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ORIGINAL ARTICLE – PANCREATIC TUMORS

Surgical Management of Advanced Pancreatic Neuroendocrine Tumors: Short-Term and Long-Term Results from an International Multi-institutional Study

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ABSTRACT

Background. The role of extended resections in the management of advanced pancreatic neuroendocrine tumors (PNETs) is not well defined.

Methods. Between 1995 and 2012, 134 patients with PNET underwent isolated (isoPNET group: 91 patients) or extended pancreatic resection (synchronous liver metastases and/or adjacent organs) (advPNET group: 43 patients).

Results. The associated resections included 27 hepatectomies, 9 vascular resections, 12 colectomies, 10 gastrectomies, 4 nephrectomies, 4 adrenalectomies, and 3 duodenojejunal resections. R0 was achieved in 41 patients (95 %) in the advPNET. The rates of T3–T4 (73 vs 16 %; $p < .0001$) and N+ (35 vs 13 %; $p = .007$) were higher in the advPNET group. Mortality (5 vs 2 %) and major morbidity (21 vs 19 %) rates were similar between the 2 groups. The 5-year overall survival (OS) of the series was 87 % in the isoPNET group and 66 % in the advPNET group ($p = .006$). Only patients with both locally advanced disease and liver metastases showed worse survival ($p = .0003$). The advPNET group developed recurrence earlier [disease-free survival (DFS) at 5 years: 26 vs 81 %; $p < .001$]. In univariate analysis, negative prognostic factors of survival were: poor degree of differentiation ($p < .001$), liver metastasis ($p = .011$), NE carcinoma ($p < .001$), and resection of adjacent organs ($p = .013$). The multivariate analysis did not highlight any factor that influenced OS. In multivariate analysis independent DFS factors were a poor degree of differentiation ($p = .03$) and the European Neuroendocrine Tumor Society stage ($p = .01$).

Conclusions. An aggressive surgical approach for locally advanced or metastatic tumors is safe and offers long-term survival.

Pancreatic neuroendocrine tumors (PNETs) are rare and evolve over long periods of time.[1,2] In recent years, PNETs have been diagnosed in increasing numbers, often as *incidentalomas*, because of the widespread use of cross-sectional imaging.[2–4] PNETs represent a heterogeneous group of neoplasms with a variable clinical profile that depends on histological features and disease staging.[5] The optimal treatment for PNET is curative surgical resection, which controls tumor growth and reduces excessive hormone production in patients with liver metastases and provides a 5-year overall survival (OS) exceeding 60 %.[6–8] However, only 20–40 % of patients diagnosed with PNETs are eligible for complete surgical resection.[4,9,10] At diagnosis, distant metastases are present in up to 60–80 % of PNETs.[4,9,10] Pancreatic resection is usually not performed when pancreatic malignancies involve other organs. However, in PNETs, aggressive surgical resections may be performed to achieve useful palliation, and excellent survival has been demonstrated for patients with small locally advanced tumors.[11–15] The favorable prognosis of PNET encourages aggressive treatments; but the treatment strategy is

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under debate. Some studies have suggested aggressive resection, whereas others recommend observation.[7,8,13,14,16–21]

It is difficult to determine relevant guidelines because these tumors are uncommon, and most studies are small and retrospective.

To determine whether extended resections for advanced PNET influence survival, we conducted a multicentric retrospective review of patients with advanced PNET undergoing surgery over the last 2 decades. We analyzed short- and long-term outcomes compared with isolated PNETs.

MATERIALS AND METHODS

Data Collection

Patients with PNET undergoing pancreatic resection in four European centers [Institut Paoli-Calmettes, Hôpital Nord, Hôpital de la Conception (Marseille, France), and Ospedale Maurizano (Turin, Italy)] from January 1, 1995 to December 31, 2012 were considered. Patients were identified from prospective, institutionally approved databases, and their data were reviewed retrospectively. Patients with symptoms and/or biochemical evidence of excess hormonal secretion were considered to have functional tumors. The diagnosis of multiple endocrine neoplasms (MEN1) and Von Hippel-Lindau (VHL) diseases was based on standard criteria.[22,23]

Preoperative tumor staging was based on computed tomography (CT) and/or magnetic resonance (MR), endoscopic ultrasound, or somatostatin receptor scintigraphy at the discretion of the surgeon. In recent years, PET-CT was performed in selected patients.

