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*Original Article*

# Exploration of the lymphadenectomy strategy for elderly pancreatic ductal adenocarcinoma patients undergoing curative-intent resection

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**Abstract:** There has been a long-standing controversy regarding the number of lymph nodes (LNs) examined intraoperatively for accurate lymphatic staging and significantly better survival of patients with pancreatic ductal adenocarcinoma (PDAC), and no consensus has been reached for the elderly with the age of over 75 years. Given these, the present study aims to investigate the appropriate number of examined lymph nodes (ELNs) for elderly patients mentioned above. In this study, population-based data on 20,125 patients in 2000 to 2019 from the Surveillance, Epidemiology, and End Results database were reviewed retrospectively. The eighth edition staging system of the American Joint Committee on Cancer (AJCC) was applied. Propensity score matching (PSM) was performed to reduce the effects of multiple biases. By using binomial probability law and maximally selected rank statistics, the minimum number of ELN (MNELN) for accurate nodal involvement assessment and optimal ELN number for significantly better survival were calculated, respectively. In addition, Kaplan-Meier curves and Cox proportional hazard regression models were constructed for further survival analysis. As a result, 6623 patients were enrolled in total in the study. Elderly patients had fewer lymph node metastases and a smaller lymph node ratio (LNR) (all $P<0.05$). However, poorer overall survival (OS) and cancer-specific survival (CSS) of elderly patients were observed in each pN stage (all $P<0.05$), except for CSS in N2. The proportions of N2 and N0 stages increased and decreased respectively with increasing number of ELN significantly. MNELN for accurate nodal assessment was 19 according to binomial probability law, and the optimal ELN number for significantly better survival was 17. Additionally, the number of ELN (<17 or ≥17) was also considered a strong prognostic predictor for elderly PDAC patients (≥75 years) in the Cox proportional hazard regression model (Overall survival: hazard ratio [HR]=0.74, 95% confidence interval [CI]: 0.65-0.83, $P<0.001$; Cancer-specific survival: HR=0.75, 95% CI: 0.66-0.85, $P<0.001$). In conclusion, extended lymphadenectomy is suitable for elderly PDAC patients undergoing curative-intent surgery owing to an accurate assessment of nodal status and improved long-term prognosis. However, a random, prospective clinical trial is warranted before the recommendation of extended lymphadenectomy for the elderly.

**Keywords:** Pancreatic ductal adenocarcinoma, examined lymph node, extended lymphadenectomy, elderly patients, long-term survival, accurate staging

## Introduction

Pancreatic cancer (PAC) has caused a great disease burden in the world and is on track to become the leading cause of cancer-related mortality [1]. The annual number of diagnosed PAC patients worldwide surged exponentially in recent decades from 196,000 in 1990 to 441,000 in 2017 [2]. Among the various subtypes of PAC, pancreatic ductal adenocarcinoma (PDAC) accounts for the majority. The long-term prognosis of PDAC patients is abysmal with an overall 5-year survival rate of 8% [3]. To date, surgical resection is still the only potentially curative management for it [4]. Lymph node (LN) status has proved to be one of the strongest prognostic predictors for PDAC patients [5]. An appropriate number of examined lymph node (ELN) is of great importance to achieve an accurate assessment of nodal status and improves long-term survival [6]. A threshold of 11 to 22 ELNs is recommended for

PDAC patients according to studies from multiple countries and regions [7-11]. From the guidelines, American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) recommend the resection of ≥10 LNs to evaluate nodal involvement status [12]. A minimum of 15 ELNs is recommended for accurate staging assessment according to the European Society for Medical Oncology (ESMO) and the International Study Group on Pancreatic Surgery (ISGPS) [6, 13]. However, the National Comprehensive Cancer Network (NCCN) has not given a specific indication of the exact number of ELNs [5].

Tumor stage and grade are associated with the likelihood of lymph node metastasis in PDAC [14, 15]. Nevertheless, relying solely on staging and grading to forecast lymph node metastasis is not adequate. Including other crucial prognostic factors, such as age, could enhance patient risk stratification, allowing for the selection of more optimal, multi-modal treatments for high-risk individuals and ultimately improving their prognosis. Considering the relationship between LN metastasis and the age of patients, a variety of studies achieved a relatively consistent conclusion that there were significantly fewer positive-LNs detected in elderly patients with various cancer types, such as colon cancer [16-18], bladder urothelial carcinoma [19], melanoma Patients [20] and so on. However, there was no investigation published to determine such association for PDAC patients. Such effect of age on positive-LNs in multiple cancer types may be owing to various biological heterogeneity between the young and the old. As individuals age, their bodies undergo numerous changes, including alterations in their lymph nodes [21]. The aging process can lead to a decline in the cortex and medulla of the lymph nodes, as well as an increase in the degeneration of lymph nodes, resulting in the development of inactive nodes without lymph node tissue. These changes ultimately lead to reduced lymph flow and retraction of the lymph nodes [22, 23].

