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ORIGINAL ARTICLE – PANCREATIC TUMORS

Substaging of Lymph Node Status in Resected Pancreatic Ductal Adenocarcinoma Has Strong Prognostic Correlations: Proposal for a Revised N Classification for TNM Staging

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ABSTRACT

Background. The current tumor-node-metastasis staging system for the pancreas does not incorporate the number of lymph nodes (LNs) with metastasis.

Methods. Among 1649 pancreaticoduodenectomies, 227 stringently defined pancreatic ductal adenocarcinomas (PDACs) that had undergone a specific approach of LN harvesting were analyzed for the prognostic value of LN substaging protocols used for other gastrointestinal (GI) organs.

Results. The median number of LNs harvested was 18, and the median number of LNs with metastasis was 3. Lymph node metastasis was detected in 175 cases (77 %). The number of LNs involved correlated significantly with clinical outcome. When cases were substaged with the protocol already in use for the upper GI organs (N0: no metastasis, N1: metastasis to 1–2 LNs; N2: metastasis to ≥3 LNs), the median overall survival times were 35, 21, and 18 months, and the respective 3-year survival rates were 46, 34, and 20 % ($p = 0.004$). Analysis of the Surveillance, Epidemiology and End Results (SEER) database also confirmed the survival differences between these substages (median overall survival times of 23, 15, and 14 months and respective 3-year survival rates of 37, 22, and 18 %; $p < 0.0001$). The substaging protocol for the lower GI organs (N0: no metastasis; N1: metastasis to 1–3 LNs; N2: metastasis to ≥4 LNs) also was significant, with median overall survival times of 35, 21, 18 months and respective 3-year survival rates of 46, 26, and 23 %; $p = 0.009$). The association between higher N stage and shorter survival persisted with multivariate modeling for both protocols, although the prognostic value of the upper GI protocol appeared to be slightly stronger according to the Akaike Information Criterion method.

Conclusion. In conclusion, with proper LN harvesting, the LN metastasis rate in PDACs is very high (77 %). Substaging of LN metastasis has significant prognostic value and needs to be considered in the N staging of PDACs. The protocol already in use for other upper GI tract organs, which currently also is proven significant for ampulla,

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would be preferable, although the lower GI tract protocol also is applicable.

Current nodal N staging of pancreatic ductal adenocarcinoma (PDAC) by the tumor-node-metastasis (TNM) guidelines of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) distinguishes only between node-negative and node-positive disease[1] and does not capture the prognostic impact of the number of lymph nodes (LNs) with metastasis. For many organs, including the gastrointestinal (GI) tract, the number of LNs with metastasis has been incorporated into the staging protocols, with significant prognostic value.[1] Cases involving the upper GI tract with LN metastasis are substaged as N1 (metastasis to 1–2 LNs) and N2 (metastasis to $\geq$3 LNs), and cases involving the lower GI tract with LN metastasis are substaged as N1 (metastasis to 1–3 LNs) and N2 (metastasis to $\geq$4 LNs). Recently, Kang et al. and Balci et al. tested the upper GI protocol for ampullary carcinomas in their institutional cohorts and in the SEER database. Both studies found their results correlating independently and strongly with clinical outcome.[2–5]

The prognostic value of the LN status in PDAC has been controversial, with some studies failing to disclose an association and others showing significant correlation.[6–18] These different results are attributable to methods defining what constitutes PDAC as well as to how the LNs are sampled, evaluated, and documented. This is reflected in the wide range of reported frequencies of LN metastasis, from 57 to 81 % of cases.[6,10,12–14,16,17,19–33] In many studies, no pathologic verification was performed to exclude non-PDAC carcinomas (e.g., acinar, neuroendocrine) or secondary cancers [ampullary, duodenal, common bile duct (CBD)].

The LN count also is markedly affected by the method of LN harvesting in the macroscopy rooms of pathology departments. In the recent analysis of the SEER database by Tomlinson et al.,[34] the median number of LNs examined was only 7 although the number of LNs required to attain the optimal separation of survival curves was 15.[35] On the other hand, more exhaustive grossing approaches that involve indiscriminate total sampling of pancreatic surfaces for purposes of examining the margins[6,36–38] inevitably lead to overcounting of LNs because individual LNs are not grossly separated out.

