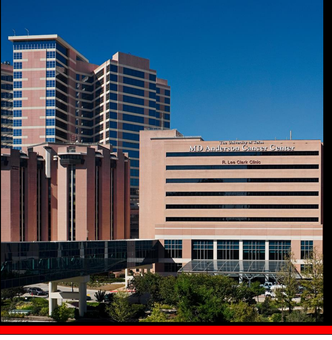

Prognostic Value of Lymph Node Status and Extent of Lymphadenectomy in Pancreatic Neuroendocrine Tumors Confined To and Extending Beyond the Pancreas

Claudius Conrad[1], Onur C. Kutlu[2], Arvind Dasari[3], Jennifer A Chan[4], Jean-Nicolas Vauthey[1], David B. Adams[2], Michael Kim[1], Jason B. Fleming[1], Matthew H.G. Katz[1], Jeffrey E. Lee[1]

[1]Dept of Surgical Oncology, UT MD Anderson Cancer Center, Houston, TX, [2]Medical University of South Carolina, Charleston, SC, [3]Dept of Medical Oncology, UT MD Anderson Cancer Center, [4]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Introduction

- Gastroenteropancreatic neuroendocrine tumors are increasing at a rate of 3–10% per year.
- Hypothesis: small, low and intermediate grade pNET have an indolent clinical course and are unlikely to harbor nodal metastases.
- Increasing rate of enucleation and limited resections of small pNET, which typically do not include lymph node sampling.
- Optimal timing and extent of resection remain controversial in early pNET due to the uncertain impact of lymph node metastasis on survival.

Aim

To identify:

- factors associated with the presence of lymph node metastases in patients with resected pNET and to examine the impact of lymph node metastases on disease specific (DSS) and overall survival (OS).
- association of extend lymphadenectomy with prognostis and survival in this population.

Material and Methods

Inclusion

The Surveillance Epidemiology and End Results (SEER) database was queried for patients with histologically proven pNET who underwent surgery from 1998-2012. We defined NET to include the following International Classification of Diseases for Oncology third edition (ICD-O3) codes: islet cell carcinoma (8150), insulinoma (8151), glucagonoma (8152), gastrinoma (8153), vipoma (8155), somatostatinoma (8156), enteroglucagonoma (8157), carcinoid (8240), enterochromaffin cell carcinoid (8241), enterochromaffin-like cell tumors (8242), goblet cell carcinoid (8243), composite carcinoid (8244), adenocarcinoid (8245), neuroendocrine carcinoma (8246), and atypical carcinoid(8249).

Exclusion

Patients with unknown T-stage, grade, M-status, tumor size, mixed islet-cell/exocrine adenocarcinoma (ICD-O3 8154), multifocal pNET, and no or less than 1-month of follow-up for survival outcomes were excluded.

Outcome measurement

The primary outcome measure was disease specific survival (DSS), which was defined as net survival measure representing survival to death attributable to the primary cancer in the absence of other causes of death. A secondary outcome measure was overall survival (OS), defined as net survival measure representing survival to any cause of death.

Statistical analyses

Binary logistic regression analyses were performed to analyze for factors associated with nodal status in the entire cohort and in the subgroups of tumors confined to the pancreas and tumors extending beyond the pancreas. Factors included in the analyses were age and size as continuous variables, T-stage (T1-T2, T3-T4), nodal status (N0, N1, NX), sex (male, female), grade (low, high), and location (head, body/tail, overlapping, not specified) as categorical variables.

Kaplan-Meier survival analyses and the log-rank test and were performed to assess the impact of nodal status on DSS and OS. Two groups were formed based on extent of disease: those with disease within the pancreas (T1-T2) and those with extension beyond the pancreas (T3-T4).

Material and Methods (cont.)

Nodal status was determined by number of lymph nodes dissected and number of positive lymph nodes recorded in the SEER database (N0, node negative or N1, node positive). When no lymph nodes were retrieved or no nodes were found in the pathology specimen the lymph node status was defined as Nx.

DSS and OS comparisons of patients based on nodal status (N0 vs N1, N0 vs NX, N1 vs. NX) were performed within each of the two T-stage (T1-T2 and T3-T4) groups. . Mean survival with 95% confidence interval was recorded. Cox proportional hazards regression was used to determine the impact of potential confounders on outcomes.