Given the aforementioned considerations, the present population-based study was designed and conducted primarily to determine the minimum number of ELN (MNELN) for accurate nodal involvement evaluation and optimal ELN count for significantly better survival, while investigating the relationship between positive-nodes number and age of PDAC patients.

## Methods

### *Patients and study design*

The clinicopathologic and demographic data of patients with pancreatic cancer (PAC) was investigated from the Surveillance, Epidemiology, and End Results (SEER) database, which is an authoritative program supported by National Cancer Institute (NCI). "SEER Research Plus Data. 17 Registries. Nov2021 Sub (2000-2019)" was selected and individual-level data of patients with one primary malignant carcinoma of the pancreas were consecutively collected. All these patients were histologically diagnosed with complete information of age, sex, race, year of diagnosis, primary site, therapy record, and follow-up record. The inclusion criteria were as follows: (i) Patients with pancreatic ductal adenocarcinoma; (ii) Patients undergoing curative surgery; (iii) Patients diagnosed pathologically. Then, exclusion criteria were listed hereafter: (i) Patients with any neoadjuvant therapy before surgery; (ii) Patients with distant metastasis; (iii) Patients with incomplete information, such as examined lymph node, positive lymph node, tumor size, and pTNM stage. After screening according to the criteria mentioned above, 6623 patients were included in the study. **Figure 1** was the flow chart showing the patient selection process. All the data was collected under the SEER data with the agreement (ID: 16402-Nov2021).

### *Covariates and data reprocessing*

There are four main parts about covariates in this study: (a) Clinical characteristics data, such as gender, age, race and so on; (b) Pathologic characteristics data, such as tumor size, location (rearrangement into pancreas head and body/tail), grade (differentiation), pTNM stage (all the staging data were organized according to American Joint Committee on Cancer staging system, AJCC, 8th edition), examined lymph node (ELN), regional node positive (RNP), lymph node ration (LNR, the ratio of RNP divided by ELN); (c) Treatment record, such as radiation, chemotherapy, systemic therapy and so on; (d) Survival information, such as overall survival (OS) and cancer-specific survival (CSS).

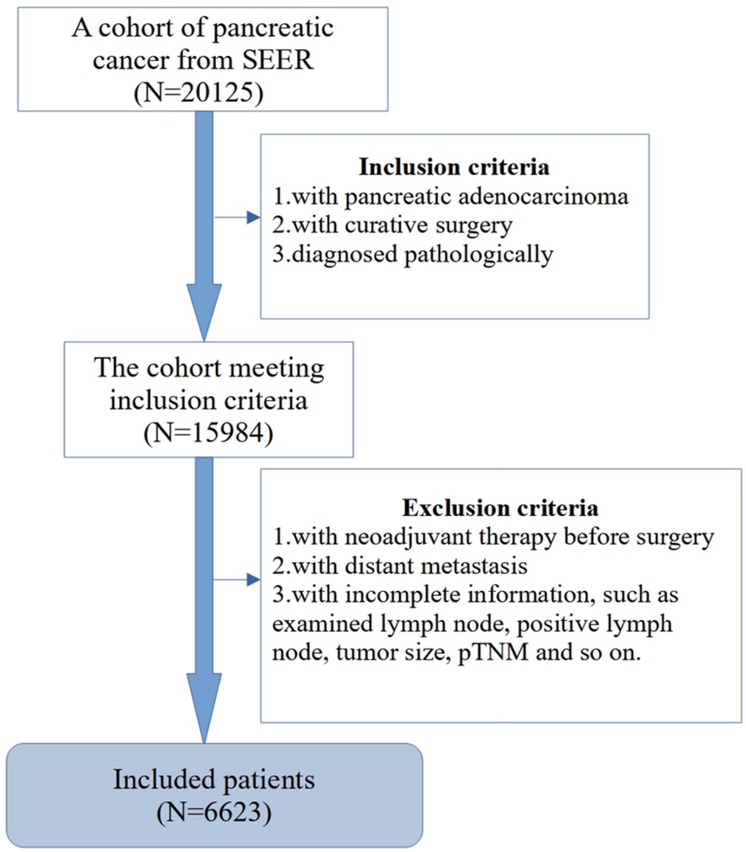


**Figure 1.** Flow chart for the patient selection process.

*Statistical analysis*

All the two-sided statistical tests in this study were conducted using GraphPad Prism for Windows (version 8.0.1) and R software for Windows (version 4.2.0). Positive lymph nodes number and LNR of various age groups were analyzed with Brown-Forsythe and Welch ANOVA tests. Symbol "###" in figures represented a reference group compared by other groups. To identify the different quantitative and categorical variables in the baseline characteristics of the elderly and non-elderly PDAC patients (with a cut-off of 75 years), one-way analysis of variance (one-way ANOVA) and chi-square test were performed, respectively. We defined statistical significance as $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, and $^{****}P<0.0001$.

Propensity score matching (PSM) was conducted using R software to adjust the imbalance of sex, race, tumor size, grade, chemotherapy, radiation, systemic therapy, tumor location, and pT staging between <75 and ≥75 years patient groups (ratio =1, caliper =0.02).

