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Update on surgical treatment of pancreatic neuroendocrine neoplasms

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Abstract

Pancreatic neuroendocrine neoplasms (PNENs) are rare and account for only 2%-4% of all pancreatic neoplasms. All PNENs are potential (neurendocrine tumors PNETs) or overt (neuroendocrine carcinomas PNECs) malignant, but a subset of PNETs is low-risk. Even in case of low-risk PNETs surgical resection is frequently required to treat hormone-related symptoms and to obtain an appropriate pathological diagnosis. Low-risk PNETs in the body and the tail are ideal for minimally-invasive approaches which should be tailored to the individual patient. Generally, surgeons must aim for parenchyma sparing in these cases. In high-risk and malignant PNENs, indications for tumor resection are much wider than for pancreatic adenocarcinoma, in many cases due to the relatively benign tumor biology. Thus, patients with locally advanced and metastatic PNETs may benefit from extensive resection. In experienced hands, even multi-organ resections are accomplished with acceptable perioperative morbidity and mortality rates and are associated with excellent long term survival. However, poorly differentiated neoplasms with high proliferation rates are associated with a dismal prognosis and may frequently only be treated with chemotherapy. The evidence on surgical treatment of PNENs stems from reviews of mostly single-center series and some analyses of nation-wide tumor registries. No randomized trial has been performed to compare surgical and non-surgical therapies in potentially resectable PNEN. Though such a trial would principally be desirable, ethical considerations and the heterogeneity of PNENs preclude realization of such a study. In the current review, we summarize recent advances in the surgical treatment of PNENs.

Key words: Surgery; Laparoscopy; Liver metastases; Pancreatic neuroendocrine neoplasms; Pancreatic neuroendocrine neoplasm

Core tip: Surgical resection is the only curative treatment for pancreatic neuroendocrine neoplasms (PNENs). Surgical resection should be tailored and parenchyma-preserving whenever possible. Laparoscopic approaches are feasible and safe for pancreatic body and tail lesions. Regional lymph node dissection may prolong disease free survival. Cytoreductive surgery and palliative debulking (> 90%) of PNET liver metastases may extend survival. The most relevant prognostic factors are surgical intervention, tumor differentiation, patient age, and distant metastases.

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INTRODUCTION

Pancreatic neuroendocrine neoplasms (PNENs) are rare with an incidence of about 1/100000 per year causing

only 1%-4% of all clinically apparent pancreatic neoplasms[1-3]. Most PNENs are sporadic but about 10% are part of inherited disorders such as multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis and tuberous sclerosis.

PNENs seem to arise from the islet cells of the pancreas and may or may not secrete functionally active hormones and can therefore be classified as functional or non-functional tumors. Functional tumors are usually detected early due to the symptoms caused by hormone production. Recent studies suggest that most PNENs are non-functional and therefore diagnosed either incidentally or late due to unspecific symptoms caused by the local or distant tumor mass. However, the traditional distinction between functional and non-functional tumors has become clinically largely irrelevant since this distinction does not influence prognosis or treatment options.

A clinically much more relevant classification is the generally accepted grading of PNENs on the basis of the 2010 WHO classification for gastroenteropancreatic neuroendocrine tumors and the expression of the cell proliferation marker Ki-67. Accordingly, PNENs are graded as G1 [mitotic count < 2/10 high power fields (HPF) and a Ki-67 index < 3 %], G2 (mitotic count of 2-20/10 HPF and a Ki67 index of 3%-20%), and G3 (mitotic count > 20/10 HPF and/or a KI-67 index > 20%). Differentiation on the other hand refers to the extent to which the neoplastic cells resemble their non-neoplastic counterparts[4]. In general, well differentiated PNENs are either low or intermediate grade (G1 + G2) and are termed neuroendocrine tumors (PNETs), while poorly differentiated PNENs are considered high grade (G3) and are called neuroendocrine carcinomas (PNECs).