Patients with an isolated endocrine tumor localized to the pancreas (isoPNET) and patients with an advanced PNET (patients with synchronous liver metastases and/or with local infiltration into adjacent organs; advPNET) were separated based on surgical descriptions and pathology. Inclusion criteria were a complete surgical resection of both the primary tumor and liver metastases. Patients with incomplete resections (R2) or unresected synchronous PNET liver metastases were excluded. Only patients with histologically documented PNET were included. Patients with extrahepatic metastases were not included.

Surgical indications were discussed in a multidisciplinary pancreatic tumor board (MPTB). The histological diagnosis of PNET was based on conventional histology and immunohistochemistry (chromogranin A, synaptophysin and Ki67). All specimens were reviewed and classified based on the WHO 2010 (World Health Organization) classification and assigned an European Neuroendocrine Tumor Society (ENETS)/TNM-based stage and grading score.[24,25]

Surgery

All PNETs were treated with curative intent, i.e., pancreaticoduodenectomy (PD), left pancreatectomy (LP), total pancreatectomy (TP), central pancreatectomy (CP), or enucleation (EN) based on the primary tumor localization.

Standard pancreatectomies (PD and LP) were performed at the discretion of the surgeon. Pancreatic-sparing resections (EN) were performed when the tumor was near or at the surface of the head or body of the pancreas, sufficiently far (at least 1–2 mm) from the main pancreatic duct. If EN was not possible, CP was performed.

In patients with synchronous liver metastases, pancreatectomy was associated with 1- or 2-stage liver resection, based on hepatic involvement.[26] Hepatic resection was considered major if at least 3 or more contiguous Couinaud segments were resected.[27]

Perioperative treatment with a somatostatin analog was used to minimize hormonal symptoms. Chemotherapy (including gemcitabine, VP16, streptozotocin, and 5-fluorouracil/doxorubicin) was administered when recommended by the MPT.

Postoperative Course and Follow-Up Postoperative mortality included all deaths occurring prior to hospital discharge or within 30 days of the surgery. Morbidity included all complications following the surgery until discharge and/or readmission and was graded based on the Clavien-Dindo classification system.[28] Postoperative pancreatic fistula was classified based on the International Study Group of Pancreatic Surgery (ISGPS).[29] Bile leak was defined as a bilious drainage from drains or bile collection requiring drainage and postoperative bleeding as the requirement of transfusion or endoscopic or operative intervention.

Follow-up was based on clinical, radiological, and laboratory assessments. Visits were scheduled every 6 months for the 5 first years and yearly thereafter. Detection of recurrence was based on CT scans and chromogranin A serum levels in appropriate cases.

Statistical Analyses

Data were analyzed using R 3.0.2 and SAS 9.3. Overall survival (OS) time was measured from the time of pancreatic resection until death or the final follow-up. Disease-free survival (DFS) was defined as the time elapsed between the date of resection and the date of death or the occurrence of metachronous metastasis or final follow-up. Differences between the groups were assessed using the Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The Kaplan–Meier method was used to calculate OS and DFS, and groups

were compared using the log-rank test. Multivariate analysis was done using a Cox proportional hazard model to identify independent prognostic factors of OS and DFS. Multivariate analysis was completed for factors with a p value $\leq .10$ in the univariate analysis. A p value $<.05$ was considered significant for all tests.

RESULTS

Clinical Characteristics

A total of 161 patients with PNET underwent surgical resection; 27 with unresected synchronous PNET liver metastases were excluded. Of the remaining 134 patients who underwent complete resection, 91 patients (68 %) had isoPNET and 43 (32 %) had advanced PNET.

Patient and tumor characteristics are summarized in Table 1. A total of 115 patients (85 %) had nonfunctional tumors, 8 patients had MEN, and 3 patients were diagnosed with VHL syndrome. The median age was 58 years (range, 20–83 years). Tumors were typically located in the tail ($n = 76$; 57 %) of the pancreas.

