Review Article

Role of surgery in pancreatic neuroendocrine tumor

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Abstract: Pancreatic neuroendocrine tumours (PNETs) are rare. They are generally accepted to be slow-growing and have an indolent course. These tumours can be non-functioning or functioning, consisting of a biochemically heterogeneous group of tumours including insulinomas, gastrinomas, carcinoids and glucagonomas. Although surgery remains the mainstay of treatment, controversy still exists especially for non-functioning tumours <2 cm in size. Whether these should be resected or undergo intensive surveillance remains unclear. The surgical approach depends on local expertise. Many studies have shown comparable short-term surgical outcome with laparoscopic pancreatic resection compared to open techniques, however data on long-term oncological outcome are still lacking. On the other hand, liver metastasis occurs in as high as 80% of PNET patients. Five-year survival rate is only 30% if left untreated compared to 60–80% if complete resection is achieved. Current evidence supports liver resection with an aim for symptomatic control and to improve survival in those with respectable disease and no extra-hepatic metastasis. Palliative debunking can be considered in those with intractable symptoms. This article reviews the current evidence on pancreatic resection for PNETs, in particular the role of laparoscopic resection and the management of liver metastasis.

Keywords: Pancreas; neuroendocrine tumor; pancreatectomy; surveillance; liver metastasis

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Introduction

Due to widespread use of cross sectional imaging, incidence of overall neuroendocrine tumour including pancreatic neuroendocrine tumour (PNET) have increased substantially (1,2). PNET are rare and generally slow growing. They represent 3% of all pancreas neoplasms (3). At least 50% of PNETs are non-functioning and hence asymptomatic. As a result, PNETs are commonly an incidental finding diagnosed from imaging for other complaints. Due to the recent widespread use of high-resolution radiological and endoscopic imaging techniques, there is a dramatic rise in the incidence of such tumours. Most PNETs are sporadic in nature. Risk factors include smoking, a high body mass index, and a positive family history which accounts for a variable percentage of patients with inherited syndromes such as multiple endocrine neoplasia type 1 (MEN1). Prognosis of PNETs depends on clinico-pathological factors including tumour size, differentiation and proliferative index which give an indication of the biological aggressiveness of the tumour and likelihood of lymph node involvement (4-6).

Although several guidelines exist to guide the treatment of functioning and non-functioning PNETs (7,8). It is generally accepted that tumours >2 cm and functioning tumours should be resected but the management of non-functioning tumours <2 cm remains controversial. Further controversy exists as to the approach of resection (open *vs.* laparoscopic) and the management of PNETs with liver metastasis which occurs in up to 80% of patients. The aim

of this paper is to review the current evidence of surgical resection in PNETs, the role of laparoscopic surgery and the management of liver metastasis.

Surgery *vs.* active surveillance

In general, it is recommended that PNET which is symptomic, functional, size ≥2 cm or with presence of aggressive features like pancreatic duct dilation should undergo pancreatic resection (9,10). However, it is controversial whether surgery should be recommended for PNET ≤2 cm as primary treatment. Some surgeons recommended upfront surgery, while other guidelines recommended active surveillance for asymptotic small PNET (7,11). Most less than 2 cm PNET were likely in benign and indeterminate risk in malignancy. Only 6% of incidental found smaller than 2 cm non-functioning PNET is confirmed to be malignancy (12). Small PNET (<2 cm) were slowing growing with indolent course, it is considered to be amenable to observation (12-14).

Jung *et al*. reported a retrospective cohort of 145 patients with NET ≤2 cm, in which 85 patients undergoing active surveillance (15). After years of clinical and 1 year of radiological follow up, 82% of patients under active surveillance did not find any change in size of tumor. Sadot *et al.* reported a case-matched comparative study between observation and surgery on patients with treatment naive PNET ≤3 cm (16). While patients in observation was older and tended to be shorter in follow up (44 *vs.* 57 months, P=0.06), median size did not change and no patients in either group was died from the disease at the end of study. Five-year metastasis free survival was comparable between observation and resection (99% *vs.* 88%, P=0.08). Sallinen *et al.* reported a meta-analysis on surveillance strategy for small asymptotic non-functional PNET (17). It included 9 articles with 344 patients with sporadic and 64 patients with MEN1 related non-functional PNET. Majority of patients who selected for active surveillance were having small tumor with tumor size less than 2 and low grade. Some study even considered tumor size ≥4 cm for active surveillance (13). After mean duration of follow up ranged from 32 to 45 months, no patients developed lymph node and distant metastasis. Pool estimate of 22% (range, 0–51%) patients have a growing tumor on follow up. A growth rate of 0.12 mm 1.5%±5.5% per year was reported (14). In another systemic review on active surveillance for 327 patients with sporadic, asymptotic small non-functioning PNET, no disease-specific death was reported during the follow up (18). No distant metastasis was found in PNET ≤2 cm. In one retrospective reported by Rosenberg *et al.*, three patients developed distant metastasis after surveillance for median follow up of 28 months. However, all three patients had the tumor larger than 2 cm (19). Under active surveillance, about 14.1% of patients proceed for pancreatic resection after median follow up of 28–45 months. About 3–14% tumor noted to have increased in size for more than 20% on follow up (14,15). Increasing tumor size, and patient choice were the main reason of surgery. Other reasons of failure in continuous observation included appearance of symptoms and pancreatic duct dilation (18).

