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Determining the optimal number of examined lymph nodes for accurate staging of pancreatic cancer: An analysis using the nodal staging score model

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ABSTRACT

Introduction: The aim of this study was to determine the optimal number of examined lymph nodes (ELNs) for accurate staging of pancreatic cancer using the nodal staging score model.
Materials and methods: Clinicopathological data for patients with resected pancreatic cancer were collected from SEER database (development cohort [DC]) and Fudan University Shanghai Cancer Center database (validation cohort [VC]). Multivariable models were constructed to assess how the number of ELNs was associated with stage migration and overall survival (OS). Using the β-binomial distribution, we developed a nodal staging score model from the DC and tested it with the VC.
Results: Both cohorts exhibited significant proportional increases from node-negative to node-positive disease (DC: odds ratio [OR], 1.047; $P < 0.001$; VC: OR, 1.035; $P < 0.001$) and improved OS (DC: hazard ratio [HR], 0.982; $P < 0.001$; VC: HR, 0.979; $P < 0.001$) as ELNs increased. Nodal staging scores escalated separately as ELNs increased for different tumor (T) stages, with plateaus at 16, 21, and 23 LNs (cut-offs) for T1, T2, and T3 tumors, respectively. Multivariable analysis indicated that examining more LNs than the corresponding cut-off value was a significant survival predictor (DC: HR, 0.813; $P < 0.001$; VC: HR, 0.696; $P = 0.028$).
Conclusion: The optimal number of ELNs for adequate staging of pancreatic cancer was related to T stage. We recommend examining at least 16, 21, and 23 LNs for T1, T2, and T3 tumors, respectively, as a nodal staging quality measure for both surgery and pathological analysis.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths with an estimated 44,330 deaths expected to occur in the United States in 2018 [1]. Surgical resection in combination with systemic chemotherapy or chemoradiation offers the only chance of long-term survival and a potential cure. However, only 20% of patients present with potentially curable pancreatic cancer, and the 5-year survival rates are only 25% even after successful resection [2].

The lymph node (LN) status of patients with resectable pancreatic cancer is an important predictor of survival. Nearly all patients with node-positive disease will experience local or distant recurrence compared with 40% of patients with pathologically negative LNs [3]. Previous studies have reported the prognostic value of the number of positive LNs and the LN ratio (number of positive nodes/number of examined nodes) in node-positive

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patients [4–7]. More positive LNs and an LN ratio greater than 0.2 were predictors of decreased survival. With regards to the number of examined LNs, the optimal number is still a matter of debate. Recommendations range from 11 to 17 nodes [8], and a minimum of 15 nodes has been embraced as a standard [9,10]. However, most proposals regarding the optimal number of examined LNs are based on identifying a threshold that maximizes the prognostic discrimination among the groups [11–15]. The methods for identifying the cut-off points are not robust. In addition, although extended lymphadenectomy provides no survival benefit [16], a complete pathological LN examination is necessary to avoid stage migration and increase staging accuracy [17]. However, the impact of the examined LN count on staging accuracy in pancreatic cancer has not been fully studied.

One pertinent change in the staging of pancreatic cancer in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system is the subdivision of nodal (N) stage [18]. N1 tumors are those with one to three positive LNs, and those with more than four positive LNs are classified as N2. This reclassification of the N stage emphasizes the importance of the LN status in staging for pancreatic cancer [19,20]. In addition, the definition of the tumor (T) stage has been altered to be based on tumor size. Because there exists a significant interaction between tumor size and LN involvement [21], we hypothesized that the T and N stages may be correlated under the new staging system.

In this study, we performed an in-depth analysis of two cohorts to explore the potential association between the T and N stages and to reappraise the influence of the number of examined LNs on stage migration and survival. We further used a previously validated method to develop a nodal staging score (NSS) model, which may help guide the assessment of the true nodal status in patients with declared node-negative disease [22]. Based on the NSS model, we identified the optimal number of examined LNs for accurate staging separately for each T stage.

Materials and Methods

Data sources and patient selection

Development cohort (DC). Details regarding stage I-II (based on the 7th edition of the AJCC staging system) pancreatic adenocarcinoma cases from 2004 to 2014 that were in the Surveillance, Epidemiology, and End Results (SEER) database were retrieved using SEER*Stat version 8.3.4. Only patients who underwent surgery and had microscopically confirmed pancreatic ductal adenocarcinoma (PDAC; ICD-O-3 histology/behavior codes 8500/3 and 8140/3) or ductal adenocarcinoma variants (ICD-O-3 histology/behavior codes 8560/3, 8480/3, 8576/3, 8510/3, 8490/3, 8020/3, and 8035/3) were included. Other variants of pancreatic cancer such as intraductal papillary mucinous neoplasm with associated invasive carcinoma, mucinous cystic neoplasm with associated invasive carcinoma, neuroendocrine carcinoma, solid pseudopapillary neoplasm, acinar cell carcinoma, and pancreatoblastoma were excluded. Patients were uniformly reviewed and re-staged according to the 8th edition of the AJCC staging system (Supplementary Methods) [18]. Patients for whom the number of examined nodes was zero or unreported, the number of positive nodes was unknown, or tumor size was unknown were excluded; thus, the final DC included 10,182 patients (Supplementary Fig. 1).

Validation cohort (VC). The VC comprised 585 patients with non-metastatic PDAC who underwent upfront surgery without neoadjuvant therapy between January 2010 and December 2014 at the Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center (FUSCC). All surgical specimens were processed according to standard pathological procedures. All removed lymphoid tissues, including LNs that were intraoperatively harvested by surgeons and LNs that were postoperatively identified by pathologists, were submitted for histological examination. Survival time was calculated from the date of diagnosis to the date of death or last follow up. This study was approved by the institutional review board of our institute, and the requirement for written informed consent was waived due to the retrospective nature of the study.

