Institutional Variants For Lymph Node Counts After Pancreatic Resections

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Abstract

Background: Lymph node (LN) counts from pancreatectomy are postulated as quality metric for surgical therapy of pancreatic malignancy.

Methods: Prospectively collected data from a single surgeon's pancreatectomy experience were analyzed for predictors of LN counts.

Results: Of 315 consecutive patients (54% female, median age: 65, range 18-88), 239 had a proven cancer diagnosis (76%). Operations included pancreatoduodenectomy (69%), distal pancreatectomy (26%), total pancreatectomy (1%) and others (4%). Patients were treated in 4 different tertiary cancer center settings (Institution A: 11%; B: 46%; C: 27%; D: 16%) with consistent regional dissection standards. Mean total LN counts differed between institutions for malignancies (A: 18, B: 13, C: 26, D: 26, $p<0.0001$) and benign diseases ($p=0.003$). At least 15 LNs were reported in 63% of cancer patients (institution range: 34-92%, $p<0.0001$).

Conclusions: Pathologic processing should be standardized if LN numbers are to be adopted as quality metric for pancreatic cancer resections.

Background

Pancreatic cancer and other periampullary cancers remain formidable health care challenges for which few effective therapeutic options exist. For apparently localized tumors, resection continues to provide some important benefit, albeit rarely curative [1]. Complexity of pancreatectomy and a high morbidity potential call for appropriate specialty expertise when performing such operations. Adhering to high technical and oncological resection standards, among other important selection and care parameters, has become a critical mandate to deliver appropriate care and achieve best possible outcomes such as obtaining low rates of margin positivity, minimizing locoregional recurrence and prolonging survival. Although efforts to extend the regional dissection during pancreatectomy for cancer have failed to show measurable survival benefits in several randomized controlled trials [2-5], total lymph node (LN) counts after pancreatic resections nevertheless are linked to staging accuracy and may impact regional disease control [6]. Conclusive data that support a causative impact of increased lymph node removal on improved pancreatic cancer survival outcomes are lacking. A minimum total LN count of 12 is recommended for pathologic staging of pancreatic cancer [7], although this requirement is not only not often met throughout the U.S. but missed in the majority of cases, based on population data [8-11]. Meeting this expectation or exceeding it has been discussed as one possible aspect representing the quality of operative dissection and histopathologic analysis of pancreatectomy specimens, analogous to currently accepted guidelines for regional lymphatic dissection of colorectal cancers [11]; nevertheless, controlling for operative versus pathologic influences on LN counts has been challenging for the concept of accepting LN counts as quality metric. This

analysis of a surgical experience with a consistent operative approach seeks to study institutional variability among LN counts and related parameters after pancreatectomy.

Patients and Methods

The analysis is based on prospectively collected data from a single surgeon's consecutive pancreatectomy experience within four different institutions. These included a nonacademic tertiary cancer center (Institution A), a university HPB practice (B), an academic cancer center (C) and a community cancer center (D). All procedures were generally deemed to yield a complete resection with curative intent. Patients underwent some form of pancreatic resection including pancreatoduodenectomy (PD), distal pancreatectomy (DP), total pancreatectomy (TP) or others including central resection and enucleation. Resections performed for proven, suspected or possible malignant neoplasms all included standardized regional dissection components: pancreaticoduodenal, peripancreatic, common hepatic, retroportal, aortacaval and right lateral superior mesenteric LNs for PD; splenic and left gastric LNs for DP with splenic artery and vein resection but a preference for spleen preservation; and a combination of these for TP. Additional nodal areas were only included when deemed appropriate based on specific findings. Laproscopic DP became the preferred choice for cystic lesions and NETs since the early experience in institution B, and open DP remained the preferred choice for suspected PDAC or locally advanced tumors. Pathologic processing was done as per institutional standard protocols and was not influenced by the surgeon, but expectations to obtain LN counts beyond minimum staging requirements were communicated. Fat clearing methods were not routinely employed but

selectively utilized when deemed indicated by the pathologist based on fat content and the ability to grossly identify LNs. Standard nodal processing included bihalving and standard histologic H&E staining techniques; immunohistochemical techniques were not routinely applied. Requests for specimen reexamination were routinely directed towards the pathologist if total LN counts did not exceed 15. Demographic, clinicopathologic and outcomes data were collected prospectively based on institutional review board approved protocols. Postoperative morbidity was defined as minor for Clavien-Dindo grades of 1-2, and major for grades 3-5. Statistical analysis of covariates associated with various LN counts was performed using StatView software (SAS, Cary, NC). Significant relationships were examined with ANOVA, t-test, Mann-Whitney, Kruskal-Wallis, chi-square and logistic regression analyses, as indicated. Significance of differences was accepted at $p<0.05$.