Other than indolent natural history of small PNET, surgical morbidity is the other reason advocating active surveillance. Pancreatic surgery is considered as high-risk in morbidity and mortality. Even though post-operative mortality has been reported to be low and around 1% in high-volume center, it increased up to 10% in nationwide study (20,21). It is especially true for tumor locating at the head of pancreas requiring pancreatioduodenectomy. In consideration of management strategy, age, comorbidity, natural history of tumor, morbidity and mortality of treatment have to be taken into account. Therefore, European Neuroendocrine Tumor Society (ENETS) guideline recommended a "wait and see" policy as for PNET <2 cm. Active surveillance with six-monthly and then yearly follow up with imaging were recommended (7,22).

However, there were limitations with the current evidence supporting active surveillance. As PNET is a slow-growing tumor, studies with follow-up up to 3 to 4 years cannot reflect the long-term prognosis. It is important in stratifying patients for surgical interventions, especially young individuals who had found a small PNET. Young patients are likely to live long but have to cope with the stress and the presence of the disease. As the majority of reasons for pancreatic resection is tumor growth, there is a cumulative need for operation in long-term follow up. On the other hand, nearly all studies were retrospective in nature. They did not state the criteria in selecting surgery or observation. The treatment decision was based on patients' age, pre-morbid conditions and patients' decision. It was reflected by the fact that patients in observation were usually older (13,16).

In contrary to retrospective comparative studies supporting active surveillance, registry studies based on nationwide database reported contradictory results. Sharpe

et al. evaluated 380 patients with ≤2 cm PNET from the US National Cancer Data Base (NCDB) from 1998 to 2006 (23). Patients undergoing observation were likely to be older and receiving non-surgical therapy. Five-year overall survival was less than those undergoing surgical treatment (34.3% *vs.* 82.2%, P<0.0001). After controlling the cofounding factors, observation, poorly differentiated histology, lymph node positivity, and nonsurgical therapies were associated with increased mortality. Expectant management had a 2.8-fold risk of having death on follow up. Another study by Gratian *et al.* reported a similar finding. A longer period [1998–2011] and number of patients (1,854 patients) were retrieved from NCDB (24). To evaluate the effect of pancreatectomy, they included non-functional PNETs and non-specific neuroendocrine tumours. They also excluded those patients with unknown surgical status or type of surgery and those with more than one malignant primary tumor. In this study, 303 patients (16%) presented with regional metastasis and 180 (10%) patients presented with distant metastasis were included. Twenty-seven percent of patients who did not underwent surgery were older, more likely to have metastasis, poorly differentiated tumor and be treated in non-academic hospital. After excluding distant metastasis, not offering surgery because of comorbidity and death before surgery, unadjusted 5-year overall survival for patient with small PNET undergoing observation was 27.6% and patients undergoing pancreatic resection was 72.3–86.0%. There was no difference in overall survival between different types of operation. These two studies showed different conclusions with other retrospective studies. Several reasons could explain this finding. Firstly, patients were in the disease status between different studies, as cohort in NCDB study included patients with regional and distant metastasis. While we considered overall survival as the outcome measure, the effect of surgery could be overestimated as patients with lower stage and better performance status would be selected for operation. Secondly, the reasons on surveillance and surgery were not well reported in registry-based studies. The decisions between observation and surgery were multifactorial which included financial status, co-morbidity and access to medical service. It might lead to fundamental difference between patients on decision-making. Thirdly, patients with mild and less aggressive tumor were often underreported. More symptomic tumours with aggressive behavior, like pancreatic duct or bile duct dilation, should be undergoing surgical treatment. It is unsure if these patients were inappropriately chosen for observation.

Laparoscopic resection *vs.* open

Pancreatic surgery with minimally invasive technique was first described in 1990s. Cuschieri *et al.* described a report on laparoscopic distal pancreatectomy, while by Gagner *et al.* reported the first case on laparoscopic pylorus-preserving pancreatioduodenectomy (25,26). Since then, numbers of retrospective study have been reported with satisfactory outcome. Our group has reported one of the earliest series on laparoscopic resection of PNET. Four patients with insulinoma underwent laparoscopic surgery. Two enucleations and two distal pancreatectomies have been performed. Neither major complication nor conversion were reported (27). Zerbi *et al.* conducted a prospective multi-center study including 310 patients with PNET in 24 Italian centers (28). While only 21 out of 262 patients (6%) were operated through laparoscopic approach. Majority of patient (18 cases) had their tumor at body or tail, and 3 tutors were located at head. Majority of laparoscopic pancreatic surfer was successful with the need of conversion. Early reports on laparoscopic pancreatic resection reviewed conversion rate ranged from 9% to 41% (29). Deep adhesions, tumor deeply immersed in the parenchyma and inability to locate the tumor during laparoscopic procedure were the major reasons for conversion (30-32).