In this study, the number of LNs with metastasis and its prognostic significance as well as the potential value of N substaging protocols of both the upper and lower GI tract were analyzed in well-characterized PDACs, all of which were processed using a uniform LN harvesting protocol.[39]

METHODS

This study was approved by the appropriate institutional review committees. Among 1649 pancreatoduodenectomy specimens at Wayne State University (1998–2006) and Emory (2006–2013) University, 227 specimens processed according to a uniform grossing protocol[39,40] with a tissue diagnosis of conventional PDAC established by the authors were included in this study. Accordingly, unusual variants of carcinomas of ductal differentiation such as medullary, colloid, or intraductal papillary mucinous neoplasms with invasive adenocarcinoma were excluded from the study, together with nonductal tumors (neuroendocrine, solid-pseudopapillary, acinar, pancreatoblastoma tumors), secondary carcinomas, cases with questionable tumor origin, and patients who had received neoadjuvant therapy. Cases with a follow-up period shorter than 3 months also were excluded, as has become customary.

All the patients underwent diagnostic laparoscopy before surgery. None of the patients in this study underwent "extended pancreatectomy." Standard Whipple procedure was performed for 70 % and pylorus-preserving pancreaticoduodenectomy for 30 % of the patients. Moreover, the LN dissection technique has been standardized to ensure that all the hepatic artery and the retroportal LNs are dissected. The tissue to the right of the superior mesenteric artery starting on the adventitia and for 180° on that side also was removed, but no circumferential dissection of the superior mesenteric artery was performed because findings have shown that this does not improve the survival of patients but could significantly jeopardize their quality of life.

All cases were processed according to a practical protocol devised for a more accurate LN harvesting, the details of which have been published previously.[39,40] With this standardized approach, currently routine at many institutions, in the gross laboratory, the LN areas are removed before dissection of the pancreatic head (Fig. 1) to ensure complete harvesting. In other words, the potential LN regions are dissected and put aside before further cutting of the pancreatic head to avoid the under-evaluation of tissues that contain the LNs. In essence, all this simple protocol advocates is the removal of the LN regions before they can be lost. After this protocol was put in place, the LN yield jumped from 6 to 14 in the one institution and 7 to 14 in the other institution hosting this study.[39,40] This simple approach has been adopted and used with ease by ordinary gross room personnel in conventional gross rooms using routine procedures.

In addition, all cases were subjected to detailed pathologic reevaluation by the authors, including reexamination of all LNs for metastatic carcinoma. Tumor (T) and node

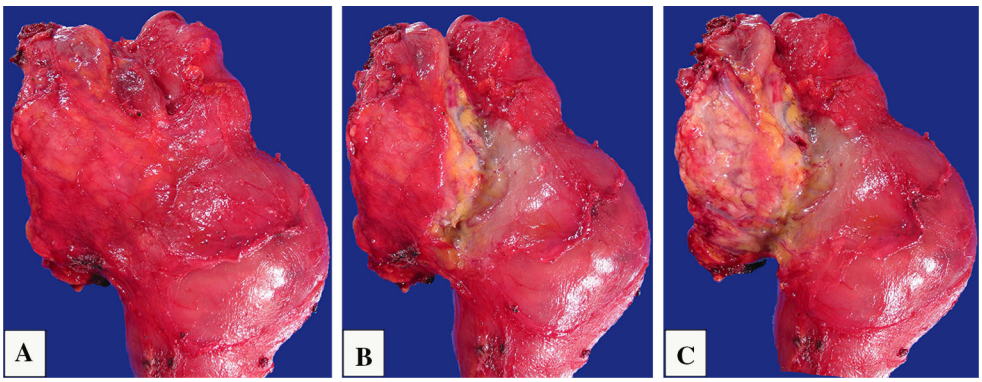


FIG. 1 Orange-peeling method of lymph node examination. Peripancreatic soft tissue is removed facilitating complete removal of the areas that potentially contain lymph nodes. **a** Posterior surface of a pancreaticoduodenectomy before the orange peeling. **b** View after the posterior pancreaticoduodenal lymph node (LN) area (groove between the pancreatic head and the duodenal wall) has been shaved off. **c** View after the posterior pancreatic LN area also has been shaved off

