) and detects more than 90% of patients who have metastatic liver disease [33]. EUS is reported to localize 75% of primary gastrinomas, particularly within the pancreatic parenchyma [38].

The following guidelines will help us perform an adequate operation: (1) The abdominal cavity should be systematically explored for evidence of disease by examining the liver, pelvis, small intestine, and large intestine. (2) A Kocher maneuver will allow examination of the pancreatic head, duodenum and periportal lymph nodes, celiac axis lymph nodes, and peripancreatic and periduodenal lymph nodes. The lesser sac is opened to examine the pancreatic body and tail. (3) Palpation alone can identify 65% of duodenal gastrinomas; 71% are in the first part of the duodenum, 21% in the second part, and 8% in the third part [36]. (4) When palpation fails in localizing duodenal tumors, endoscopic transillumination and intraoperative ultrasonography may identify the tumor. (5) When gastrinomas are not localized by preoperative localization studies and by operative methods, a 3-cm longitudinal duodenotomy centered on the anterolateral surface of the descending duodenum should be performed [39]. If a primary tumor is not on the medial duodenal wall, it is elliptically excised with a margin of 2 to 3 mm. If the primary tumor is located on the medial duodenal wall, a separate submucosal excision is performed through the duodenotomy. The rationale to perform a longitudinal duodenotomy are: (a) the frequency of sporadic gastrinomas arising in the duodenum, occurring in 25% to 50% of patients operated on for ZES; and (b) that duodenal gastrinomas tend to be smaller than pancreatic gastrinomas and are often occult ($<$1 cm). (6) Suspicious lymph nodes are removed and sent to pathology. Although duodenal gastrinomas are often small, 50% to 67% of patients with duodenal primaries can have lymph node metastasis found at operation [33,40,41]. Zogakis et al [39] have reported that patients who had primary duodenal tumors located above the ampulla of Vater, in general, harbored positive lymph nodes in the superior periduodenal area, celiac axis, or periportal area. Those with primary tumors in the third or fourth position of the duodenum had positive lymph nodes in the superior mesenteric artery or inferior periduodenal nodes. Lymph nodes have not been shown to adversely affect survival after resection with curative intent. (7) Enucleation is recommended in tumors in the pancreatic head and in tumors in the body-tail of the pancreas. Distal pancreatectomy or Whipple resection is performed if multiple tumors are present in the left or right pancreas. (8) The role of surgery for MEN-1 ZES patients is debatable [2,33,42,43]. In patients who have MEN-1 with ZES, 70% to 95% of primary tumors arise in the duodenum and 30% to 25% in the pancreas. Akerstrom and Hessman [2] have advocated excision of duodenal gastrinomas, enucleation of possible tumors in the head of the pancreas, regional lymphadenectomy, and distal pancreatic resection (to remove nonfunctioning tumors and thereby reduce the risk of recurrence). However, Cadiot et al [43] have reported in patients who had MEN-1 and ZES, the only independent factor associated with the development of liver metastasis was a pancreatic primary tumor larger than 3 cm. According to these results, surgery should be performed in patients with tumors greater than 3 cm or when gastric excess could be regionalized. The reason for this discrepancy is that biochemical relapse occurs in more than 95% of patients 3 to 5 years after surgery but is associated with an excellent prognosis [42]. Several reports have shown a 62% to 87% 5-year survival rate and a 47% to 77% 10-year survival rate for all patients who had ZES [33,44]. Among patients who had sporadic gastrinoma, 34% were biochemically and radiologically free of disease at 10 years compared with none who had MEN-1 and ZES; the survival rate, however, was 94% [42].

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