Statistical analysis

Baseline characteristics in patients with node-negative disease versus node-positive disease were compared using the χ [2] test for categorical variables and the Mann-Whitney *U* test for continuous variables. Based on the hypothesis that examining more LNs will increase the likelihood of detecting positive LNs, the association between the number of examined LNs and nodal stage was assessed by using a binary logistic regression model after adjusting for other potential confounders [23]. The correlation between the number of examined LNs and the mean number of positive LNs was modeled using simple linear regression. The effect of the number of examined LNs on overall survival (OS) was evaluated by using a Cox proportional hazards regression model after adjusting for other covariables [24]. The optimal model was selected using a backward stepwise procedure based on the minimum Akaike information criterion value [25]. The proportional hazards assumption was assessed both graphically (using a log-log plot) and analytically (using the scaled Schoenfeld residuals test) [26,27]. Violation of the proportional hazards assumption was addressed by use of a stratified Cox regression model for categorical covariables or an extended Cox regression model for continuous covariables. Adjusted hazard ratios (HRs) of each examined LN count with one examined LN as a reference were fitted by using a LOWESS model with a bandwidth of 2/3 [28]. A break point was determined by piecewise linear regression with the least squares method [29]. Statistical analyses were performed with SPSS version 19.0 (IBM Corporation, Chicago, IL, USA) and R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Nodal staging score model development

Probability of missing nodal disease. A previously described mathematical model of the number of examined LNs was used to estimate the probability of missing nodal disease [22]. We first fitted the percentage of LNs that were positive in all patients within the DC to a β-binomial distribution model. The VGAM package was used to fit the α and β parameters of the β-binomial distribution using a maximum likelihood approach. The precision of the α and β parameters was assessed by creating 1000 bootstrap samples from the DC data set and replicating the estimation process. We then calculated the probability of missing nodal disease [$P(FN_m)$] at each possible value of number of nodes examined as follows:

$$P(FNm) = P(0|m,\alpha,\beta) = \frac{Beta(\alpha,\beta+m)}{Beta(\alpha,\beta)}$$

where *m* denotes the number of nodes examined from 1 to 90, and *Beta()* represents the beta function.

Estimation of the prevalence of nodal disease. The apparent prevalence of nodal disease, which was an underestimation, was adjusted for false negatives (FNs) in two steps. First, the number of patients who were false LN-negative ($\#FN_m$) as a function of *m* was estimated:

$$\#\mathrm{FNm} = \frac{P(FNm)*\#TPm}{1 - P(FNm)}$$

where $\#TP_m$ indicated the number of patients identified as node-positive (true positive) when m nodes were examined and $P(FN_m)$ indicated the probability of missing nodal disease when m nodes were examined. Second, the adjusted prevalence was obtained by summing over all m:

$$\mathrm{Prev} = \frac{\sum_m(\#TPm + \#FNm)}{\sum_m(\#TPm + \#TNm + \#FNm)}$$

where $\#TN_m$ indicated the number of patients with true-negative LN evaluation.

Nodal staging score. Adequate staging was assessed by calculating NSS, the probability that a pathologically node-negative patient was correctly staged as node-negative:

$$\mathrm{NSS} = \frac{1 - \mathrm{Prev}}{1 - \mathrm{Prev} + [\mathrm{Prev}*P(FNm)]}$$

Break points in the NSS curves were further estimated using the piecewise linear regression model.

Prediction model validation

Since the model developed herein did not use survival data, we were provided a natural way to internally validate our findings. In addition, external validation using the VC was also performed.

Results

Patient characteristics

A total of 10,182 patients from the SEER database (DC) and 585 patients from the FUSCC database (VC) met the inclusion criteria (Table 1). The distributions of the examined LN count were similar for the two cohorts (Supplementary Fig. 2). The median numbers of examined LNs were 14 (interquartile range, 9 to 20) in the DC and 15 (interquartile range, 10 to 21) in the VC. In both cohorts, the percentage of patients with node-positive disease increased from the T1 stage to the T3 stage ($P < 0.001$ for DC and $P = 0.041$ for VC; Supplementary Figs. 3a–b). Among patients with node-positive disease, a similar intrinsic association between the T and N classifications was observed, with the percentage of individuals with N2 disease increased with advancing T stage ($P < 0.001$ for DC and $P = 0.042$ for VC; Supplementary Figs. 3c–d).

Number of examined LNs and stage migration

The proportion of patients with positive LNs increased with an increasing number of examined LNs. In patients with node-positive disease, the proportion of N2 disease also increased as the number of examined LNs increased (Fig. 1). After adjusting for potential confounders, the regression model revealed a significant proportional increase in N stage (from N0 to N1 and N2) with an increasing number of examined LNs (DC: odds ratio [OR], 1.047; 95% confidence interval [CI], 1.042 to 1.053; $P < 0.001$; VC: OR, 1.035; 95% CI, 1.015 to 1.056; $P < 0.001$). Within the node-positive category, a similar trend of N stage (from N1 to N2) was observed with the

Table 1
Baseline patient characteristics in the development and validation cohorts.