(N) stages were reassigned according to the current AJCC guidelines.[1]

The study analyzed the prognostic significance of the protocols used in both the upper GI tract (N0: no LN metastasis; N1: metastasis to 1–2 LNs; N2: metastasis to ≥3 LNs) and the lower GI tract (N0: no LN metastasis; N1: metastasis to 1–3 LNs; N2: metastasis to ≥4 LNs). The quality of each protocol relative to each of the other protocols was estimated using Akaike Information Criteria (AIC). The data also were analyzed separately for those cases that had 12 or more LNs examined (the minimum number required by CAP' guidelines).[1,41]

External validation of the upper GI protocol, recently also found to be correlated strongly with survival in ampullary carcinomas,[2–5] was performed using the SEER database by two of the authors who had specific expertise with this database. The analysis included resected PDACs reported between 2004 and 2010. These years were selected because the AJCC 6th-edition criteria[1] were integrated into SEER in 2004. Only cases that had complete information relevant to survival were included.

Kaplan–Meier survival curves were estimated and compared between substages using the log-rank test. Multivariate analysis was conducted using Cox proportional hazard models adjusted for age, race, sex, primary tumor site, and AJCC T stages. The proportional hazard assumption was evaluated using log–log survival curves. All analyses were conducted using SAS software version 9.3 and SPSS version 22.

RESULTS

Study Population

The study enrolled 227 patients with a confirmed diagnosis of ordinary PDAC, all processed according to a uniform grossing protocol. The mean age of the patients was 65 years (range 33–87 years), and 57 % were females ($n = 129$). The median PDAC size was 3.1 cm (range 0.6–7 cm). The majority of the PDACs (95 %) showed carcinoma foci in the orange-peeled soft tissue (pT3).

Follow-up information during a period of 3 to 154 months (median, 15 months; patients with less than 3 months of follow-up data were eliminated from the study) was available for all the patients. At the last follow-up assessment, 143 patients (63 %) had died of disease during a median follow-up period of 14 months. A median follow-up assessment at 21.5 months found that 84 patients (37 %) were alive with disease. The clinicopathologic characteristics of the study cohort/SEER data are summarized in Table 1.

Lymph Node Analysis

The median number of regional LNs examined from a given patient, including LNs sent as separate specimens, was 18 (range 3–45). The median number of LNs harvested from the pancreaticoduodenectomy specimen itself was 17 (range 2–43), and 81 % of these specimens had 12 or more LNs. In analysis of the SEER database, the median number of regional LNs examined was 11 (range 1–89), and only 47 % of the specimens had 12 or more LNs (Table 1).

During the pathologic reevaluation of the cases, 6 cases originally classified as N-negative were reclassified as N-positive. After this thorough reexamination, 175 cases (77 %) were classified as N-positive. The SEER database had 6281 patients (59.5 %) with LN metastases. The median number of LNs with metastasis was 3 (range 1–20) in our cohort and 1 (range 1–47) in the SEER database. When N-positive cases were reclassified according to the upper GI protocol (N1: metastasis to 1–2 LNs; N2: metastasis to ≥ 3 LNs), 60 cases (26 %) were N1 and 115

