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ORIGINAL ARTICLE

Surgery and Staging of Pancreatic Neuroendocrine Tumors: A 14-Year Experience

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Abstract
Background The aims of this study were to evaluate contemporary outcomes associated with the surgical management of pancreatic neuroendocrine tumors (PNETs) and to assess the prognostic value of the World Health Organization (WHO) classification and TNM staging for PNETs.
Methods The medical records of 73 consecutive patients with PNETs treated at a single institution from January 1992 through September 2006 were reviewed. Survival was analyzed with the Kaplan-Meier method (median follow-up: 43 months).
Results Median patient age was 52 years (range, 19-83 years), and 36 (49%) patients were male. Thirty-three patients had a well-differentiated neuroendocrine tumor (WDT), 26 had a well-differentiated neuroendocrine carcinoma (WDCa), and 14 had a poorly differentiated neuroendocrine carcinoma (PDCa). Fifty (68%) patients underwent potentially curative resection, and the 5-year disease-specific survival (DSS) rate for the entire cohort was 62%. WHO classification and TNM staging system provided good prognostic stratification of patients; 5-year DSS rates were 100% for WDT, 57% for WDCa, 8% for PDCa, respectively, by WHO classification ($p<0.001$), and 100% for stage 1, 90% for stage 2, 57% for stage 3, and 8% for stage 4, respectively, by TNM stage ($p<0.001$). Among the patients who underwent potentially curative resection, nodal status, distant metastasis, and tumor grade were significant prognostic factors.
Conclusion WHO classification and TNM staging are useful for prognostic stratification among patients with PNETs.

Keywords Pancreatic neuroendocrine tumor · Surgery · Staging

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare, with an estimated incidence of four to five cases per million individuals annually in the USA. These tumors account for less than 3% of all pancreatic neoplasms, although the diagnosis is increasing in frequency.[1–3] In addition, PNETs are heterogeneous collection of tumors encompassing a wide biological spectrum. As a result, reported outcomes associated with surgical therapy for PNETs are varied, and it has been challenging to identify factors affecting the long-term survival of patients with PNETs.[4] Furthermore, a widely accepted staging system to stratify patients with PNET is not yet established.

The World Health Organization (WHO) introduced a system to classify PNETs in 2000.[5] This classification defines three types of PNETs according to their clinical and histopathological features: "well-differentiated endocrine tumor (WDT)", "well-differentiated endocrine carcinoma (WDCa)", and "poorly differentiated endocrine carcinoma (PDCa)". In 2006, a new TNM staging system for PNETs was proposed by the European Neuroendocrine Tumor Society (ENETS).[6] This system is analogous to the TNM classification systems used for other solid tumors,

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enabling patient stratification using basic clinicopathological information.

The purpose of this study was to document our institutional surgical experience with PNETs. Our goals were to identify clinical factors associated with prolonged survival of patients with PNETs following surgical treatment and to assess the prognostic utility of the WHO classification and TNM staging systems.

Material and Methods

The medical records of all patients with PNETs admitted to the inpatient unit of Brigham and Women's Hospital during the period spanning January 1992 through August 2006 were analyzed. Patients were identified using the International Classification of Disease-9 codes for malignant and benign pancreatic neoplasms (codes 157.× and 211.6) and the computer-assisted hospitalization analysis for the study of efficacy management system. All patients with histologically confirmed PNETs were included in this study. This study protocol was approved by our Institutional Review Board.

Parameters obtained from the medical records included demographic data (patient age and gender), signs and symptoms present at the time of diagnosis, the operation performed and whether it was curative (complete resection with no gross residual cancer present at the completion of surgery) or palliative (gross residual cancer present at the completion of surgery), and pathological findings. Pathological parameters analyzed were tumor diameter, regional lymph node status (N), margin status, tumor grade, and presence of lymphovascular invasion (LVI).

Patients with appropriate signs, symptoms, and biochemical evidence of hormonal excess were classified as having a functional tumor. Patients without a recognizable clinical syndrome or with normal serum hormone levels were classified as having a nonfunctional tumor, regardless of results on specimen immunohistochemistry. The criterion for malignancy was the identification of nodal or distant metastasis at the time of surgery or during follow-up.