Variables	Development Cohort				Validation Cohort			
	All Patients (n = 10182)	Node-Negative (n = 3582)	Node-Positive (n = 6600)	P†	All Patients (n = 585)	Node-Negative (n = 281)	Node-Positive (n = 304)	P†
Age (years)				<0.001				0.038
<65	4549 (44.7)	1515 (42.3)	3034 (46.0)		344 (58.8)	149 (53.0)	177 (58.2)	
≥65	5633 (55.3)	2067 (57.7)	3566 (54.0)		241 (41.2)	132 (47.0)	127 (41.8)	
Sex				0.724				0.551
Male	5155 (50.6)	1805 (50.4)	3350 (50.8)		334 (57.1)	164 (58.4)	170 (55.9)	
Female	5027 (49.4)	1777 (49.6)	3250 (49.2)		251 (42.9)	117 (41.6)	134 (44.1)	
Tumor location				<0.001				0.039
Head	7783 (76.4)	2500 (69.8)	5283 (80.1)		331 (56.6)	139 (49.5)	176 (57.9)	
Body and tail	1488 (14.6)	726 (20.3)	762 (11.5)		248 (42.4)	137 (48.8)	127 (41.8)	
Other/unspecified	911 (9.0)	355 (9.9)	556 (8.4)		6 (1.0)	5 (1.7)	1 (0.3)	
Operation				<0.001				0.021
Pancreatoduodenectomy	7629 (74.9)	2542 (71.0)	5087 (77.1)		267 (45.7)	123 (43.8)	144 (47.3)	
Distal pancreatectomy	1152 (11.3)	543 (15.2)	609 (9.2)		234 (40.0)	124 (44.1)	110 (36.2)	
Total pancreatectomy	1279 (12.6)	435 (12.1)	844 (12.8)		71 (12.1)	25 (8.9)	46 (15.2)	
Other/unknown	122 (1.2)	62 (1.7)	60 (0.9)		13 (2.2)	9 (3.2)	4 (1.3)	
Histology				<0.001				NA
Ductal adenocarcinoma	9603 (94.3)	3299 (92.1)	6304 (95.5)		585 (100.0)	281 (100.0)	304 (100.0)	
Other variants	579 (5.7)	283 (7.9)	296 (4.5)		0 (0.0)	0 (0.0)	0 (0.0)	
Grade				<0.001				0.029
Well	971 (9.5)	447 (12.5)	524 (7.9)		67 (11.5)	28 (10.0)	39 (12.8)	
Moderate	4898 (48.1)	1716 (47.9)	3182 (48.2)		308 (52.6)	164 (58.4)	144 (47.4)	
Poor	3542 (34.8)	1010 (28.2)	2532 (38.4)		210 (35.9)	89 (31.6)	121 (39.8)	
Undifferentiated	112 (1.1)	50 (1.4)	62 (0.9)		0 (0.0)	0 (0.0)	0 (0.0)	
Unknown	659 (6.5)	359 (10.0)	300 (4.6)		0 (0.0)	0 (0.0)	0 (0.0)	
T stage				<0.001				0.041
T1	1767 (17.4)	877 (24.5)	890 (13.5)		113 (19.3)	66 (23.5)	47 (15.5)	
T2	5960 (58.5)	1957 (54.6)	4003 (60.6)		332 (56.8)	154 (54.8)	178 (58.5)	
T3	2455 (24.1)	748 (20.9)	1707 (25.9)		140 (23.9)	61 (21.7)	79 (26.0)	
ELN count*	14 (9–20)	12 (6–18)	15 (10–22)	<0.001‡	15 (10–21)	15 (9–19)	17 (11–22)	0.002‡
PLN count*	1 (0–3)	0 (0–0)	3 (1–5)	<0.001‡	1 (0–3)	0 (0–0)	3 (2–5)	<0.001‡

Values in parentheses are percentages unless indicated otherwise; *values are expressed as median (i.q.r.). †Based on a χ^2 test, with the exception of values marked with ‡, which were obtained using the Mann-Whitney *U* test.
ELN, examined lymph node; PLN, positive lymph node; NA, not applicable.

increase of the examined LNs count (DC: OR, 1.057; 95% CI, 1.052 to 1.064; $P < 0.001$; VC: OR, 1.054; 95% CI, 1.027 to 1.083; $P < 0.001$). In addition, a greater number of examined LNs was associated with a greater number of positive LNs ($P < 0.001$ for both cohorts), particularly in patients with node-positive disease ($P < 0.001$ for both cohorts; Supplementary Fig. 4).

Number of examined LNs and overall survival

After adjusting for covariables, a greater number of examined LNs was positively correlated with better OS in multivariable analyses (DC: HR, 0.982; 95% CI, 0.979 to 0.985; $P < 0.001$; VC: HR, 0.979; 95% CI, 0.967 to 0.990; $P < 0.001$). Given the nonlinear relationship between mortality and the number of examined LNs, a LOWESS smooth curve was fitted for the adjusted HRs, and an estimated break point at approximately 20 LNs (DC: 19 LNs; VC: 21 LNs) was obtained using the piecewise regression model (Fig. 2). However, there was a trend that the risk of death continued to decrease beyond the break point, albeit slowly (DC: HR, 0.992; 95% CI, 0.986 to 0.997; $P = 0.006$; VC: HR, 0.989; 95% CI, 0.979 to 0.999; $P = 0.013$).

Number of examined LNs and nodal staging scores

The DC derived from the SEER database was used to generate the NSS model. The β-binomial parameters α and β were estimated to be 2.03 (95% CI, 1.93 to 2.14) and 6.68 (95% CI, 6.28 to 7.21), respectively. The probability of missing nodal disease decreased as the number of examined LNs increased (Fig. 3a); this probability was 77%, 17%, 10%, and 5% for one, 10, 15, and 25 examined LNs, respectively. Approximately 12.4% of pN0 patients were estimated to have undetected nodal disease. The apparent prevalence of nodal