In the advPNET group, 16 patients (37 %) underwent en bloc resection of adjacent organs, 18 (42 %) underwent primary tumor resection with complete synchronous liver metastases resection, and 9 (21 %) underwent en bloc resection of adjacent organs with complete liver metastases resection. Of the 27 patients with liver metastases, 10 (37 %) had bilobar liver metastases, and 9 (33 %) had more than 4 liver metastases.

Surgery and Postoperative Course

Pancreatic surgical procedures and postoperative courses are summarized in Table 1. The most common resection types were PD ($n = 51$; 38 %) and LP ($n = 65$; 48 %). Pancreatic-sparing resections were performed in 14 patients (10 %), including only 1 advPNET patient. In the advPNET group, the resection of adjacent organs included 10 gastric (7 %), 12 colonic (9 %), 4 renal (3 %), 3 adrenal (2 %), and 3 duodenojejunal resection (2 %). In 9 patients (21 %), the portal vein was resected as a result of macroscopic neoplastic infiltration. Also, 27 patients (63 %) underwent associated liver resection, including 3 2-stage hepatic procedures. Of the 24 patients who underwent 1-stage procedures, 19 had minor and 5 had major hepatectomies.

The overall mortality and morbidity were 3 % ($n = 4$) and 50 % ($n = 67$), respectively, including severe complications (Clavien-Dindo grade 3–4) in 19 % of patients ($n = 26$). Pancreatic fistulas occurred in 32 % of patients ($n = 43$), and 19 % ($n = 26$) developed clinically significant fistulas (i.e., grade B or C). Hemorrhage occurred in

TABLE 1 Patient and tumor characteristics based on the circumstances of diagnosis, surgical procedure, and postoperative complications in both groups

	Overall	Isolated PNET $n = 91$; n (%)	Advanced PNET $n = 43$; n (%)	p value
Age (years, median)	58 (20–83)	57 (20–83)	60 (31–82)	0.357
Male gender	72 (54)	44 (48)	28 (65)	0.069
Type of tumor				
Non-functional tumor	115 (85)	75 (82)	40 (93)	0.100
Functional tumor	19 (15)	16 (18)	3 (7)	
Tumor location				
Head	51 (38)	38 (42)	17 (39)	0.912
Body	7 (5)	3 (3)	2 (5)	
Tail	76 (57)	50 (55)	24 (56)	
Surgical resection				
Standard pancreatectomies	120 (90)	78 (86)	42 (98)	0.034
Pancreatic sparing resection	14 (10)	13 (14)	1 (2)	
Postoperative mortality	4 (3)	2 (2)	2 (5)	0.435
Morbidity				
Overall	64 (50)	45 (49)	19 (44)	0.145
1–2	38 (28)	28 (31)	10 (23)	0.475
3–4	26 (19)	17 (19)	9 (21)	
Pancreatic fistula	43 (32)	33 (36)	10 (23)	0.132
Postoperative bleeding	12 (9)	10 (11)	2 (5)	0.230
Biliary fistula	5 (4)	1 (1)	4 (9)	0.019

TABLE 2 Pathological characteristics in both groups

	Overall	Isolated PNET $n = 91$; n (%)	Advanced PNET $n = 43$; n (%)	p value
Tumor size (mm)	30 (8–160)	22 (8–120)	40 (10–160)	<0.001
<20	42 (31)	38 (42)	4 (9)	0.0002
TNM classification				
T1–T2	79 (65)	68 (84)	11 (27)	<0.0001
T3–T4	43 (35)	13 (16)	30 (73)	
Nodal status				
N0	87 (65)[a]	63 (69)[b]	24 (56)[c]	0.007
N1	27 (20)	12 (13)	15 (35)	
ENETS stage				
Stage I–II	60 (54)	58 (83)	2 (5)	<0.0001
Stage III–IV	52 (46)	12 (17)	40 (95)	
Resection margin				
R0	126 (98)	87 (100)	39 (95)	0.037
R1	2 (2)	0	2 (5)	
WHO 2010 grading				
NET-G1	49 (44)	42 (54)	7 (21)	0.001
NET-G2	46 (42)	29 (38)	17 (52)	
NEC-G3	15 (14)	6 (8)	9 (27)	
Microangio invasion	49 (56)	25 (50)	24 (75)	0.007
Perineural invasion	46 (55)	22 (41)	24 (83)	0.0002
Mitotic count (/10 HPF)				
>2 mitosis/10 HPF	23 (28)	9 (16)	14 (54)	0.0004
Ki67				
>2 %	58 (60)	34 (51)	24 (83)	0.003

[a] No nodes were present in the specimen (Nx) in 20 cases

[b] No nodes were present in the specimen (Nx) in 16 cases

[c] No nodes were present in the specimen (Nx) in 4 cases

9 % ($n = 12$) of patients. Also, eight patients required reoperations for hemorrhage.