Results

Of 315 patients who underwent pancretectomy, 54% were female and 46% male, with a median age of 65 years (range: 18-88). A proven cancer diagnosis was established in 239 (76%), including ductal or periampullary adenocarcinomas (n=204), neuroendocrine tumors (NETs, n=22), other malignancies (n=13); seventy-six patients had nonmalignant conditions including cystic neoplasms, benign NETs or focal pancreatitis. Operations included PD (69%), DP (26%), TP (1.3%) and others (4%); pylorus preservation was part of 91 PDs (42%). Preoperative therapy had been given in 10% of pancreatic ductal adenocarcinomas (PDAC). Patient distribution encompassed 33 in institution A (11%), 145 in B (46%), 86 in C (27%) and 51 in D (16%). The

breakdown of clinicopathologic and outcome parameters between institution cohorts is shown in Table 1. As listed, significant differences between institutions were identified for age, diagnoses and length of stay, but not regarding tumor size, R category and length of stay. Additional institutional differences existed in ASA class ($p<0.0001$), pathologic T category ($p=0.04$) and preoperative therapy ($p=0.015$).

LNs were identified in 99% of PD, 100% of TP, 80% of DP, but 23% of other, lesser resection specimens ($p<0.0001$). Detailed metrics reflective of LN evaluation are listed in Table 1 and depicted in Figure 1. Total pathologic LN counts (median 16, range 1-88) differed between pancreatic/periampullary cancers (median: 19) and other diagnoses (median: 9; $p<0.0001$), and among procedures (PD: 17, DP: 14, total: 11, others: 2; $p=0.048$). Total LN counts in cancer patients did not have significant associations with preoperative therapy, ASA class or R category. Mean LN counts differed between institutions for both malignancies (A: 18, B: 13, C: 26, D: 26; $p<0.0001$) and benign diseases (A: 8.5, B: 5, C: 16 D: 18; $p=0.003$). Minimum total LN counts of 10, 12 or 15 were reported in 80, 74 and 63% of cancer patients, respectively; frequencies ranged among institutions from 63-98% for 10+, 52-98% for 12+ and 34-92% for 15+ LNs examined ($p<0.0001$ for all three cut points; Table 1). There were no differences between institutions regarding number of positive LNs and percent of N+ staging categories for cancer patients. The number of positive LNs correlated to total LN counts ($r=0.415$, $p<0.0001$; Figure 1F). Nodal positivity for patients with pancreatic and periampullary malignancy was 49 vs. 66% below vs. at or above a cutpoint of 10 total LNs ($p=0.034$); for the 12 LN cutpoint, they were 52 and 67% ($p=0.049$), and for the 15 LN cutpoint 53 and 69%, respectively ($p=0.022$). When controlled for other covariates such as diagnosis and resection type, the institution was the only significant variable linked to the likelihood to obtain a total LN count of 15 or more; odds ratios compared

to institution A were 0.269 (95% CI: 0.1-0.7) for B (p=0.009), 3.01 for C (0.9-10.0, p=0.07) and 6.8 for D (1.7-28.4, p=0.008).

Discussion

The potential clinical impact or value of lymphadenectomy for pancreatic and periampullary malignancies has been debated for some time. In contrast to other GI neoplasms such as gastric or colorectal cancer where standardized or extended LN dissection and formal examination of 12 to 15 LNs may have a disease-control impact beyond the known staging benefit, most periampullary cancers are high-risk lesions with high propensity for distant metastasis and resulting poor survival odds, limiting the possibility of better regional disease control to result in superior survival outcomes. For this reason, convincing data to support higher LN counts to support greater overall survival or locoregional control rates do not exist. Nevertheless, population based analyses have shown an association of increased total or negative LN counts with better survival, independent of stage-specific survival [8,9]. It is acknowledged, however, that higher LN counts may also be a surrogate for other variables such as greater administration of chemotherapy [11]. Several randomized trials of extended LN dissection during pancreatectomy for cancer have failed to show convincing support for any survival benefit. Extending the regional dissection beyond a standard dissection has likely failed in this setting because the “standard” dissection already included reasonable LN groups for dissection and acceptable counts beyond which further lymphadenectomy is less likely to mediate further measurable benefit [3-5].