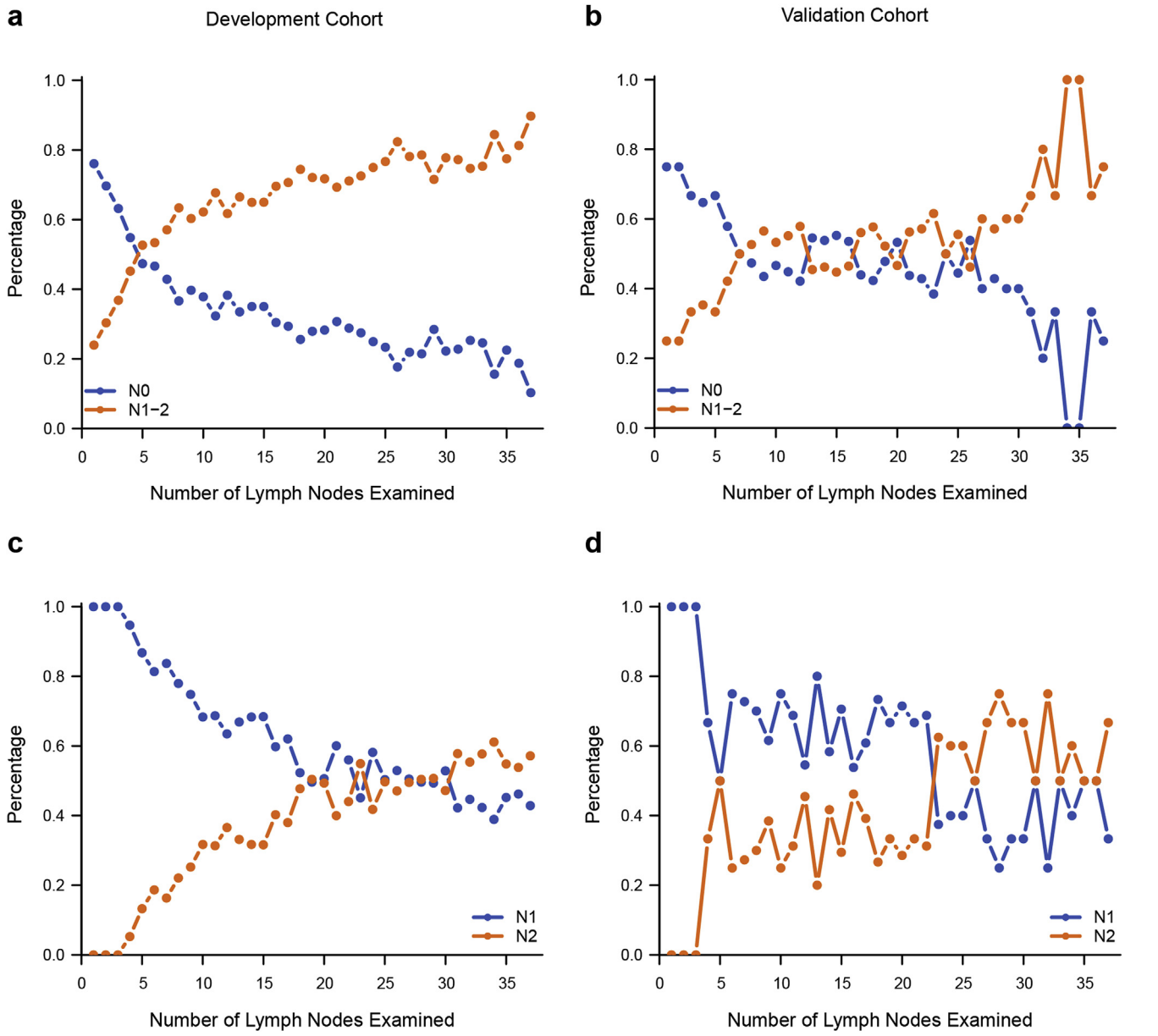

Fig. 1. Stage migration with an increasing number of examined lymph nodes in pancreatic cancer. Distributions of percentages of node-negative versus node-positive patients (a: development cohort; b: validation cohort) and N1 versus N2 patients (c: development cohort; d: validation cohort) were plotted with the number of examined lymph nodes on the horizontal axis.

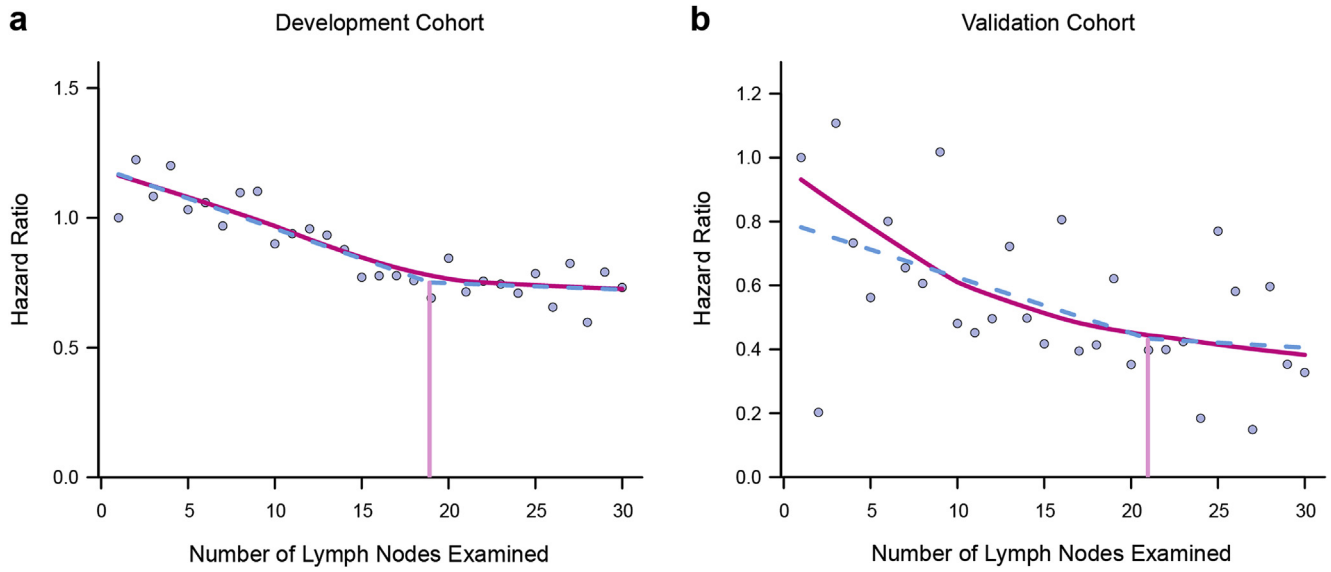

Fig. 2. Adjusted hazard ratios with an increasing number of examined lymph nodes in pancreatic cancer. (a) Development cohort; (b) Validation cohort. Light blue dots represent the Cox adjusted hazard ratios corresponding to the examined lymph node counts. Solid magenta lines represent the LOWESS curves for the Cox adjusted hazard ratios versus the number of lymph nodes examined, with a bandwidth of 2/3. Dashed blue lines represent fitted broken lines determined using the piecewise linear regression model. Vertical pink lines represent the break points at 19 (a) and 21 (b) examined nodes determined via piecewise linear regression analysis.