Further the impact of extent of lymphadenectomy (LA) on survival was analyzed using Cox multivariable regression analysis, accounting for confounding factors interference. DSS and OS of stage-matched patients were examined separately and the effect of extent of nodal dissection (≥ 10 vs. <10) was evaluated.

Definition of extend of Lymphadenectomy

Lymph node yield of less than 10 nodes was identified as limited LA, while lymph node yield of 10 or more nodes was defined as extended LA. Therefore, number of nodes was the variable utilized for the definition of extended vs limited resection and extended LA and it does not imply dissection of lymph node stations beyond the primary surgical site.

Categorical variables were compared with $\chi 2$ or Fisher exact test where appropriate. Continuous variables were analyzed using the Wilcoxon rank sum test.

SPSS 21 (IBM corp. Armonk, NY) was used for all statistical analyses. P value of 0.05 was selected to reject the null hypothesis.

Results

During the examined time period, 5,349 patients with a diagnosis of pNET were identified in the SEER database. Of these, 981 were included in this analysis. Baseline characteristics and demographics of patients are presented in table 1. 51.7% of the patients were male; mean age was 56.4; mean tumor size was 38.14 mm. Most patients (67.4%) had disease confined to the pancreas (T1-T2). 76.4% were low grade. The mean number of lymph nodes harvested in the entire cohort was 9.27. 16.9% of patients did not have any node retrieval (NX), 50.8% had N0, and 32.3% had nodal disease (N1).

Table 1 : Patient demographics and breakdown based on T stage groups

	Entire cohort	T1-T2	T3-T4	p-value
Number	981	662	319	
Sex				**0.014**
Female	474 (48.3%)	338 (51.1%)	136 (42.6%)	
Male	507 (51.7%)	324 (48.9%)	183 (57.4%)	
Age- range (mean)	19-85 (56.33)	19-85 (56.79)	19-85 (55.38)	0.85
Size- range (mean)	4-185 (38.13)	4-170 (31.69)	5-185 (55.38)	**<0.001**
Nodes				
Yield	0-49 (9.27)	0-46 (7.6)	0-49 (12.72)	**<0.001**
N0	498 (50.8%)	384 (58%)	114 (35.7%)	0.096
Yield	1-46 (9.39)	1-46 (9.07)	1-41 (10.46)	0.94
N1	317 (32.3%)	128 (19.3%)	189 (59.2%)	**<0.001**
Yield	1-49 (13.92)	1-40 (12.9)	2-49 (15.16)	**0.005**
Positive	1-47 (3.32)	1-14 (2.38)	1-47 (3.96)	**<0.001**
Lymph node ratio	31.36%	31.84%	31.04%	0.796
NX	166 (16.9%)	150 (22.7%)	16 (5.0%)	**<0.001**
T-Stage (n-%)				
T1	268 (27.3%)	268 (40.5%)	-	
T2	394 (40.2%)	394 (59.5%)	-	
T3	286 (29.2%)	-	286 (89.7%)	
T4	33 (3.4%)	-	33 (10.3%)	
Grade				**<0.001**
Low	749 (76.4%)	536 (81%)	213 (66.8%)	
High	232 (23.6%)	126 (19%)	106 (33.2%)	
Location				
Head	329 (33.5%)	187 (28.2%)	142 (44.5%)	**<0.001**
Body	143 (14.6%)	112 (16.9%)	31 (9.7%)	**<0.001**
Tail	329 (33.5%)	239 (36.1%)	90 (28.2%)	**0.014**
Overlap	57 (5.8%)	38 (5.7%)	19 (6.0%)	0.885
NOS	123 (12.5%)	86 (13.0%)	37 (11.6%)	0.607
Procedure				
Whipple	387 (39.4%)	219 (33.1%)	168 (52.7%)	**<0.001**
Total resection	92 (9.4%)	51 (7.7%)	41 (12.9%)	**0.008**
Partial resection	445 (45.4%)	337 (50.9%)	108 (33.9%)	**<0.001**
Enucleation	57 (5.8%	55 (8.3%)	2 (0.6%)	**<0.001**

Results (continued)

Among the patients who underwent nodal harvest, significant factors associated with nodal positivity were grade (II or higher), increasing tumor size, and tumor extension beyond the pancreas (T3-T4 disease). When the cohort was further broken down; for T1-T2 tumors, N-status was affected only by tumor size. For this group, age, sex, location, and grade did not measurably impact N-status (table 2). For T3-T4 tumors, neither age, grade, sex, location, nor size impacted N-status.