Overall mortality ($p = .435$) and morbidity ($p = .145$) were not more frequent in advPNET. Anastomotic biliary fistulas were more frequent in the advPNET group ($p = .019$) than in the isoPNET group. Major morbidity was not different between the two groups ($p = .475$).

Of the patients who received a portal vein resection/reconstruction, mortality and morbidity rates were 11 % ($n = 1$) and 44 % ($n = 4$), respectively, including severe complications (Clavien-Dindo grade 3–4) in 3 patients (33 %). No thrombosis or hemorrhagic complication occurred. None of the patients with portal vein resection developed specific postoperative portal vein thrombosis or hemorrhage.

Pathological Findings

Results from the pathological analyses are summarized in Table 2. The median tumor size was 30 mm (range 8–160 mm). There were 25 tumors (22 %) classified as stage I, 35 (31 %) as stage II, 24 (22 %) as stage III, and 28 (25 %) as stage IV.

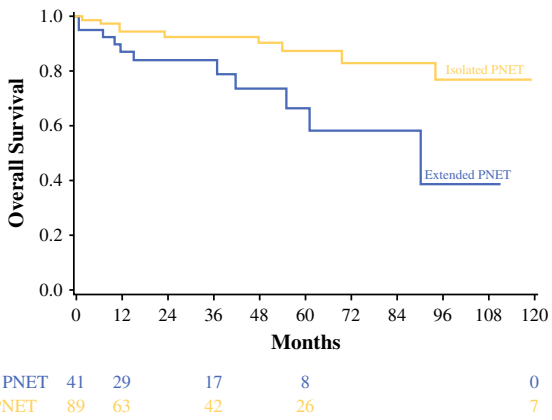

FIG. 1 Overall survival rate in the isoPNET and advPNET groups

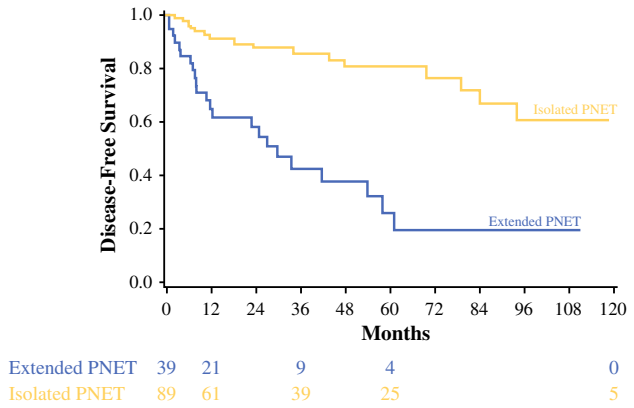

FIG. 2 Disease-free survival rate in the isoPNET and advPNET groups

AdvPNET patients showed fewer tumors ≤20 mm ($p = .0002$) and fewer tumors staged as T1–T2 ($p < .0001$) or N0 ($p = .007$) than isoPNET patients. Microangioinvasion ($p = .007$), perineural invasion ($p = .0002$), mitotic counts >2/10 ($p = .0004$), and the Ki67 index >2 % ($p = .003$) were lower in the isoPNET group than in the advPNET group.

Survival

Median survival time was not reached in the isoPNET group and was 90 months in the advPNET group. The 1-, 3-, and 5-year overall survival rate in the isoPNET and advPNET groups was 95, 93, and 87 % versus 87, 84, and 66 %, respectively ($p = .006$; Fig. 1).