WHO classification and TNM staging systems are summarized in Tables 1 and 2.[5,6] The criteria for WHO classification includes tumor size, tumor grade (mitotic index), vascular invasion on histology, and Ki-67 index. As Ki-67 staining was not routinely performed for PNETs at our institution during the study period, we omitted Ki-67 index from our analysis. Ki-67 usually correlates with mitotic rate. It is unusual to have a high number of Ki-67-positive cells in the setting of a low mitotic rate.[7]

Disease-specific survival (DSS) was calculated from time of operation (or time of diagnosis for patients who did not undergo any surgery) through last follow-up. Recurrence-free survival (RFS) was calculated from time of pancreatic resection to time when first recurrence was detected. The survival curves for selected patient groups were derived using the method of Kaplan-Meier.[8] Survival durations for these groups were determined from the corresponding Kaplan-Meier curves and compared using the log-rank test.

Comparison of categorical variables was performed using Fisher's exact test and Pearson chi-square test as appropriate. Continuous variables are presented as mean values ± standard error unless otherwise indicated, and were compared using t tests. A p value <0.05 was considered significant.

Results

Patients

During the study period, 73 patients with PNETs were identified. The median age for this patient cohort was 52 years (range, 19-82 years). Thirty-six (49%) patients were male.

Presenting Symptoms and Signs

The frequencies with which symptoms and signs were present at the time of diagnosis are summarized in Table 3. Twenty-six (36%) patients had clinical manifes-

Table 1 WHO Classification and TNM Staging

WHO classification					
Tumor type	Size	Mitotic index (/10HPF)	LVI	Metastasis (N1 or M1)	Ki-67 index
Well differentiated endocrine tumor (WDT)					
Benign	<2 cm	<2	−	−	<2%
Uncertain	≥2 cm	2-10	+	−	>2%
Well-differentiated endocrine carcinoma (WDCa)		<10	+	+	>2%
Poorly differentiated endocrine carcinoma (PDCa)		>10	+	+	>30%

Table 2 TNM Staging

T-primary tumor	
T1	Tumor contained to the pancreas and size <2 cm
T2	Tumor contained to the pancreas and size 2-4 cm
T3	Tumor contained to the pancreas and size >4 cm or invading to duodenum/bile duct
T4	Tumor invading adjacent organs, or large vessels
N-regional lymph nodes	
N0	Metastasis absent
N1	Metastasis present
M-distant metastasis	
M0	Metastasis absent
M1	Metastasis present
Overall stage[a]	
Stage 1	T1N0M0
Stage 2	T2/3N0M0
Stage 3	T4N0M0 or T*any*N1M0
Stage 4	T*any*N*any*M1

[a] Patients with pNx were designated as N0 for overall staging

tations of hormonal excess: neuroglycopenia (n=15) for insulinoma, diarrhea (n=6) for gastrinoma and PPoma, peptic ulcer (n=5) for gastrinoma, dermatitis (n=3) for glucagonoma, palpitations (n=2) for insulinoma, and Cushing's syndrome (n=1) for ACTHoma. The distribution of tumor types according to their hormonal function is shown in Table 4. Among the 47 (64%) patients with nonfunctional tumors, more than half (64%) had abdominal pain; other symptoms and signs included weight loss (9%), jaundice (8%), nausea and vomiting (6%), and palpable abdominal mass (6%). Eight (17%) patients were found to have PNETs incidentally, during workup for unrelated conditions.

Surgical Procedures

Eighteen (23%) patients were found to have extensive liver metastasis (n=15) and/or locally advanced disease (n=3) at the time of presentation and were deemed unresectable. Sixteen of these patients underwent biopsy only, and two underwent biliary and gastric bypass procedures.

Fifty-five patients underwent primary pancreatic tumor resection: 32 (58%) patients underwent distal pancreatectomy, 12 (22%) patients underwent pancreaticoduodenectomy, 10 (18%) patients underwent enucleation, and one (2%) patient underwent central pancreatectomy. Three patients with liver metastasis underwent liver resection or radio frequency ablation (RFA) along with their pancreatic resection. One patient with adrenal metastasis underwent adrenalectomy and colectomy en-bloc in addition to pancreatic resection. There were no perioperative deaths.