disease as well as the corrected prevalence was distinct for each T stage (Supplementary Table 1). By combining the probability of missing nodal disease and the corrected estimates of the true LN-positive prevalence, we obtained the NSS (Supplementary Table 2). The scores differed for different T stages; however, for each T stage, scores increased continuously as the number of examined LNs increased, with plateaus at 16, 21, and 23 LNs for T1, T2, and T3 tumors, respectively (Fig. 3b). The nodal staging accuracy at the estimated break points were 87%, 80%, and 79% for T1, T2, and T3 tumors, respectively. Multivariable analysis of patients with node-negative disease validated that examining more LNs than the relevant estimated break point was a significant predictor of survival (DC: HR, 0.813; 95% CI, 0.721 to 0.917; $P < 0.001$; Fig. 4; VC: HR, 0.696; 95% CI, 0.503 to 0.962; $P = 0.028$; Supplementary Fig. 5).

Discussion

In our current study, the number of examined LNs was positively correlated with OS after adjusting for other covariables. Among node-negative patients, the survival benefits from the increase in the number of examined LNs may be attributed to stage migration, as there would be a chance that patients with few nodes examined would have been incorrectly deemed node-negative. By using the β-binomial distribution, we computed the probability of missing nodal disease and found that even when 15 nodes were examined (the current recommendation for adequate staging), more than 10% of node-positive patients would be incorrectly staged as negative. In addition, the proportion of patients with positive nodes increased with advancing T stage, which strongly indicated that LN

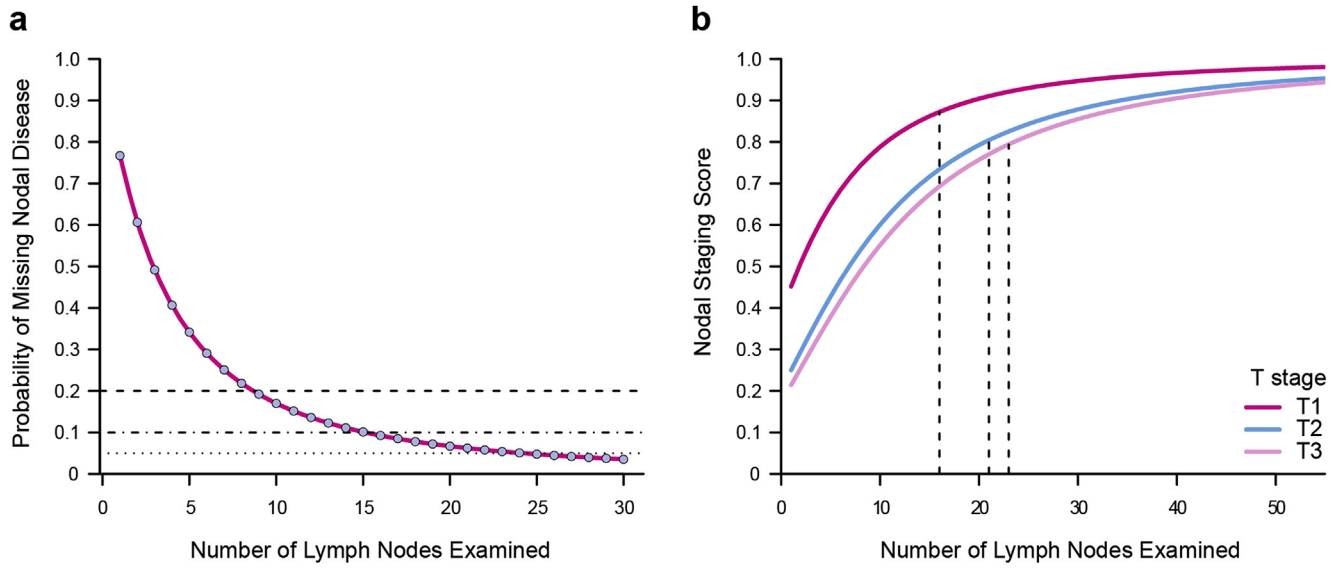

Fig. 3. Probability of missing nodal disease and nodal staging score as a function of the number of examined lymph nodes. (a) Probability of missing nodal disease; (b) Nodal staging score.