Should a minimum number of LNs examined thus be recommended for pancreas cancer resections? It is clear that throughout the US population, the minimum staging recommendation of 12 LNs is missed in the majority of cases [8-10]. Under this perspective, creating a LN count based quality metric appears reasonable. However, the question of variability in pathologic examination may challenge the feasibility and reliability of such approach. Multi-institutional assessment of LN numbers would struggle with variability of surgical dissection practices, differences in patient cohorts and varying pathologic practices. The current series attempts to control for the operative variability by comparing pancreatectomy-associated LN counts in a single-surgeon experience within four different institutions. While methodologically not protected from possible biases as result of different patient populations, this approach nevertheless represents an intriguing opportunity for the ability to examine variations in LN counts based on institutional influences with consistent operative dissection standards.

The results show that pancreatectomy-associated LN counts varied considerably between institutions. While the recommended staging requirements were met or exceeded in between 80 to 98% of cases in three institutions, this was the case in just around half of cases in the fourth institution. Reasons will likely originate in gross pathologic specimen preparation and examination standards, but certainly could reflect other differences between institutions in patient overall health, nutrition status, therapeutic aspects etc. Reliable data that LN counts after pancreatectomy vary between institutions do not exist; however, examples from other disease types such as endometrial or colon cancers suggest that this is indeed the case [12,13]. In addition, interobserver and intraobserver variability among pathologists is a well-documented phenomenon [14]. Although is is methodologically challenging to define the impact of surgeon, pathologist, patient and institution on variations in the resulting LN count, it has been suggested

that for resected colon cancer, surgeon and pathologist impact was observed to be smaller than those of institution and patient variability [13].

Should pathologists invest effort in finding additional LNs once a positive LN has been identified? While for pancreatic cancer this may be an appropriate question, for other nonpancreatic periampullary cancers with generally more moderate survival hazards this will be less debatable. For all these epithelial cancers, number of positive LNs as well as number of negative LNs (or total LN counts) have shown significant overall survival impact at least in large population database or multi-institutional trial analyses [6,8]. Consequently, defining appropriate LN numbers seems to be a reasonable pathologic objective, if at a minimum to meet proper staging objectives. How relevant may LN counts be for benign conditions leading to resection? It should be noted that in the current series, in a considerable number of resections the definitive malignant or benign nature of the underlying process was not known at the time of the procedure, as for most neuroendocrine or mucinous cystic neoplasms, and that the resulting resection extent included regional dissection with splenic vascular resection in case a malignant process was to be identified. Interestingly, the institution with the lowest average LN counts for cancerous lesions also was found to have the lowest LN numbers reported for benign conditions.

It appears noteworthy that the consistently highest counts in the current series were obtained in the community practice environment. Perhaps the proximity between surgeon and pathologist and the lack of potential challenges in a pathology laboratory training environment can lead to persistently diligent results. Along this notion, differences in LN counts for benign diagnoses may also result from a varying degree of importance lent to LN analysis in nonmalignant disease. The data also support an association between LN counts and nodal positivity, i.e. a greater sensitivity for staging and the potential for some stage migration with increasing LN counts up to

15. Based on these results, however, it would be difficult to delineate which exact cutoff point should be considered appropriate for pancreatic cancer resections.

Limitations of this study relate to its modest size, the longitudinal comparison of four institutional cohorts over time, the (albeit unlikely) potential for changed operative practice, the retrospective nature of evaluation and confounding factors not discernable within the data set. Nonstandardized pathologic processing, variation in pathologic dissection technique such as routine fat clearing measures, variability between individual pathologists and lack of a separate pathologic review, often limitations to quality reporting of clinical series, are nevertheless precisely desirable shortcomings to be addressed in this study. It should be stated, however, that the results obtained herein are generally rather favorable compared to other institutions regarding LN counts, quality of staging, margin status assessment and other clinical aspects [6,11,15].