Tumor Characteristics

Clinicopathological characteristics of tumors are summarized in Table 5. Thirty-one (42%) tumors were located in the head of the pancreas and 42 (58%) tumors were located in the body or tail. Forty-one (56%) tumors were classified as malignant because of the presence either of regional lymph node metastasis or distant metastasis (n=35) at time of diagnosis or exploration or detection of metastasis during follow-up (n=6). Mean tumor diameter was greater for malignant than for benign tumors (5.1±0.47 vs. 2.8± 0.58 cm, p=0.002). The median tumor diameter for our entire cohort was 3.0 cm (range 0.4-15 cm) and 22 patients (30%) had a tumor less than 2 cm in maximal diameter. Histological lymph node status was assessed in 38 patients; 11 patients (31%) had metastasis to regional lymph nodes (N1). There was no significant correlation between size of the primary tumor and N stage (mean diameter of primary tumor: 4.2±0.80 cm for N0 vs. 5.2±0.63 cm for N1, p= 0.38). Fourteen (19%) patients had tumor classified as high grade and 22 (30%) patients had tumors with documented LVI. In terms of WHO classification, 33 (45%) patients had tumors classified as WDT, and 40 (55%) patients had endocrine carcinoma (26 WECa and 14 PECa). WDT were further sub-classified into benign tumor (ten) and uncertain tumor (16). It was not possible to subclassify seven patients

Table 3 Symptoms and Signs at Presentation

Symptoms and sign	Functioning, n=26	Nonfunctioning, n=47
Abdominal or back pain	4 (16)	30 (64)
Weight loss	3 (10)	4 (9)
Jaundice	0 (0)	3 (6)
Nausea/vomit	0 (0)	3 (6)
Palpable mass	0 (0)	3 (6)
Fatigue/weakness	6 (20)	2 (4)
Ascites	0 (0)	1 (2)
Asymptomatic	0 (0)	8 (17)
Other	1 (3)	5 (11)
Hormone-related		
Neuroglycopenia	15 (50)	
Diarrhea	6 (20)	
Peptic ulcer	5 (19)	
Dermatitis	3 (10)	
Palpitations	2 (7)	
Cushing syndrome	1 (3)	

Some patients presented with more than one symptom.

Table 4 Distribution of Tumor Types

Type of tumor	Patients (%)
Functional	26 (36)
Insulinoma	16
Gastrinoma	6
Glucagonoma	3
ACTHoma	1
Nonfunctional	47 (64)

with WDT due to lack of complete histological information. In terms of TNM stage, 39 (53%) patients were assigned to stages 1 or 2 and 34 (47%) patients were assigned to stages 3 or 4 (metastatic to regional lymph nodes or distant organ).

Complete resection (R0) was achieved in 48 (86%) of 55 patients who underwent primary tumor resection; a microscopic positive margin was present in two (4%) patients. Five patients (9%) underwent primary tumor resection with distant metastatic disease left alone.

The relationship between WHO classification and TNM stage is shown on Table 6. Most patients with PDCa were stage 4 at presentation, with few of these patients undergoing complete resection, while patients with WDT were either stage 1 or 2, with all of them achieving complete resection.

Survival and Prognostic Factors

The median follow-up period was 43 months (range, 1-216 months). The 5-year DSS rate for our entire cohort was 62%. The 5-year DSS rates for patients with WDT, WDCa, and PDCa by WHO classification were 100%, 57%, and 8%, respectively ($p<0.001$, Fig. 1a). The 5-year DSS rates for patients stratified by TNM stage 1, 2, 3, and 4 were 100%, 90%, 75%, and 21%, respectively, ($p<0.001$, Fig. 1b). The 5-year DSS rates among patients who underwent R0/1 resection, those who underwent R2 resection and those who did not undergo resection were 87%, 30%, and 16%, respectively ($p<0.001$, Fig. 1c).