TABLE 1 Clinicopathologic features of Institutional Cohort and SEER data

	Institutional Cohort $N = 227$ (%)	SEER data $N = 10{,}554$ (%)
Gender		
Female	129 (57)	5327 (50.5)
Male	98 (43)	5227 (49.5)
Age		
Year	65 (33–87)	66 (4–85)
Tumor size (median, mm)	31 (6–70)	33 (1–99)
T stage (AJCC 7th ed)		
T1	4 (2)	723 (7)
T2	4 (2)	1913 (18)
T3	213 (95.5)	7031 (67)
T4	2 (1)	887 (8)
LN Stage (AJCC 7th ed)		
N-negative	52 (23)	4273 (40.5)
N-positive	175 (77)	6281 (59.5)
Median number of LNs examined (range)	18 (3–45)	11 (1–89)
Median number of LNs with metastasis (range)	3 (1–20)	1 (1–47)
Outcome		
Dead	143 (63)	6524 (62)
Alive	84 (37)	4030 (38)
Median survival (months)	16	17

(51 %) were N2, and when these cases were reclassified according to the lower GI protocol (N1: metastasis to 1–3; N2: metastasis to ≥4 LNs), 90 cases (40 %) were N1 and 85 cases (37 %) were N2.

Notably, the frequency of LN metastasis in the seven arbitrarily defined regions of peripancreatic tissue was 41 % in the posterior pancreatoduodenal region, 37 % in the posterior pancreatic region, 34 % in the anterior pancreatic region, 24 % in the anterior pancreatoduodenal region, 24 % in the common bile duct region, 31 % in the superior head region, and 25 % in the inferior head region. The superior mesenteric artery (uncinate) margin sections, submitted entirely as a perpendicular margin, often harbored LNs, with 78 % of all cases harboring LNs in this region and 38 % harboring LN metastases.

Survival Analyses

The median overall survival with N-negative cases was significantly longer than with N-positive cases both in our cohort (35 vs 19 months; $p = 0.004$) and in the SEER database (23 vs 15 months; $p < 0.0001$) (Table 2). When tested with the upper GI protocol, the median overall survival times for N0 vs N1 vs N2 were respectively 35, 21, and 18 months, and the respective 3-year survival rates were 46, 34, and 20 % in our cohort ($p = 0.004$) (Table 3). These values were respectively 23, 15, and 14 months and 37, 22, and 18 % in the SEER database ($p < 0.0001$) (Table 3). The lower GI protocol also had statistically significant correlation, with median overall survival times for N0 vs N1 vs N2 of 35, 21, and 18 months and respective 3-year survival rates of 46, 26, and 23 %; ($p = 0.009$) (Table 4).

These results were even more evident when separate analyses were performed for cases with 12 or more LNs harvested. In our cohort, the median overall survival time was 47.5 months for the N-negative cases and 20 months for the N-positive cases ($p = 0.004$). In the SEER database, the corresponding survival times were 30 and 17 months ($p < 0.0001$) (Supplementary Table 1). Also, the median overall survival times for the upper GI protocol N0, N1, and N2 cases were respectively 47.5, 30, and 20 months, and the respective 3-year survival rates were 51, 37, and 21 % ($p = 0.003$) in our cohort (Supplementary Table 2), whereas the corresponding median overall survival times were respectively 30, 20, and 15 months, and 3-year survival rates were respectively 44, 29, and 19 % ($p < 0.0001$) in the SEER database (Supplementary Table 2). When the lower GI protocol was tested in cases with 12 or more LN harvested, it also showed significant correlation, with median overall survival times of for N0 vs N1 vs N2 of 47.5, 25, 19 months and respective 3-year survival rates of 51 %, 27 %, 27 % ($p = 0.01$) (Supplementary Table 3).

Kaplan–Meier survival curves comparing these substages are illustrated in Fig. 2 and Supplementary Fig. 1. Based on log-rank tests of each protocol, the main driver of the p value appeared to be N0 versus N2 ($p = 0.001$ for the upper GI protocol and $p = 0.004$ for the lower GI protocol). However, for the lower GI protocol, a significant difference between N0 and N1 was evident ($p = 0.02$) but not between N1 and N2 ($p = 0.3$). Although the upper GI protocol showed a trend between N0 and N1 and between N1 and N2, neither reached statistical significance ($p = 0.1$ for both). Notably, the p value of the test for trend was 0.001 for the upper GI protocol and 0.003 for the lower GI protocol.