The differential diagnosis between PNENs and pancreatic ductal adenocarcinoma (PDAC) is especially important because major differences in tumor biology require different surgical treatment strategies. Since PNET patients have a much better prognosis than PDAC patients, surgery is more frequently the treatment of choice. This review will provide an update on current surgical treatment options for patients with PNENs.

SURGICAL TREATMENT OF PNETS

Surgical resection of PNETs remains the only curative approach and must therefore be regarded as the current standard of care even in many cases where advanced disease is found[5-7]. However, only about two thirds of the patients present with technically resectable disease. Tailored surgical approaches are therefore needed to deal with this very heterogenic disease.

Management of low risk disease

PNETs show a benign biological behavior in 10%-40%, most of them being insulinomas[8]. If benign PNETs are solitary and easily accessible, local resection/enucleation is generally preferred[9]. In this respect, a recent study demonstrated the importance of intraoperative bi-digital palpation and ultrasonography (IOUS) in localizing these lesions[10]. Besides, IOUS is useful in clarifying the association of the tumor lesions, the pancreatic vasculature and particularly, the main pancreatic duct. Therefore, it provides important information in deciding between enucleation and resection[10]. When the tumor is located further than 2-3 mm from the pancreatic duct, an enucleation is generally preferred to pancreatic resection[5]. Furthermore, preoperative endoscopic tattooing of lesions in the pancreatic head or tail seems to be a feasible alternative for intraoperative localization of the tumor especially for laparoscopic surgical procedures[11]. When enucleation seems possible, the tumor is carefully dissected off the surrounding pancreatic tissue[12]. After resection, a drain may be placed at the resection site[12]. As an alternative in cases where enucleation seems impossible, middle segmental pancreatic resection may be performed as a parenchyma-preserving technique[13]. Such organ preserving strategies are nowadays safe in experienced hands with low morbidity and mortality[13,14]. Although parenchyma-preserving techniques have slightly increased morbidities (76%) and pancreatic fistula (69%) compared to standard resections (58% and 42%), the patients do clearly benefit in terms of pancreatic endo- and exocrine function[14]. Organ preserving pancreatic surgery leads to only 3%-5% impairment of endo- and exocrine function, whereas in standard resections this rate can increase up to 21%-32%[14]. Furthermore it seems evident, that while performing organ preserving and locally limited surgery the patients are not put at risk concerning postoperative survival compared to standard resections[14].

Laparoscopic resection seems to be ideal for insulinomas that are usually benign, small, and located in the body or tail of the pancreas; this procedure has been shown to carry a low risk of morbidity and mortality[15,16]. However, because of the difficult preoperative assessment of the nature and extension of the tumor, a conversion to open surgery is frequent. Recently, robot-assisted minimally-invasive pancreatic resections have been suggested to be superior to the laparoscopic approach since conversions to open surgery can be significantly reduced (conversion rate of 0% *vs* 16%) without increased morbidity[17]. The robot-inherent disadvantages of a lack of haptics, a steep learning curve and high costs however prevent many centers from implementing this technique. Nevertheless, in the presence of tumors with a high probability of malignancy, or in the absence of a cleavage plane to duct and blood vessels, open surgery may be considered in the first place[12].

There is an ongoing debate on the role of lymph node dissection in PNEN surgery. When considering organ preserving surgery for low risk PNENs other than insulinomas, recent data showing a positive lymph node status in up to 23% of low risk PNENs with significantly shorter disease free survival (mean 4.5 years *vs* 14.6 years; $P < 0.0001$) should be considered[18]. The frequency of lymph node metastases was reported to be higher for tumors > 15 mm, tumors in the head as compared to tumors in the

body and the tail, tumors with higher proliferation rates (G3), and with lymph vessel invasion (L1)[18,19]. Partelli and colleagues developed two predictive models to assess the risk of positive lymph nodes in non-functional PNENs, one with histopathological grading and one without[20]. In addition to the previously mentioned factors, radiological nodal status was associated with lymph node metastases in their study[20]. However, considering current evidence, it seems that preoperative variables are not able to predict the probability of nodal involvement sufficiently enough to omit regional lymphadenectomy. Therefore, regional lymphadenectomy is suggested for patients undergoing pancreatic resections for PNENs.