Quality of staging and operative therapy for cancer is expected to become more heavily scrutinized in the near future, and metrics that may reflect value aspects could gain increasing clinical and financial importance. If LN counts are to be used as performance metric for pancreatic and periampullary cancers, goals should be clearly stated and gross as well as histopathologic examination procedures should be standardized. Surgeons are encouraged to take an active role not only in the operative and multidisciplinary aspects of cancer care but also within the diagnostic and pathologic staging domains.

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Table 1

Clinical and pathologic characteristics of patients undergoing pancreatectomy, by institution

Characteristic	Subgroup	Total cohort	Institution A	Institution B	Institution C	Institution D	p value
Patients, n		315	33	145	86	51	
Gender, n	Male	146	15	57	46	28	NS
	Female	169	18	88	40	23	
Mean age, yrs (range)		64.6 (18-88)	62.7 (44-88)	65.2 (34-86)	61.3 (18-84)	69.5 (37-85)	0.001
Diagnoses, n (%)	PDAC	146 (46)	15 (45)	63 (43)	38 (44)	30 (59)	0.0004
	periampullary	58 (19)	7 (22)	32 (22)	7 (8)	12 (23)	
	PNET	22 (8)	1 (3)	2 (1)	14 (16)	5 (10)	
	other cancer	13 (4)	1 (3)	8 (6)	4 (5)	0	
	no cancer	76 (23)	9 (27)	40 (28)	23 (27)	4 (8)	
Operative procedures, n (%)	PD	218 (69)	27 (82)	99 (68)	58 (68)	34 (67)	NS
	DP	80 (25)	6 (18)	34 (24)	24 (28)	16 (31)	
	TP	4 (1)	0	2 (1)	2 (2)	0	
	others	13 (4)	0	10 (7)	2 (2)	1 (2)	
Mean tumor size, cm (SD)		3.5 (2.6)	3.3 (1.8)	3.4 (2.2)	4.1 (3.8)	3.3 (1.9)	NS
LNs identified in specimen, %		91.1	97	84.8	94.2	100	0.024
Median overall LN count, n (range)		16 (0-88)	15.5 (0-39)	10 (0-39)	23 (0-88)	26 (2-51)	<0.0001
Median overall cancer patient LN count, n (range)		19 (1-88)	17 (4-39)	12 (1-39)	24 (5-88)	26 (8-41)	<0.0001
Median positive LN count, n (range)		1 (0-22)	1 (0-7)	1 (0-20)	2 (0-22)	1 (0-21)	NS
Median LN count without cancer diagnosis, n (range)		9 (0-65)	8 (0-30)	5 (0-25)	14 (0-65)	18 (1-51)	0.0009
Cancer patients with 10+ LNs, %		80.4	91.3	62.5	91.5	97.9	<0.0001
Cancer patients with 12+ LNs, %		74.2	82.6	52.1	88.1	97.9	<0.0001
Cancer patients with 15+ LNs, %		63.1	69.6	34.4	84.7	91.5	<0.0001
Cancer patients with N+ disease, %		62.6	50.0	58.9	70.7	66.0	NS
R category, n (%)	R0	184 (82)	19 (83)	73 (75)	51 (86)	41 (87)	NS
	R1	38 (17)	3 (13)	24 (25)	7 (12)	5 (11)	
	R2	4 (1)	1 (4)	0	1 (2)	1 (2)	
Postoperative morbidity, %	None	57.8	63.6	62.8	53.5	47.1	NS
	Minor	26.3	24.3	23.4	27.9	33.3	
	Major	15.9	12.1	13.8	18.6	19.6	
Median length of stay, d (range)		9	12	9	8.5	8	0.0032

Figure Legends

Figure 1

Lymph node counts, by institution and other characteristics

1A Mean total LN counts, by institution (n=315; error bars: 95% CI; p<0.0001)