In the multivariable Cox regression model adjusted for age, race, sex, tumor site, tumor size, T stage (AJCC 7th ed), and distant metastasis, the association between higher proposed N stage and shorter survival persisted. Using the N0 group as a reference, for the upper GI protocol, the adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) for N1 and N2 were respectively 1.2 (0.7–2.1; $p = 0.4$) and 1.6 (1.0–2.6; $p = 0.06$) for all the cases and 1.4 (0.7–2.5; $p = 0.3$) and 2.0 (1.1–3.6; $p = 0.01$) for the cases with 12 or more LNs harvested. For the lower GI protocol, the adjusted HRs (95 % CIs) for N1 and N2 were

TABLE 2 Current AJCC pancreas n stages and median survivals of Institutional Cohort and SEER data (all cases)

Survival	Institutional cohort cases			SEER data		
	N-negative	N-positive	*p* value	N-negative	N-positive	*p* value
N (%)	52 (23)	175 (77)		4273 (40.5)	6281 (59.5)	
Median (months)	35	19	0.004	23	15	<0.0001
1 year (%)	77	67		67.5	57	
3 year (%)	46	24		37	20.5	

TABLE 3 UPPER GI PROTOCOL N substages and median survivals of Institutional Cohort and SEER data (all cases)

	Institutional Cohort				SEER data			
	N0	N1 (metastasis in 1–2 LNs)	N2 (metastasis in ≥3 LNs)	*p* value	N0	N1 (metastasis in 1–2 LNs)	N2 (metastasis in ≥3 LNs)	*p* value
N (%)	52 (23)	60 (26)	115 (51)		4273 (40.5)	3430 (32.5)	2851 (27)	
Median (months)	35	21	18	0.004	23	15	14	<0.0001
1-year (%)	77	73	64		67.5	59	55.5	
3-year (%)	46	34	20		37	22	18	

TABLE 4 LOWER GI PROTOCOL N substages and median survivals of Institutional Cohort (all cases)

	Institutional Cohort			
	N0	N1 (metastasis in 1–3 LNs)	N2 (metastasis in ≥4 LNs)	*p* value
N (%)	52 (23)	90 (40)	85 (37)	
Median (months)	35	21	18	0.009
1-year (%)	77	73	61	
3-year (%)	46	26	23	

respectively 1.4 (0.9–2.3; $p = 0.18$) and 1.6 (1.0–2.8; $p = 0.07$) for all the cases and 1.6 (0.9–2.8; $p = 0.1$) and 2.0 (1.1–3.7; $p = 0.03$) for the cases with 12 or more LNs harvested.

In these models, age, and tumor size also were significantly associated with survival. For the upper GI protocol, the HR (95 % CI) was 1.2 (1.0–1.4; $p = 0.02$) for a 10-year increase in age and 1.2 (1.0–1.4; $p = 0.03$) for a 10-mm increase in tumor size. For the lower GI protocol, these HRs (95 % CIs) were respectively 1.2 (1.0–1.4; $p = 0.02$) and 1.2 (1.0–1.4; $p = 0.02$).

Quality of the Protocols

Using the Akaike Information Criterion (AIC), which estimates the quality of each protocol relative to each of the other protocols, the upper GI protocol appeared to be the preferred model because it had the minimum AIC value:

Current AJCC N staging protocol AIC = 1272.6

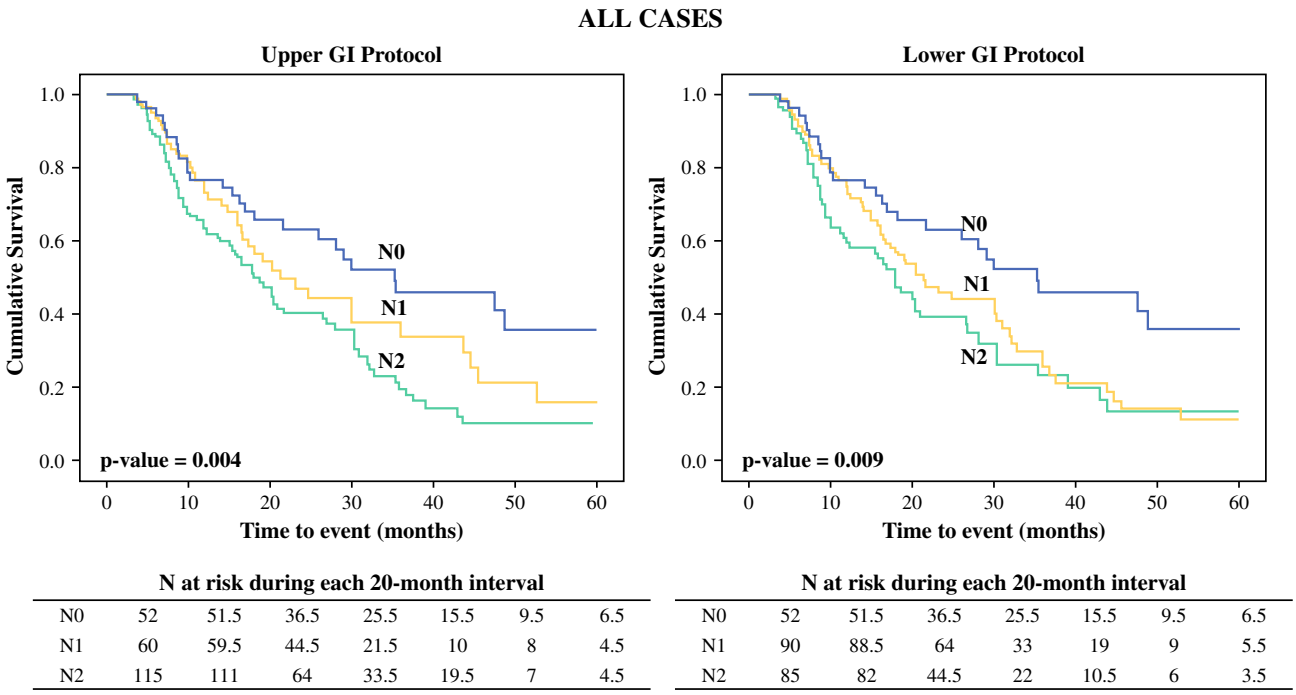
Upper GI N staging protocol AIC = 1270.4

Lower GI N staging protocol AIC = 1274.1

DISCUSSION

In this study, the prognostic implication of the LN substaging protocols used by the AJCC/UICC for upper and lower GI organs were tested in a well-characterized cohort of resected pancreatic head PDACs that had been subjected to a uniform and simple LN harvesting protocol. To have a more uniform cohort for analysis, only ordinary PDACs were included, whereas other carcinoma types as well as secondary tumors were carefully excluded, which may account for the slightly lower survival rates in this cohort than those reported in the literature.[6,42,43] In fact, when studies published with stringently defined cohorts are evaluated separately, our results are in accordance with those results.[12,32,35,44,45]

In this stringently defined and processed cohort, 77 % of the resected PDACs were found to have metastatic carcinoma in the LNs. In the literature, this number ranges from



N at risk during each 20-month interval

N0	52	51.5	36.5	25.5	15.5	9.5	6.5
N1	60	59.5	44.5	21.5	10	8	4.5
N2	115	111	64	33.5	19.5	7	4.5

N at risk during each 20-month interval

N0	52	51.5	36.5	25.5	15.5	9.5	6.5
N1	90	88.5	64	33	19	9	5.5
N2	85	82	44.5	22	10.5	6	3.5

FIG. 2 Comparison of survival between proposed substages in an institutional cohort, which includes all cases including left upper gastrointestinal (GI) protocol (*N0* no LN metastasis, *N1* metastasis in 1–2 LNs, *N2* metastasis in ≥3 LNs) and right lower GI protocol (*N0* no LN metastasis, *N1* metastasis in 1–3 LNs; *N2* metastasis in ≥4 LNs). The number of patients taken into consideration at each interval is shown in the table below the Kaplan–Meier curves