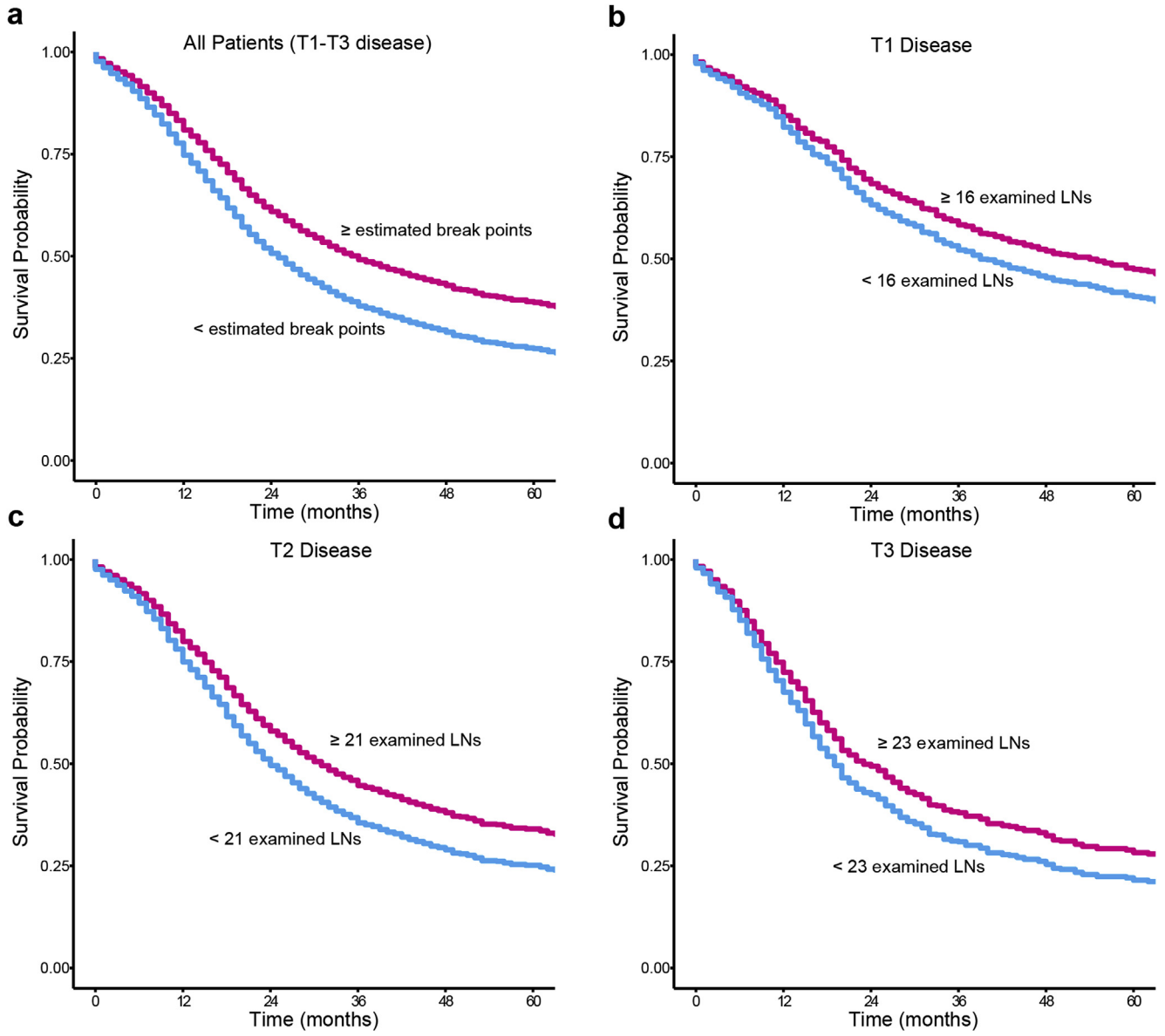

Fig. 4. Cox adjusted survival curves stratified by the estimated break points among patients with node-negative disease in the development cohort. (a) All stage T1-T3 patients; (b) Patients with stage T1 disease; (c) Patients with stage T2 disease; (d) Patients with stage T3 disease.

metastatic rate might be associated with T stage. Therefore, we subjected nodal staging to a mathematical model that incorporated the number of examined LNs and the T stage to define a score that captures the adequacy of node-negative classification (Fig. 5).

At present, precision medicine is on the cutting edge of cancer care, but accurate staging for pancreatic cancer still lacks an effective quality measure. The NSS model, which was first proposed in colon cancer and then validated in other solid tumors (including papillary thyroid cancer, bladder cancer and prostate cancer), is of particular importance in nodal staging [22,30–32]. Using this model, we found that as the number of examined LNs increased, nodal staging accuracy increased separately for each T stage. The proposed NSS can not only provide node-negative patients with an estimation of true nodal status but also predict the required number of LNs with expected accuracy based on preoperative clinical T stage as the 8th edition of the AJCC staging system has altered the definition of T stage (tumor size-based staging), which can be easily obtained from preoperative imaging. Therefore, the NSS can provide a more precise estimation of nodal staging accuracy than a one-size-fits-all approach, which conforms to the essence of precision medicine.

There remains a dispute regarding the optimal number of examined LNs after pancreatic surgery. Previous studies using single-institution or multicenter databases showed a wide range of cut-off values [6,11–15,33]. The drawbacks of these studies were the manual division of the examined LNs into groups and the search for a threshold that maximizes the survival differences among the groups. Based on the NSS model, we identified optimal cut-off points of the number of examined LNs corresponding to each T stage (T1: 16 LNs; T2: 21 LNs; T3: 23 LNs), which may be considered a quality indicator because this number is associated with improved survival owing to more accurate staging. This result is generally consistent with a recent population-based propensity score-adjusted study demonstrating that more examined LNs (≥20 LNs) improve the oncological outcome in patients with either node-negative or node-positive pancreatic cancer [34].