In the advPNET group patients with completed liver metastases clearance ($n = 18$), the median survival time was not reached with a 5-year OS of 66 %. There was no difference in overall survival between the isoPNET group and this subgroup of patients ($p = .124$). For patients undergoing en bloc resections of adjacent organs ($n = 16$), the median survival time was 90 months with a 5-year OS of 84 %, which was not different from the isoPNET group ($p = .175$). However, when patients underwent en bloc resections of adjacent organs with liver metastases resections ($n = 9$), the median survival time was 55 months with a 5-year OS of 39 % and was lower than for patients with isolated disease ($p = .0003$). Univariate analyses showed that WHO classifications ($p < .001$), grading tumor ($p < .001$), Ki67 >2 % ($p < .001$), liver metastases ($p = .011$), biliary fistula ($p = .004$), and resection of adjacent organs ($p = .013$) were the only prognostic factors of survival. The multivariate analysis did not highlight any factor that influenced OS.

Local nodal recurrence was experienced by 1 patient (1 %), and 33 patients (25 %) showed liver recurrence.

TABLE 3 Multivariate analysis of clinicopathologic- and treatment-related factors for disease-free survival after PNET resection

Parameters/classes	Disease-free survival		
	Univariate	Multivariate analysis	
	p value Log rank	*p* value Log rank	OR (95 % CI)
Gender			
Female	0.956	n.s.	
Male			
Functioning tumor			
No	0.104	n.s.	
Yes			
Tumor size (mm)			
<20	0.002	n.s.	
≥20			
Advanced PNET			
No	<0.001	n.s.	
Yes			
Synchronous liver metastases			
No	<0.001	n.s.	
Yes			
Vascular resection			
No	0.022	n.s.	
Yes			
Adjacent organ resection			
No	0.001	n.s.	
Yes			
Dindo classification			
1, 2	0.669	n.s.	
3, 4			
pT			
T3, T4	0.013	n.s.	
T1, T2			
pN			
N−	0.398	n.s.	
N+			
pM			
M0	<0.001	n.s.	
M1			
Resection margin			
R0	0.251	n.s.	
R1			
Mitotic count			
<2 mitosis/10 HPF	0.002	n.s.	
≥2 mitosis/10 HPF			
WHO 2010 grading			
NET-G1	<0.001	.0398	1
NET-G2			1.520 (.519–4.454)
NEC-G3			6.069 (1.349–27.308)
KI67 (%)			

TABLE 3 continued

Parameters/classes	Disease-free survival		
	Univariate	Multivariate analysis	
	p value Log rank	*p* value Log rank	OR (95 % CI)
<2	<0.001	n.s.	
≥2			
ENETS stage			
III–IV	<0.001	.0104	1
I–II			.278 (.090–.855)

Treatment of recurrent liver metastases was multimodal including liver resection ($n = 9$), chemoembolization ($n = 11$), radiofrequency ablation or chemotherapy ($n = 17$), and liver transplantation ($n = 1$). Patients with extended resections developed tumor recurrence earlier ($p < .0001$); the 1-, 3-, and 5-year DFSs for patients with isoPNET and advPNET resections were 91, 88, and 81 % versus 65, 58, and 26 %, respectively ($p < .001$) with a median DFS of 171 versus 30 months, respectively (Fig. 2). In the advPNET group, patients with complete liver metastases clearance showed a 5-year DFS of 15 %. There was a difference in the DFS rate between the isoPNET group (81 % at 5 years) and this subgroups of patients ($p < .001$). For patients undergoing en bloc resections of adjacent organs, the 5-year DFS was 42 % and was not different from the isoPNET group (81 % at 5 years; $p = .011$). Furthermore, when patients underwent en bloc resections of adjacent organs with liver metastases resection, the 5-year DSF was 15 % and was lower than patients with isolated disease ($p < .0001$).

Multivariate analyses including typically reported PNET prognostic factors (such as tumor size, presence of positive lymph nodes, and tumor grade) showed that the WHO 2010 grade ($p = .03$) and ENETS stage ($p = .01$) were the only independent prognostic factors of DFS (Table 3).