Table 2: Binary regression analyses of factor affecting nodal metastasis grouped for T stage.

	Entire Cohort				T stage: T1-T2				T stage: T3-T4			
Factor	p value	OR	95% Confidence Interval		p value	OR	95% Confidence Interval		p value	OR	95% Confidence Interval	
			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.146	0.992	0.981	1.003	0.228	0.991	0.976	1.006	0.540	0.994	0.977	1.012
Sex	0.28	0.851	0.636	1.14	0.741	1.073	0.708	1.624	0.355	0.799	0.496	1.286
Location												
Head	0.054	0.616	0.376	1.008	0.526	0.803	0.406	1.585	0.403	0.713	0.323	1.575
Body/tail	0.795	1.067	0.656	1.734	0.544	1.227	0.634	2.373	0.595	0.807	0.366	1.778
Overlap	0.62	1.208	0.573	2.548	0.399	1.594	0.540	4.702	0.869	0.904	0.272	3.008
Grade (Low/High)	***0.003***	***0.604***	***0.432***	***0.844***	0.097	0.657	0.400	1.079	0.307	0.767	0.460	1.277
Size	***<0.001***	***1.012***	***1.007***	***1.017***	***<0.001***	***1.015***	***1.008***	***1.023***	0.195	0.995	0.987	1.003
T-Stage (T1-T2/T3-T4)	***<0.001***	***0.239***	***0.173***	***0.332***	-				-			

In patients with T1-T2 tumors, there was a significant relationship between DSS and OS based on nodal status (Figure 2, Table 3). In this subgroup of patients with tumors confined to the pancreas, DSS and OS were longer for patients with N0 disease compared to N1 disease (DSS, p<0.001; OS, p=0.008), while N0 and NX patients had similar outcomes (DSS, p=0.80; OS p=0.59).

Although difference was seen for DSS when NX group was compared to the N1 (p=0.04), this was insignificant for OS (p=0.08). In contrast, no significant impact of nodal status was observed on DSS and OS for patients with T3-T4 disease with tumors extending beyond the pancreas.

Table 3: Kaplan Meier statistics comparing overall and disease specific survival based on nodal status and T stage.

	p-value			OS			DSS		
	OS	DSS	N stage	Mean	95% Confidence Interval		Mean	95% Confidence Interval	
T1-T2									
N0 vs NX	0.59	0.822	N0	146.678	136.867	156.488	154.939	146.221	163.657
N0 vs N1	***0.008***	***<0.001***	NX	122.869	105.945	139.792	134.410	120.119	148.702
N1 vx NX	0.08	***0.04***	N1	122.505	107.175	137.836	129.010	114.128	143.891
T3-T4									
N0 vs NX	0.371	0.511	N0	122.937	104.623	141.252	123.691	105.315	142.067
N0 vs N1	0.303	0.704	NX	94.484	79.907	109.060	103.534	89.970	117.098
N1 vx NX	0.108	0.322	N1	65.909	38.424	93.394	71.152	43.363	98.940

The relationship between nodal status and outcome (DSS and OS) remained unchanged after adjusting for potential confounding factors (Table 4). For patients with T1-T2 tumors, those with N1 disease compared to N0 had higher hazard ratios (HR) for cancer-related death and death from all causes (DSS, HR 3.528 OS, HR 2.467). In this group of patients, in addition to nodal status other factors affecting OS and DSS were grade (p<0.001, P<0.001), patient age (p=0.001, p=0.001) and sex (p=0.007, p=0.006) respectively. Tumor size (p=0.260, p=0.181) and tumor location (p=0.331, p=0.496) did not impact OS and DSS (Table 4).