Comparing to conventional pancreatic resection, laparoscopic approach has showed comparable surgical outcome. Drymousis *et al.* reported a meta-analysis of 906 patients with PNET comparing laparoscopic to conventional surgery (29). They found that laparoscopic resection had less blood loss (by 67 mL, P=0.008) and shorter length of stay (by 5 days, P≤0.00001). There was no significant difference in rate of pancreatic fistula, operative duration and mortality (29). Tamburrino recently conducted a meta-analysis and reported the similar findings. Comparing to open pancreatic surgery, shorter length of hospital stay (less 4.5 days, P<0.001) and less blood loss (less 66.84 unit, P=0.008) were found in laparoscopic group. There was no difference in duration of operation, overall postoperative complication, rate of pancreatic fistula, re-operation and post-operative mortality. In terms of oncological outcome, two studies have reported the rate of recurrence between laparoscopic and open pancreatic surgery (33,34). In the pooled analysis of two studies, there was 4.2% recurrence in patients undergoing laparoscopic surgery, while it was 9.3% in conventional surgery group. However, it is not statistically significant (odd ratio =0.46, P=0.15) (35).

Due to rarity of the disease, majority of the reported study were retrospective with small sample size. Small low-grade tumours were more likely to be selected for laparoscopic surgery. Selection bias on surgical modality is not negligible. It is reflected by the fact that there was significant difference in age, sex and tumor size between laparoscopic arm and conventional surgical arm (27,28). Therefore, these results have to be interpreted cautiously. Despite the potential bias, these studies confirmed that laparoscopic resection is feasible and safe in patients with PNET. Further studies will be indicated to decide which patients and extent of disease would be best treated with laparoscopic approach. On the other hand, there were limited studies evaluating the oncological outcome after laparoscopic resection. Future randomized controlled trial will be worthwhile to explore the outcome.

Management with liver metastasis

Liver metastasis is very common in patients with NET. 28.3–77% of patients with PNET develop liver metastasis during the course of their disease (36,37). In managing NET with liver metastasis, surgery helps in reducing tumor burden and hormonal secretion in functioning tumor (38,39). If liver metastasis is left untreated, 5-year survival was only 30–40% (40,41). Improved survival has been reported if liver metastasis was resected, especially if complete resection was achieved. 5 years overall survival can be up to 60–80% (42-44). Glazer *et al.* reported a series of 172 patients with NET liver metastasis undergoing liver resection. Median overall survival was 9.6 years, while positive margin did not affect overall survival probability (44). Watzka *et al.* reported their series of 204 patients with hepatic metastasis of NET. In patients with R0 resection, 10-year survival was 90.4% comparing to 53.4% and 51.4% in patients with R1 and R2 resection respectively. On the other hand, poor 10-year overall survival of 19.4% was found in patients cannot undergo liver resection (45). Saxena *et al.* published a systemic review of 29 article in evaluating the efficacy of liver resection in NET liver metastasis (46). Five-year overall survival rate in patients undergoing liver resection was 70.5% (range, 31–100%) and 5-progression free survival was 29% (6–66%). Resection leaded to complete symptomic improvement in 73% of patients (23–92%). On other hand, despite incomplete resection, cytoreductive surgery placed a role not only in reducing the hormonal secretion but also survival benefits. Mayo *et al.* reported a multi-center study on surgical management of NET with liver metastasis. Forty percent of patients was having pancreatic NET as the primary site. Seventy-eight percent of patients underwent liver resection, 3% underwent ablation and 19% underwent both ablation and liver resection as the treatment. Despite 94% of patients have disease recurred at 5 years, 5-year overall survival was 74%. Patients with synchronous disease, non-functional status and extra hepatic disease predicted worse survival outcome (47).

Patients with G1 or G2 PNET, functioning tumor, resectable liver metastasis, absence of extra-hepatic metastasis or Carcinoid Heart's disease should consider liver resection as the primary treatment on NET with liver metastasis (7,22). In patients with unrespectable liver metastasis, debulking surgery should be limited to those with functional tumor or those refractory to other non-surgical treatments. However, most studies reported the outcome of management of NET liver metastasis from different origins, including pancreas, colon, lung, thymus and stomach. Despite increasing number of PNET have been detected, PNET is still considered as a rare disease. There is no single study reporting the outcome on PNET with liver metastasis. Therefore, the best approach to PNET with liver metastasis is yet to be answered.

Conclusions

Due to rarity of PNET, there was limited evidence of best management of patients having PNET. Balancing the surgical risk of pancreatectomy, active surveillance on PNET less than 2 cm should be considered. Laparoscopic pancreatic surgery is feasible in the hand of experienced surgeons. Further studies on optimal management of PNET liver metastasis should be encouraged.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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