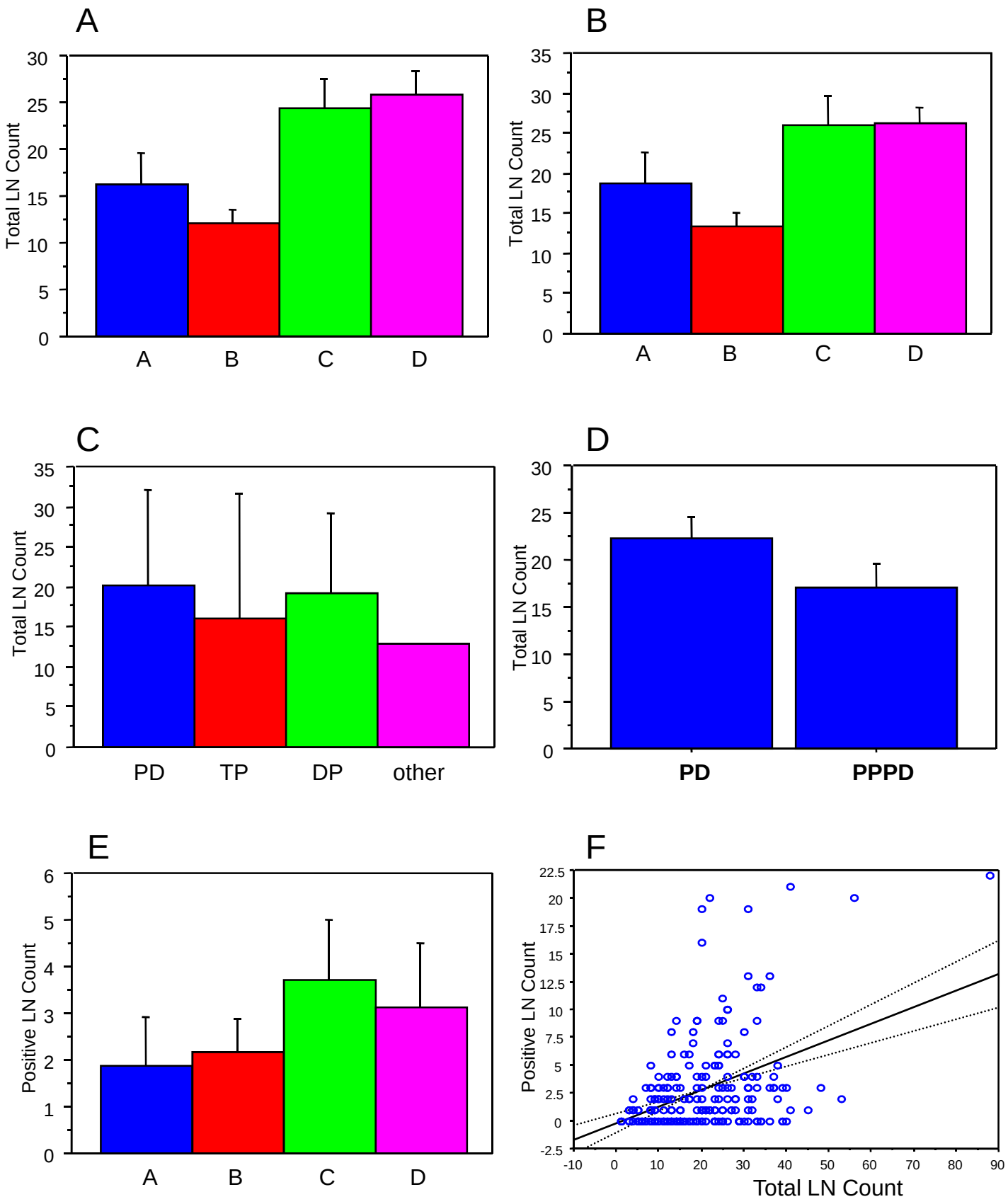
1B Mean total LN counts, pancreatic and periampullary cancers only, by institution (n=227; error bars: 95% CI; p<0.0001)

1C Mean total LN counts, cancer diagnoses only, by procedure (pancreatoduodenectomy: n=181, total pancreatectomy: n=3, distal pancreatectomy: n=40, others: n=1; error bars: standard deviation; p=NS)

1D Mean total LN counts, pancreatic and periampullary cancers only, by procedure (pancreatoduodenectomy: n=110, pylorus-preserving pancreatoduodenectomy: n=71; error bars: 95% CI; p=0.0042)

1E Mean positive LN counts, pancreatic and periampullary cancers only, by institution (n=227; error bars: 95% CI; p=NS)

1F Correlation between total and positive LN counts, pancreatic and periampullary cancers only (n=227; scattergram with regression line and 95% CI; p<0.0001)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