During follow-up, ten patients among the 48 patients who underwent R0/1 resection developed recurrence; two in the remnant pancreas, six in the liver, one in both pancreas and liver, and one in the retroperitoneal lymph nodes. Repeat resection was performed for four patients (distal pancreatectomy (two), completion pancreatectomy (one), and liver segmentectomy (one)). One patient with recurrence in the liver underwent RFA, and the remainder received chemotherapy only. The 5-year RFS rate for patients following R0/1 resection was 74%. Among patients with WDT, 5-year RFS for patients with benign tumor and those with tumor of uncertain behavior were 100% and 68%, respectively ($p=0.04$, Fig. 2).

We analyzed potential clinical prognostic factors for impact on survival following pancreatic resection. As shown in Table 7, nodal metastasis, distant metastasis, and tumor grade had significant impact on survival on univariate analysis. Tumor functional status, tumor size, and extent of resection (enucleation or formal resection) were not found to be significant prognostic predictors.

Discussion

Although the reported incidence of PNETs has increased over two- to threefold in the last 16 years,[9] PNETs are still

Table 5 Clinicopathological Features of Tumors

		N (%)
Location	Head	31 (42)
	Body/tail	42 (58)
Malignancy	Benign	32 (44)
	Malignant	41 (56)
Hormonal function	Functional	26 (36)
	Nonfunctional	47 (64)
Size (cm)	<2 cm	22 (30)
	2-4 cm	26 (36)
	>4 cm	25 (34)
Regional node	N0	26 (36)
	N1	12 (16)
	NX	35 (48)
Distant metastasis	M0	47 (64)
	M1	26 (36)
Tumor grade	Low	22 (30)
	Intermediate	13 (18)
	High	14 (19)
	Unknown	24 (33)
LVI	Yes	22 (30)
	No	19 (26)
	Unknown	32 (44)
Completeness of Resection	R0/1	50 (69)
	R2 or No resection	23 (31)
WHO classification	WDT[a]	33 (45)
	Benign	10
	Uncertain	16
	WDCa	26 (36)
	PDCa	14 (19)
TNM stage	1	21 (29)
	2	18 (25)
	3	8 (11)
	4	26 (36)

[a] Some patients had missing data to be distinguish between benign or uncertain category

Table 6 TNM Stage and Type of Surgery According to WHO Classification

	WDT (n=33)	WDCa (n=26)	PDCa (n=14)
TNM stage			
1	19 (58%)	2 (8%)	0
2	14 (42%)	4 (15%)	0
3	0	7 (27%)	1 (7%)
4	0	13 (50%)	13 (93%)
Surgery			
R0/1 resection	33 (100%)	14 (54%)	3 (21%)
R2 resection	0	3 (12%)	2 (14%)
No resection	0	9 (35%)	9 (64%)

rare and encompasses a wide spectrum of biological behavior from benign to frankly malignant. Given the lack of a widely accepted staging or classification system, compilation and comparison of surgical outcomes from individual institutions have been difficult (Table 8). In this study, we evaluated our experience of patients with PNETs using WHO classification and the new TNM staging system and demonstrated the utility of these schemes to risk-stratify patients with PNETs according to long-term prognosis.

Traditionally, the term "malignant" neuroendocrine tumor has been defined as neuroendocrine tumors with evidence of metastasis to regional lymph nodes or distant organs at presentation or during follow-up.[10–12] In our series, 56% of patients fell into this category (48% of them had metastasis either to lymph nodes or distant organs at presentation, and 8% developed metastasis during follow-up (median 28 months, range 9-56 months)) and, as expected, these patients had poorer prognosis than patients with a "benign" tumor (5-year DSS: 44% vs. 100%, $p<$ 0.001). However, this traditional classification has limited utility in predicting prognosis among individual patients undergoing surgical resection for PNET. Because some PNETs without evidence of metastasis at presentation may recur years after surgery, the term "benign" at the time of initial operation may not reflect their inherent malignant potential.