57 to 81 %,[10,12–14,16,17,20–28] although in studies from experienced institutions this typically is more than 70 % of patients.[12,14,20] Along the same lines, the median number of regional LNs examined per case was 18, and the median number of LNs involved by metastatic PDAC was 3. These median values are higher than most values reported in the literature,[21,23,26–28,30,45–49] with some exceptions.[6,12,22,24,50,51]

In the SEER database, which serves as a reflection of general practice rather than the practice of tertiary care centers alone, the median number of LNs examined in all recorded PDACs is reported to be only seven in recent studies.[34,35] When we sorted out the SEER cases that had more thorough pathologic reporting, we found this number to be slightly higher ($n = 11$), and the median number of LNs with metastasis still was 1. These figures still are significantly lower than those in our cohort and in other major studies.

In our institutional cohort, the LN sampling was performed using the orange-peeling approach, which gives a more thorough LN harvest and thus higher rates of LNs identified and fewer overlooked LN metastases. This is a very straightforward protocol involving separation of LN regions before cutting of the pancreatic head so LNs are not lost, and numerous institutions currently have adopted this protocol.

Before establishment of this approach, the median number of regional LNs examined at our own institutions also was very low, 6 and[7,40] similar to the median number in the SEER database.[34,35] The application of a better LN harvesting approach also may account for the higher percentage of N2 cases in our institutional cohort (N1: 26 %; N2: 51 %) than in the SEER database, which had more N1 cases (N1: 32.5 %; N2: 27 %).

It should be noted that it should not matter which grossing approach is used as long as complete harvesting of LNs is achieved and the requirement of College of American Surgeons (minimum of 12 LNs) is fulfilled. Our median harvested LN number of 17 was similar to those reported from most experienced institutions.

This study confirms the significant prognostic implications of LNs with metastasis in PDACs. In this uniform cohort of PDACs, the median survival of the patients with N-negative disease was 35 months compared with 19 months for patients with N-positive disease. In the SEER database, these figures were respectively 23 and 15 months. Moreover, when the cases with the ACS-required number of 12 or more LNs were analyzed separately, these results became even more striking, both in the institutional cohort and the SEER database, emphasizing the importance of proper grossing and documentation.

The primary aim of this study was to determine the prognostic value of LN substaging systems currently part of the AJCC guidelines for some organs including the GI tract[1] and recently documented also for ampullary carcinoma.[2–5] Indeed, subclassification of node-positive PDAC cases into N1 (metastasis to 1–2 LNs) versus N2 (metastasis to ≥3 LNs), as already used by AJCC/UICC for the upper GI tract, was found to have significant differences in survival, both in the institutional cohort and the SEER database. The protocol used for the lower GI tract also was found to have significant correlation with outcome. However, the upper GI protocol appears to be the preferred model because it has the minimum AIC value. Also, considering the pancreas to be part of the upper GI tract and because the same protocol was recently tested and proven very valuable also in the ampulla (another upper GI organ), the upper GI protocol ought to be the choice for this purpose.

Remarkable negative clinical implications of a higher number of LNs with metastasis are not surprising because it after all reflects the tumor burden. These findings support the lymph node ratio (LNR) concept, shown by findings to have substantial biologic significance in pancreatic cancer as well as in other malignancies.[27,53–57] This study did not test the LNR because this factor is not currently transferrable to routine clinical practice. However, LNR may become a consideration in the future because it may prove to be a better assessment of LN status.

In summary, LN status is one of the most important prognosticators in ordinary PDAC, and thus its proper documentation is crucial. When careful LN harvesting protocols such as the orange-peeling approach is used, nearly 80 % of ordinary PDACs of the pancreatic head that are resected prove to have LN metastasis. Separating the node-positive cases into N1 and N2 subsets has significant prognostic value and should be incorporated into the next AJCC/UICC LN staging protocol. For this, the protocol already in use for the other upper GI organs, whose findings also show to be an independent prognostic factor for ampullary cancers, would be preferable.

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