Management of high risk/malignant disease

In case of malignancy, recent studies proved that extensive surgery is superior to conservative therapies in extending patients' survival and in controlling local and metastatic disease.

Early and locally advanced disease

In case of localized tumors, the aim of surgery is to achieve curative resection and to prevent or delay local or metastatic recurrence. Here, oncological resections (partial pancreaticoduodenectomy or distal pancreatic resection) are required. A recent study showed a survival benefit of 79 mo for resected patients compared to those patients who were recommended for but did not undergo resection (114 mo *vs* 35 mo; $P < 0.0001$)[21]. However, one should note that in this study patients that were recommended for but did not undergo resection showed considerably more often distant metastases when compared to the group of resected patients (58.3% *vs* 28.4%). Nevertheless, the survival advantage of resection appeared to hold true also for the subgroup of patients with distant metastases (60 mo *vs* 31 mo, $P = 0.01$). Even though these data are retrospective, they suggest an impressive benefit of surgical resection in extending survival. Furthermore, resection has been shown to reduce the risk for the development of metachronous liver metastases. Patients with gastrinoma that underwent surgical resection developed significantly less metachronous liver metastasis (5%) than those without surgery (29%)[22].

In locally advanced tumors that involve surrounding organs or tissues, an aggressive surgical intervention is technically feasible in selected patients and may offer appropriate disease control[23]. Besides, resection of locally advanced tumors with major blood vessel involvement and the necessity for vascular reconstruction can be beneficial[24]. Unfortunately local recurrence is frequent after these interventions, and surgery in most cases is an intervention offering long term palliation rather than cure[25]. Interestingly, a margin-positive resection in locally advanced PNETs seems to offer a similar overall survival compared to margin-negative resections[26]. Therefore, a resection of locally advanced PNETs might even be attempted when margin-positivity is expected; however, a pre-operative assessment of putative tumor biology is the key to successful PNET surgery.

Metastatic and recurrent disease

Liver metastases are commonly observed in PNEN patients and are present in up to 60% at initial diagnosis[27]. At that point, only a small fraction of patients are technically and/or oncologically resectable[28]. However, the presence of both synchronous or metachronous liver metastases does not generally represent a contraindication to surgical treatment of PNEN patients[29,30]. It is still unclear when and whether the primary tumor should be resected in non resectable metastatic disease[31]. Concerning liver metastases, a significantly higher 5 year survival (72% *vs* 25%) and a longer median survival (96 mo *vs* 20 mo) has been observed in resected patients compared to non-resected ones[32]. A relevant oncological benefit can be achieved by palliative surgical debulking of more than 90% of liver metastases, as also advocated by the recent ENETS guidelines[7,33,34]. In the presence of bilobar hepatic PNEN metastasis, resections may be performed safely in two-stage procedures in selected patients[35]. In addition, in the palliative setting, surgical cytoreduction has proven more efficient than transarterial chemoembolisation alone[36]. Another more recent option for the treatment of disseminated liver metastases is the selective internal radiation therapy (SIRT) with yttrium-90 labeled glass microspheres[37]. This radioembolisation therapy has been shown to be especially effective for the treatment of liver metastases of colorectal and neuroendocrine tumors[38]. However, multi-disciplinary therapeutic approaches in specialized centers are frequently required to maximize tumor mass reduction. In particular, surgical resection can be complemented by other liver-directed therapies such as radiofrequency ablation[32] or transcatheter arterial (chemo)embolisation[6].

Recurrence is a frequent finding and therefore re-operation for metastatic disease is frequently needed and can result in excellent long term survival of up to 70% after 10 years[30]. For early detection of PNEN recurrence, gallium-68 DOTATATE PET-CT may be helpful[39]. PNENs with a KI-67 index of more than 5%, positive lymph nodes, and tumor size > 4 cm are associated with a significantly higher risk for recurrence[40,41]. These data demonstrate that aggressive surgical resection can improve survival even in metastatic and recurrent disease.