In contrast, the WHO classification incorporates histopathological criteria and provides a distinction between benign and malignant tumors that can be applied shortly after surgical resection. In our study, patients with "benign" WDT (defined by size <2 cm, low mitotic index and absence of LVI) developed no recurrences following surgical resection, while five of 14 patients with "uncertain" WDT (defined by presence of LVI or intermediate mitotic index) developed recurrence during follow-up. Similar observations were reported in a series from Memorial Sloan-Kettering.[7] Long-term follow-up to detect recurrences is therefore warranted for patients having undergone resection of "uncertain" WDTs, as it is for patients with PDCa or WDCa.

The TNM staging system for PNETs, proposed by the ENETS,[6] provides good patient stratification, is widely applicable, and may be more objective than systems that depend on subjective interpretation of immunohistochemical data. Our cohort included patients with advanced disease that precluded surgical resection or patients with

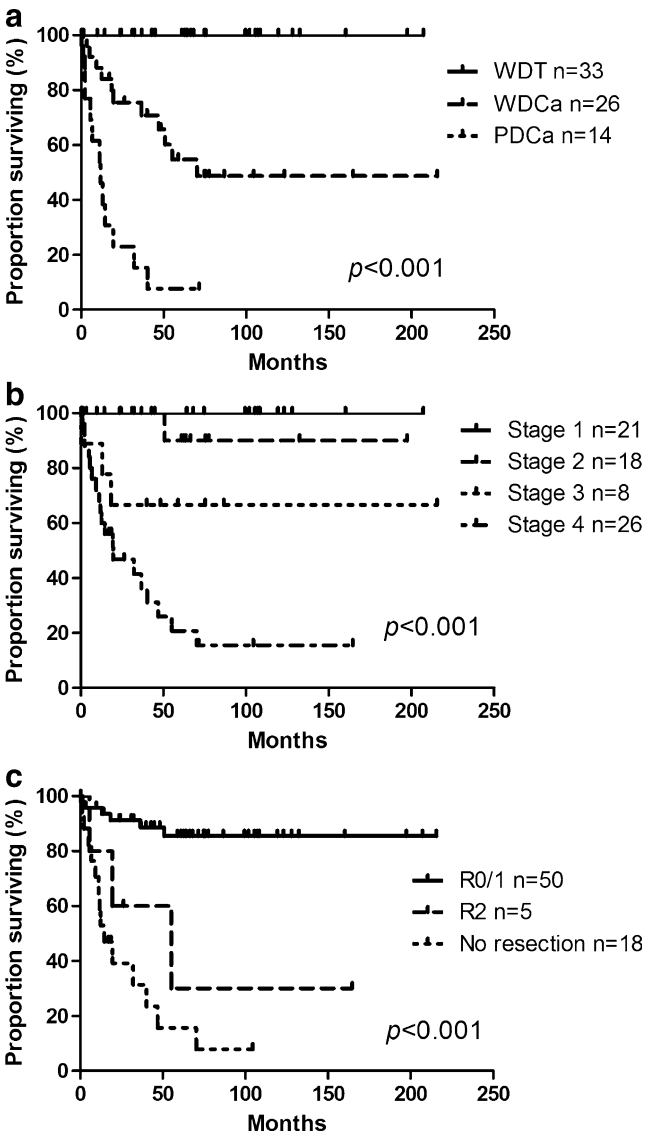

Figure 1 **a** Kaplan-Meier estimates of DSS for patients stratified by WHO classification. Five-year survival rates among patients with WDT, WDCa, and PDCa, were 100%, 57%, and 8%, respectively ($p<$ 0.001). **b** Kaplan-Meier estimates of DSS for patients stratified by TNM stage. Five-year survival rates among patients with each stage (1-4), were 100%, 90%, 88%, and 21%, respectively ($p<0.001$). **c** Kaplan-Meier estimates of DSS for patients stratified by completeness of resection (R0/1 resection, R2 resection and no resection). Five-year survival rates for these patient groups were 87%, 30%, and 16%, respectively ($p<0.001$ by log-rank test).