DISCUSSION

PNET is a rare tumor, and it is difficult to accumulate sufficient cases to determine pertinent clinical guidelines.[30] We collected a large series of extended resections for local and/or metastatic PNET. Consequently, we have shown that extended resections can be performed safely with acceptable severe morbidity (21 %) and mortality (5 %), which is consistent with results from other published series.[7,31–36] Furthermore, the 5-year overall survival of our patients was 66 %, which is higher than the survival reported for unresected patients in the literature (approximately 45 %).[21]

Concurrent resection of both the primary cancer and hepatic metastases has been criticized because of the presumed perioperative risks associated with simultaneous pancreatic and hepatic resections and the poor prognosis associated with advanced-stage cancers.[14,37] However, several studies have reported successful aggressive resections with acceptable morbidity (11–44 %) and mortality (0–17 %).[7,31–36] In our study, the morbidity rate in the advPNET group did not differ from that reported for isolated pancreatectomies (30–40 %) or partial hepatectomies (30 %) for malignancy and was not different from the isoPNET group.[38,39]

Only a few reports discuss the role of vascular resection/reconstruction in patients with locally advanced PNET.[31,40–43] In patients with locally advanced pancreatic adenocarcinoma, vascular reconstruction provides acceptable morbidity, mortality, and better survival compared with unresected patients.[44] Norton et al.[42] presented patients who underwent pancreatic resection with vascular resection and reconstruction for locally advanced PNET and demonstrated that aggressive surgery including superior mesenteric vein reconstruction and liver resection could be performed with acceptable morbidity and mortality in these patients. Our study also supports this conclusion.

Almost 10 % of liver metastases are of neuroendocrine origin. Conventional hepatectomy is rarely possible because approximately 90 % of metastases are multifocal and bilateral.[45] In our study, 37 % of the patients showed bilobar liver metastases. Some studies have reported that the presence of liver metastases was the only prognostic factor associated with poor survival.[46,47] The management of patients with liver metastases remains under debate; significant long-term survival may be achieved with aggressive treatment.[7,8,13,14,20,21] Complete surgery should be considered in all patients with completely resectable metastatic disease, and palliative surgery should also be considered in selected patients because it may delay or reduce the subsequent need for medical therapy.[7] Surgical debulking may achieve symptom palliation and prolonged survival in patients with neuroendocrine liver metastases.[8,31,37] Patients with large pancreatic neuroendocrine tumors show excellent symptom control with surgery and can expect a good outcome.[48] We have shown that advanced PNET is associated with more aggressive features than isolated PNET; however, when surgical resection is achievable, the 5-year survival rate is 66 %. Only patients with both locally advanced disease and liver metastases showed worse survival (39 % at 5 years), whereas patients with nonmetastatic locally advanced disease or those with primary tumors confined to the pancreas and isolated liver metastases showed an overall survival similar to isoPNET.

Even though PNETs are slow growing, the primary cause of death in these patients is liver metastasis. Reported recurrence rates range from 24.5 to 36.3 %, with a median time of recurrence ranging from 6 to 38 months, and the most frequent site of recurrence is the liver.[7,8,36,46] Of the therapeutic options, liver transplantation for PNET liver metastases remains controversial. It is imperative to avoid resections of the primary tumor at the same time as the transplantation and, in cases of transplantation, to avoid transplanting patients with poorly differentiated metastases (Ki67 >10 %) and/or tumor hepatomegaly.[49,50]

Several prognostic factors for PNET have been proposed.[7,32,33,35,36,51,52] Some studies reported that the presence of liver metastases was the only prognostic factor associated with poor survival.[46,47] In our series the patients with liver metastasis showed reduced survival rates. However, in multivariate analysis, synchronous liver metastasis was not a relevant factor.

Furthermore, as already reported, functioning or non-functioning PNETs did not influence survival.[34,36,51] As shown in our study, the majority of reports agree that a lymph node positive disease does not preclude resection and does not affect overall survival dramatically.[32,33,35,36,53]

Tumor grade and ENETS stage were the only independent prognostic factors of DFS in multivariate analyses, as has been reported by others.[54] Even if extended resections improved long-term survival, advPNET patients developed tumor recurrences earlier than isoPNET patients.

In conclusion, we showed that an aggressive resection may improve long-term survival with an associated acceptable rate of morbidity and mortality.

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CONFLICT OF INTEREST None of the authors have any financial or any other type of personal conflicts of interest.

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