Table 4: Cox multivariate regression analyses of factors affecting overall survival and disease specific survival by T-stage

Factor		OS		DSS	
T1-T2		HR [95% CI]	P-value	HR [95% CI]	P-value
Age		1.023-1.067	***0.001***	1.018-1.076	***0.001***
Sex	male	1 (reference)		1 (reference)	
	female	***0.531-0.968***	***0.007***	***0.407-0.863***	***0.006***
Tumor location	NOS	1 (reference)		1 (reference)	
	Head	0.289-1.675	0.418	0.224-2.062	0.496
	Body/tail	0.763-4.775	0.167	0.760-8.649	0.129
	Overlap	0.231-2.412	0.625	0.141-2.106	0.379
Grade	***Low***	0.158-0.497	***<0.001***	0.102-0.402	***<0.001***
	Intermediate/ High	1 (reference)		1 (reference)	
Size	(mm)	0.998-1.017	0.26	0.996-1.021	0.181
Node-status	N0	1 (reference)		1 (reference)	
	N1	1.161-3.773	***<0.001***	1.375-5.682	***0.005***
T3-T4					
Age	(years)	1.009-1.054	***0.007***	1.008-1.056	***0.009***
Sex	male	1 (reference)		1 (reference)	
	female	0.596-0.998	***0.004***	0.581-1.065	0.12
Tumor location	NOS	1 (reference)		1 (reference)	
	Head	0.170-1.406	0.184	0.116-1.290	0.122
	Body/tail	0.235-2.121	0.535	0.164-2.064	0.387
	Overlap	0.195-6.039	0.926	0.166-15.900	0.677
Grade	***Low***	0.228-0.699	***<0.001***	0.171-0.577	***<0.001***
	Intermediate/ High	1 (reference)		1 (reference)	
Size	(mm)	1.001-1.015	***0.013***	1.000-1.018	***0.048***
Node-status	N0	1 (reference)		1 (reference)	
	N1	0.490-1.529	0.789	0.561-1.991	0.865

Results (continued)

For patients with T3-T4 tumors, there was no significant effect of nodal status on DSS (p=0.865) or OS (p=0.789). In these patients, grade (p<0.001, p<0.001), tumor size (p=0.013, p=0.048) and patient age (p=0.007, 0.009) impacted OS and DSS respectively. Sex was significantly associated with OS (p=0.004) but not DSS (p=0.12) in these patients (Table 4).

For all T-groups and any N-status, extended LA was not associated with an improved survival. In patients with T1-T2 N0 or T3-T4 N0, extent of lymphadenectomy (>10 vs. <10 lymph nodes harvested) did not impact significantly on OS or DSS. Similar findings were seen with when N1 patients were analyzed (Table 5).

Table 5: Comparison of the effect of extent of lymphadenectomy on stage matched patients

	Reference <10 nodes harvested	HR (95% CI) ≥ 10 nodes harvested	p-value
Overall Survival			
T1-T2N0	1	1.391 (0.567-3.412)	0.471
T3-T4N0	1	0.901 (0.313-2.592)	0.847
T1-T2N1	1	1.800 (0.741-4.373)	0.195
T3-T4N1	1	1.283 (0.591-2.784)	0.529
Disease Specific Survival			
T1-T2N0	1	1.557 (0.463-5.240)	0.474
T3-T4N0	1	0.975 (0.276-3.440)	0.698
T1-T2N1	1	1.545 (0.592-4.031)	0.526
T3-T4N1	1	1.345 (0.615-2.941)	0.458

Conclusion

Our results show that for pNETs confined to the pancreas (T1-T2), N1-status is a significant predictor of negative OS and DSS, while N0 vs. NX outcomes were comparable. This would support the common practice of limited resection without LA (including enucleation) for selected T1-T2 tumors without clinical evidence of nodal metastasis.

However, for tumors confined to the pancreas focused pre-operative assessment of regional lymph nodes with high quality imaging and possibly somatostatin receptor imaging to identify high risk patients that may benefit from nodal sampling for prognostication purposes (21). Nodal sampling should be attempted in patients with radiographic or intraoperative findings of possible nodal metastasis.

Further, removal of more than 10 nodes did not show any survival advantage in any stage group. For that reason we believe the aggressive nodal dissection that targets a certain number for nods retrieved may expose patient to unnecessary risk without improved prognostication. While identification and removal of involved lymph nodes in T1-T2 tumors with planned lymphadenectomy might be helpful in providing prognostic information, it is unlikely to be of diagnostic and prognostic benefit for tumors extending beyond the pancreas (T3-T4). Contrary to the survival benefit observed in other gastrointestinal malignancies, we demonstrate no survival benefit of extended nodal dissection in pNET patients.

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