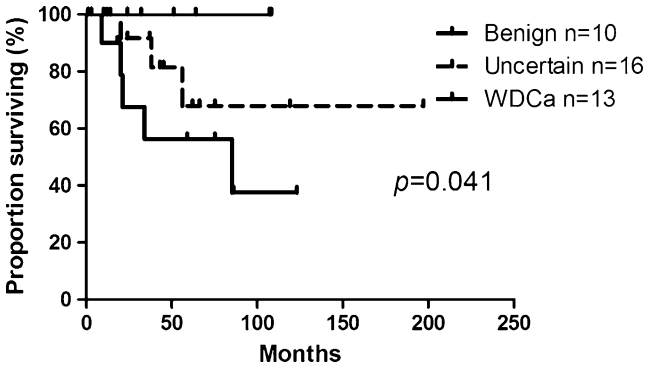

Figure 2 Kaplan-Meier estimates of RFS for patients with WDT and WDCa following surgical resection. Five-year RSS rates among patients with WDT (benign), WDT (uncertain), and WDCa were 100%, 68%, and 60%, respectively (p=0.041 by log-rank test).

small tumors that were locally excised without regional lymph node sampling. As a result, approximately half of the patients had missing information required for other classification. Nonetheless, cTNM staging was possible in all patients. This issue is particularly useful for multi-institutional trials in which accurate staging across multiple institutions is needed or evaluation of a national database including patient outcomes over multiple institutions.

Billimoria et al. tested the applicability of the TNM staging system designed for pancreatic adenocarcinoma by American Joint Committee for Cancer (AJCC) to PNETs.[13] Although AJCC TNM staging provided stage-dependent survival discrimination, nearly all of this discrimination was provided by the absence or the presence of distant metastasis. We favor the ENETS TNM staging system as it takes into consideration the more indolent course of PNETs (relative to pancreatic adenocarcinomas) and stratifies potentially respectable disease into three stages (stages 1, 2, and 3). However, we realize that our data does not allow us to determine which staging system provides most robust prognostic stratification.

We found that tumor grade, M and N stages significant as significant prognostic factors among patients having undergone resection of their PNET. Although tumor grade and distant metastasis are uniformly accepted as prognostic factors (Table 8), the prognostic significance of regional lymph node metastasis is controversial. There is conflicting evidence in the literature; Tomassetti et al. reported significantly worse outcomes for patients with regional lymph node metastasis than without such metastasis,[14] while Kazanijan et al. reported no difference in survival among these groups of patients.[10] In the study by Bilimoria et al., in which more than 3,500 patients with PNET in a national cancer database were analyzed, lymph node metastasis was a significant prognostic factor on univariate analysis, but not on multivariate analysis.[4] These disparate results can be explained at least partially by sample size considerations and the wide spectrum of biological aggressiveness of PNETs. For example, patients with small insulinomas or gastrinomas have an excellent prognosis and metastasis limited to regional lymph nodes may have minimal, if any, impact on long-term outcome.[15,16]

An important limitation of our study is incompleteness in data recorded by our pathologists for several variables (missing in 30-40% of patients for tumor grage or LVI). To detect possible bias in study findings due these missing data, we compared TNM stage distribution among patients with or without complete tumor grade and LVI data. For tumor grade, the stage distribution for patients with complete data was not different from that of patients without complete data (26% for stage 1, 28% for stage 2, 8% for stage 3, and 38% for stage 4, respectively, for patients with complete data, and 35% for stage 1, 17% for stage 2, 17% for stage 3, and 31% for stage 4, respectively, for those without complete data, p=0.45 by chi-square test).

Table 7 Univariate Analysis of Potential Prognostic Factors Predicting Survival of the Patients with PNET who Underwent R0/1 Resection (N=50)

Clinical prognostic factors	*n*	5-year DSS rate (%)	*P*
Age			
≥50 years	23	96	0.10
<50 years	27	77	
Gender			
Male	25	90	0.48
Female	25	84	
Functional tumor			
Yes	23	89	0.78
No	27	85	
Tumor size			
≥2 cm	28	82	0.26
<2 cm	22	93	
Nodal metastasis			
Positive	11	60	0.011
Negative	23	93	
Distant metastasis			
Positive	3	33	<0.001
Negative	47	92	
Grade			
Low	20	93	0.002
Intermediate	10	86	
High	3	33	
LVI			
Yes	19	79	0.103
No	19	100	
Procedure			
Formal resection	40	84	0.27
Enucleation	10	100	

Data were not available for all patients.