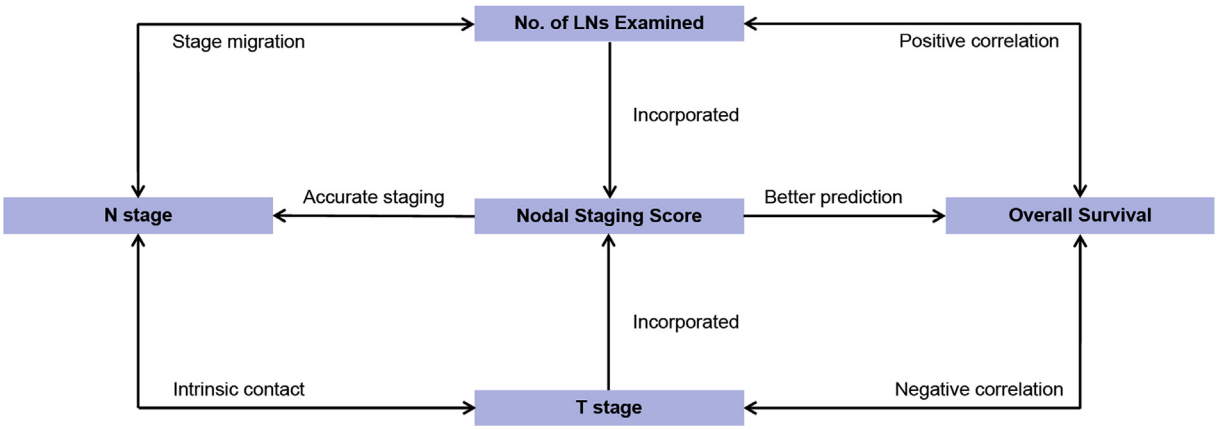

Fig. 5. Rationale for the proposed nodal staging score as a quality measure. LNs, lymph nodes.

A practical issue is whether assessment of the required number of LNs is achievable for the majority of surgical specimens. In one Italian study using standard lymphadenectomy defined by the International Study Group on Pancreatic Surgery (ISGPS), a mean number of 30.8 nodes was achieved [35]. Similarly, a large cohort of patients with resected pancreatic cancer (811 patients) from Heidelberg University Hospital showed that the median number of examined nodes was 24 with standard LN dissection [36]. In addition, a Japanese study revealed that a median number of 28 nodes can be retrieved with careful pathologic examination [37]. Indeed, our analysis is not intended to advocate for extended lymphadenectomy (which usually involves 33 to 40 LNs) for pancreatic cancer patients [38–40]. Because the number of examined LNs depends on not only the extent of the surgeon's lymphadenectomy but also the thoroughness of the pathologist's examination, a meticulous surgery and careful pathologic evaluation may improve the retrieval of LNs and therefore increase the adequacy of the LN yield [17].

Another key issue is why an increase in the number of examined LNs improves survival. The exact reason is unclear, but several potential hypotheses exist. First, certain patients with fewer examined LNs who were declared to have node-negative disease may actually have nodal disease, leading to reduced survival. Second, although adjuvant therapy is recommended for all patients with resected pancreatic cancer, only half of these patients received this treatment under real-world conditions [41]. It can be speculated that the LN status will affect the strength of recommendation for adjuvant therapy by the treating physicians and the acceptability of the patients. The examination of more LNs will result in a higher possibility of detecting positive nodes, leading to more adjuvant therapy and subsequently to improved survival. Finally, the number of examined LNs may be an indirect reflection of institutional expertise, as patients treated at high-volume centers are likely to have both a higher number of examined LNs and improved survival [42].

The current study has several limitations. First, the study is retrospective, and data regarding chemotherapeutic regimens and surgical margin status, which are established prognostic factors that influence outcomes, are not currently available from the SEER database. In addition, the SEER database does not provide the information regarding whether a patient received neoadjuvant therapy, which may affect the estimation of predictive probabilities because neoadjuvant therapy would significantly decrease the incidence of positive LNs [43]. A second limitation is that the SEER database lacks information about LN stations. As removing nodes from an area with a high likelihood of metastasis may be more valuable than removing nodes less likely to be involved, balancing the pros and cons of removing different LN stations is another problem that should be urgently addressed. Although the ISGPS has formulated a definition for standard lymphadenectomy [9], there were considerable differences in the rate of metastasis to the various LN stations in different studies [44]. In addition, one more thing to note is that we did not distinguish the types of specimens. Given that pancreaticoduodenectomy specimens account for three-fourths of all specimens and that the median numbers of examined LNs for different types of specimens in the DC were similar (14 for pancreaticoduodenectomy, 13 for distal pancreatectomy, and 15 for total pancreatectomy), we believe that our estimates of the optimal cut-off points are reliable. Finally, our model was established based on several necessary assumptions. However, since we did not observe a lack of model fit, the bias resulting from these assumptions would be minimal as was stated previously [22].