In selected individual cases liver transplantation may be a treatment option, but evidence is limited and the oncological outcome uncertain[42]. Rosneau and colleagues reported 1-, 5- and 10- years survival rates of 89%, 80% and 50% in a study involving 17 patients[43] which is not better than what can be achieved by aggressive surgical debulking[33]. Furthermore, considering the lack of organs, this indication is reserved for highly selected patients[7,44]. The UNOS/Eurotransplant waiting lists for liver transplantation stratify patients by disease severity using the (lab)MELD score based on laboratory parameters. For some diseases (*e.g.*, HCC or cystic fibrosis) this labMELD score does not sufficiently mir-

ror disease severity, therefore standard exceptions have been defined for which a matchMELD can be assigned. However, liver metastases of neuroendocrine tumors are not considered a standard exception according to current waiting list criteria of Eurotransplant/UNOS and therefore these patients do not qualify for a standard exception matchMELD. Nevertheless, in cases where the treating physicians believe that liver transplant might be a viable option, a non-standard exception matchMELD score can be applied for. These exceptional cases are then judged upon on an individual basis by an expert committee. Steve Jobs, former CEO of Apple Inc., is the most prominent of these very select cases and received a liver transplant for metachronous PNEN liver metastases at the Methodist University Hospital Transplant Institute in Memphis, Tennessee in 2009[45,46].

PNECs-high grade disease

Pancreatic neuroendocrine carcinomas with a high KI-67 index show an increased risk for recurrence and metastatic disease and survival is poor[40]. Therefore resection in patients with poorly differentiated PNECs with a high proliferation index should currently only be attempted when an R0 resections seems possible[7]. There is currently no role for cytoreductive surgery in these highly malignant cases. In advanced disease, targeted therapies (*e.g.*, VEGF and mTOR inhibitors) are increasingly acknowledged to be superior to conventional chemotherapy in case of poorly differentiated PNECs.

PROGNOSTIC CONSIDERATIONS

For all PNENs, the 5- and 10-year survival rates are about 65% and 45%, respectively[47]. Tumor grade plays a significant prognostic role since patients with high grade PNENs have a much worse 5-year survival of less than 30%[48]. Other positive prognostic factors include young age < 55 years and absence of distant metastases[48]. Of these three parameters, Bilimoria and colleagues developed a prognostic score predicting survival after surgical resection[48]. For this prognostic score, points from 0 to 3 are given for age (< 55 years = 0 points, 55-75 years = 1 point, > 75 = 2 points), differentiation (well/moderately differentiated = 0 points, poorly differentiated = 1 point), and metastases (none = 0 points, liver = 1 point, other distant = 3 points)[48]. A prognostic score from 1 to 3 can then be assigned where prognostic score 1 was defined as a total of 0 points, a prognostic score of 2 was defined as a total of 1-2 points and a prognostic score 3 was defined as > 2 points[48]. Using this scoring system - which can be easily applied to every patient as soon as histology is available - Bilimoria and colleagues were able to show that patients with a prognostic score 1 had a favorable 5 year survival of 76.7% compared to 50.9% for prognostic score 2 and 35.7% for prognostic score 3[48]. While these data have been generated retrospectively and a validation on an independent cohort is lacking, this tool may still be helpful in estimating patient's survival and may therefore assist in adjuvant treatment decisions.

CONCLUSION

PNENs are rare neoplasms of the pancreas with a disease course considerably different from PDAC. Aggressive and extensive surgery may be an option for many patients suffering from locally advanced and even metastatic disease. This may in select cases involve resection of multiple organs to achieve a significant reduction of the tumor mass. In patients with PNEN liver metastasis, debulking of > 90% of the macroscopically visible tumor mass - if technically feasible - seems to extend overall survival. However, current evidence stems from retrospective, non-randomized studies, but obvious ethical and feasibility considerations preclude realization of such a trial. In addition, exceptional heterogeneity of PNENs in terms of tumor biology renders thoughtful design of inclusion and exclusion criteria of such a trial impracticable.

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