Table 8 Recently Reported Series of PNET Predictive Indicators Documented

Authors	Year	*N*	Nonfunctional tumor (%)	Malignancy (%)	R0/1 resection (%)	5-year OS rate (%)	Identified prognostic factors[a]
Lo et al.[19]	1996	64	53	100[b]	26	49	M status
Phan et al.[12]	1997	125	48	52	N/D	65	"Malignant" tumor, Resection margin
Solorzano et al.[20]	2001	163	100	N/D	25	43	Liver metastasis
Chu et al.[21]	2002	50	58	>78[c]	N/D	36	Liver metastasis
Hochwald et al.[22]	2002	136	64	N/D	64	N/D	Mitotic index
Kazanjian et al.[10]	2006	70	71	53	N/D	89	LVI
Bloomston et al.[23]	2006	120	46	76	77	62[d]	Tumor differentiation
Schurr et al.[18]	2007	62	74	63	73	49	WHO classification
Teh et al.[24]	2007	33	55	39	N/D	N/D	
Nguyen et al.[11]	2007	73	70	100[a]	35[e]	44	
Vagefi et al.[25]	2007	168	58	23	85	77	"Malignant" tumor
Ferrone et al.[7]	2007	183	71	N/D	100	87	T stage based on size/metastasis, tumor grade
Bilimoria et al.[4]	2008	3851[f]	N/D	84	96	59	Age, tumor grade, metastasis, hormonal function
Fischer et al.[26]	2008	118	N/D	65	87	N/D	
Current study	2009	73	64	56	68	66	Lymph node metastasis, distant metastasis, tumor grade

N/D not documented

[a] Among the patients who underwent curative resection

[b] Benign tumor was excluded

[c] Based on% of liver metastasis

[d] Outcomes following R0/1 resection

[e] R0 resection only

[f] National cancer data base

For LVI, 64% of patients with missing data were stage 4, while only 23% of those with complete data were stage 4 ($p<0.001$). When we eliminated patients with unresectable tumors from analysis, the distributions of TNM stage were similar among these two groups ($p=0.821$). (Note: patients with unresectable tumors had their diagnosis confirmed on biopsy alone; these biopsy specimens were not examined for presence or absence of LVI by our pathologists.) Based on the similar distributions of TNM stage among patients with or without complete data, missing data-related bias is unlikely to have had significant impact on the findings of our analysis of prognostic factors (which included only patients who underwent primary tumor resection).

For patients with small PNETs, the extent of surgical resection is somewhat controversial. In this study, ten patients underwent simple enucleation and achieved excellent long-term outcomes. Pitt et al. recently analyzed the series of 122 patients with neuroendocrine tumors <3 cm and showed comparable long-term outcomes with less perioperative morbidity rate in patients who underwent enucleation compared to outcomes in those who underwent formal resection.[17] Despite several reports with excellent outcomes for enucleation, the oncologic efficacy of enucleation for all patients with small PNETs remains unclear. First, the reported outcomes were of highly selected patients: for example, in this study, enucleation was only selected for insulinomas or gastrinomas <2.5 cm. Second, regional lymph node metastasis has been reported in the range from 30% to 40% of patients with PNETs[4,7,18] and the size criteria cannot exclude the chance of metastasis as Ferrone showed a 25% chance of nodal metastasis for PNET <2 cm.[7] Lastly, whether lymphadenectomy makes a difference in long-term survival is uncertain. This may depend on the biological aggressiveness of the tumor and no preoperative clinical markers capable of predicting malignant behavior are currently available. Although more data is necessary to make definitive recommendations for the surgical extent for small PNETs, our practice is to limit enucleation or limited segmental resection to small insulinomas or gastrinomas without macroscopic features of malignancy.

In summary, we report our institutional experience of PNETs based on WHO classification and TNM staging system. Both staging schemes are useful for the prognostically significant risk stratification for patients with PNETs. Standardized categorization is essential to compare one individual institutional experience to others and to develop evidence-based therapeutic strategies for this rare disease with a wide spectrum of biological behavior.

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