Conclusions

In summary, a greater number of examined LNs is associated with more accurate node staging and better OS in patients with resected pancreatic cancer. From a clinical perspective, the NSS can provide a more precise estimation of nodal staging accuracy than a one-size-fits-all approach and can effectively be used routinely in clinics as a tool to decide whether a pancreatic cancer patient declared to be node-negative has been adequately staged. Our results suggest that the optimal number of examined LNs for adequate staging of pancreatic cancer is related to the T stage. We recommend examination of at least 16, 21, and 23 LNs for T1, T2, and T3 tumors as a nodal staging quality measure in the treatment of pancreatic cancer. Although these findings might not have an immediate impact on treatment decisions, they have provided a useful tool to establish quality references for both surgery and pathological analysis.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.018.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. Ca - Cancer J Clin 2018;68(2018):7–30.
[2] Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol 2009;16:836–47.
[3] Takahashi H, Ohigashi H, Ishikawa O, Gotoh K, Yamada T, Nagata S, et al. Perineural invasion and lymph node involvement as indicators of surgical outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. Ann Surg 2012;255:95–102.
[4] Tarantino I, Warschkow R, Hackert T, Schmied BM, Büchler MW, Strobel O, et al. Staging of pancreatic cancer based on the number of positive lymph nodes. Br J Surg 2017;104:608–18.
[5] Strobel O, Hinz U, Gluth A, Hank T, Hackert T, Bergmann F, et al. Pancreatic adenocarcinoma number of positive nodes allows to distinguish several N categories. Ann Surg 2015;261:961–9.
[6] Huebner M, Kendrick M, Reid-Lombardo KM, Que F, Therneau T, Qin R, et al. Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. J Gastrointest Surg 2012;16:920–6.
[7] Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg 2011;254:311–9.
[8] Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:1028–61.
[9] Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. International study group on pancreatic surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the international study group on pancreatic surgery (ISGPS). Surgery 2014;156:591–600.
[10] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. ESMO guidelines committee. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v56–68.
[11] Valsangkar NP, Bush DM, Michaelson JS, Ferrone CR, Wargo JA, Lillemoe KD, et al. N0/N1, PNL, or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. J Gastrointest Surg 2013;17:257–66.
[12] Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, et al. Accuracy of staging node-negative pancreas cancer: a potential quality measure. Arch Surg 2007;142:767–74.
[13] Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol 2008;15:165–74.
[14] Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol 2006;13:1189–200.
[15] Hellan M, Sun CL, Artinyan A, Mojica-Manosa P, Bhatia S, Ellenhorn JD, et al. The impact of lymph node number on survival in patients with lymph node-negative pancreatic cancer. Pancreas 2008;37:19–24.
[16] Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, et al. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. Eur J Surg Oncol 2009;35:79–86.
[17] Adsay NV, Basturk O, Altinel D, Khaani F, Coban I, Weaver DW, et al. The number of lymph nodes identified in a simple pancreatoduodenectomy specimen: comparison of conventional vs orange-peeling approach in pathologic assessment. Mod Pathol 2009;22:107–12.
[18] Amin MB, Edge S, Greene F, Byrd D, Brookland R, Washington M, et al. American Joint committee on cancer staging manual. eighth ed. New York: Springer; 2017.
[19] Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint commission on cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg 2017;265:185–91.
[20] Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint commission on cancer (AJCC) 8th edition staging system for patients with pancreatic adenocarcinoma: a surveillance, Epidemiology and End results (SEER) analysis. Ann Surg Oncol 2017;24:2023–30.
[21] Muralidhar V, Nipp R, Ryan DP, Ferrone CR, Hong TS, Fernandez-del Casti C, et al. Association between very small tumor size and decreased overall survival in node-positive pancreatic cancer. Int J Radiat Oncol Biol Phys 2017;99(2s):E173.
[22] Gönen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. J Clin Oncol 2009;27:6166–71.
[23] Carey V, Zeger SL, Diggle P. Modelling multivariate binary data with alternating logistic regressions. Biometrika 1993;80:517–26.
[24] Cox DR. Regression models and life tables. J Roy Stat Soc B 1972;34:187–220.
[25] Yamashita T, Yamashita K, Kamimura R. A stepwise AIC method for variable selection in linear regression. Commun Stat Theor Methods 2007;36:2395–403.
[26] Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med 1995;14:1707–23.
[27] Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
[28] Cleveland WS. LOWESS: a program for smoothing scatterplots by robust locally weighted regression. Am Statistician 1981;35:54.
[29] Muggeo VM. Estimating regression models with unknown break-points. Stat Med 2003;22:3055–71.
[30] Robinson TJ, Thomas S, Dinan MA, Roman S, Sosa JA, Hyslop T. How many lymph nodes are enough? Assessing the adequacy of lymph node yield for papillary thyroid cancer. J Clin Oncol 2016;34:3434–9.
[31] Kluth LA, Abdollah F, Xylinas E, Rieken M, Fajkovic H, Sun M, et al. Pathologic nodal staging scores in patients treated with radical prostatectomy: a postoperative decision tool. Eur Urol 2014;66:439–46.
[32] Shariat SF, Ehdaie B, Rink M, Cha EK, Svatek RS, Chromecki TF, et al. Clinical nodal staging scores for bladder cancer: a proposal for preoperative risk assessment. Eur Urol 2012;61:237–42.
[33] Vuarnesson H, Lupinacci RM, Semoun O, Svrcek M, Julié C, Balladur P, et al. Number of examined lymph nodes and nodal status assessment in pancreaticoduodenectomy for pancreatic adenocarcinoma. Eur J Surg Oncol 2013;39:1116–21.
[34] Warschkow R, Widmann B, Beutner U, Marti L, Steffen T, Schiesser M, et al. The more the better-lower rate of stage migration and better survival in patients with retrieval of 20 or more regional lymph nodes in pancreatic cancer: a population-based propensity score matched and trend SEER analysis. Pancreas 2017;46:648–57.
[35] Malleo G, Maggino L, Capelli P, Gulino F, Segattini S, Scarpa A, et al. Reappraisal of nodal staging and study of lymph node station involvement in pancreaticoduodenectomy with the Standard International Study Group of Pancreatic Surgery definition of lymphadenectomy for cancer. J Am Coll Surg 2015;221:367–79.
[36] Strobel O, Hinz U, Gluth A, Hank T, Hackert T, Bergmann F, et al. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. Ann Surg 2015;261:961–9.
[37] Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakashima A, et al. Number of metastatic lymph nodes, but not lymph node ratio, is an independent prognostic factor after resection of pancreatic carcinoma. J Am Coll Surg 2010;211:196–204.
[38] Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicentre randomized controlled trial. J Hepatobiliary Pancreat Sci 2012;19:230–41.
[39] Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, DahI TR, et al. Pancreas Cancer Working Group. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–28.
[40] Jang JY, Kang MJ, Heo JS, Choi DW, Park SJ, Han SS, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg 2014;259:656–64.
[41] Nayar P, Chandak A, Gupta N, Yu F, Qiu F, Ganti AK, et al. Postoperative mortality following multi-modality therapy for pancreatic cancer: analysis of the SEER-Medicare data. J Surg Oncol 2017;115:158–63.
[42] Lidsky ME, Sun Z, Nussbaum DP, Adam MA, Speicher PJ, Blazer 3rd DG. Going the extra mile: improved survival for pancreatic cancer patients traveling to high-volume centres. Ann Surg 2017;266:333–8.
[43] Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261:12–7.
[44] Pedrazzoli S. Extent of lymphadenectomy to associate with pancreaticoduodenectomy in patients with pancreatic head cancer for better tumor staging. Cancer Treat Rev 2015;41:577–87.