In order to determine the number of ELN for accurate evaluation of nodal involvement, we adopted the method of binomial probability law, which has been demonstrated previously [9]. We built the binomial probabilistic model according to the formula: $P=1 - (1 - p)^n$, where $p$ was global LNR (sum of all positive nodes/sum of all examined nodes), n was threshold number of ELNs to detect one or exceeding 1 positive nodes, $P$ was the probability for harvesting one or more positive nodes and we defined $P$ as 95% in this formula.

Maximally selected rank statistics was performed to find optimal number of ELN for significantly better survival. This method is a computer algorithm, which provides the classification of observations into two groups with the maximum significance by a continuous or ordinal predictor variable [24]. Then, Kaplan-Meier survival curves of groups were performed with log-rank test and depicted using R software packages "survival", and "survminer" (R version 4.2.0). In the multivariate Cox proportional hazard regression analysis, all factors in univariate model with $P<0.1$ were included to determine the independent factors of prognosis, and the predictive significance of calculated ELN count was verified by the way.

## Result

*Epidemiological trends by age group*

A total of 6623 PDAC patients met the inclusion criteria and were surveyed in the study. The baseline characteristics containing main covariates of these patients were summarized in **Table 1**. We counted the number of patients with PDAC and those with positive lymph nodes

**Table 1.** The baseline characteristics of overall patients with PDAC

| Characteristics | Overall (N=6623) |
|---|---|
| Sex, N (%) | |
| Female | 3246 (49.0%) |
| Male | 3377 (51.0%) |
| Age, N (%) | |
| <45 | 187 (2.8%) |
| ≥75 | 1562 (23.6%) |
| 45-55 | 756 (11.4%) |
| 55-65 | 1926 (29.1%) |
| 65-75 | 2192 (33.1%) |
| Race, N (%) | |
| American Indian/Alaska Native | 33 (0.5%) |
| Asian or Pacific Islander | 568 (8.6%) |
| Black | 652 (9.8%) |
| White | 5370 (81.1%) |
| Location, N (%) | |
| Body/Tail of pancreas | 1047 (15.8%) |
| Head of the pancreas | 5576 (84.2%) |
| Grade, N (%) | |
| Moderately differentiated; Grade II | 3347 (50.5%) |
| Poorly differentiated; Grade III | 2511 (37.9%) |
| Undifferentiated; anaplastic; Grade IV | 68 (1.0%) |
| Well-differentiated; Grade I | 697 (10.5%) |
| Size | |
| Mean (SD) | 34.5 (21.2) |
| Median [Min, Max] | 31.0 [1.00, 700] |
| Ajcc 8th edition T, N (%) | |
| T1 | 1112 (16.8%) |
| T2 | 3892 (58.8%) |
| T3 | 1511 (22.8%) |
| T4 | 108 (1.6%) |
| Ajcc 8th edition N, N (%) | |
| N0 | 2122 (32.0%) |
| N1 | 2758 (41.6%) |
| N2 | 1743 (26.3%) |
| Radiation, N (%) | |
| No radiation | 4506 (68.0%) |
| Radiation after surgery | 2117 (32.0%) |
| Chemotherapy, N (%) | |
| No/Unknown | 2163 (32.7%) |
| Yes | 4460 (67.3%) |
| Systemic therapy, N (%) | |
| No systemic therapy | 2158 (32.6%) |
| Systemic therapy after surgery | 4465 (67.4%) |
| ELN | |
| Mean (SD) | 16.4 (9.54) |
| Median [Min, Max] | 15.0 [1.00, 82.0] |

in multiple age groups (<45, 45-54, 55-64, 65-74, ≥75) from 2006 to 2015. The results of the line graphs were depicted and shown in **Figure 2**. It demonstrated that there was an upward trend in the number of PDAC patients ≥55 years old and those with positive lymph nodes, while there was minor trend of change in patients <55 years old.

*Lymph node involvement and stage migration*

The number of positive lymph nodes (pLNs) and LNR in various aforementioned age groups were compared and shown in **Figure 3**. Compared with patients ≥75 years old, pLNs decreased with increasing years of age, except for <45 group ($P<0.001$). In addition, the value of LNR showed a similar tendency, except for <45 and 65-74 groups ($P<0.05$). Considering the relatively small number of patients <45 years old and the potential for interference with trend judgments, we divided patients into <75 and ≥75 groups. As is shown in **Figure 4A**, **4B**, the number of pLNs and LNR of patients ≥75 years old was significantly lower ($P<0.01$). Furthermore, ≥75 years patients were divided into four groups according to the number of ELNs: ELN<10, 10≤ELN<20, 20≤ELN<30, ELN≥30. The proportion of N2 increased dramatically with increasing number of ELNs (9.1%, 26.3%, 37.6%, and 45.3%, $P<0.001$), while the proportion of N0 showed a considerably reverse trend (47.5%, 29.9%, 24.6%, and 18.8%, $P<0.001$) (**Figure 4C**). Accordingly, the results can be drawn that the elderly patients needed more ELNs for accurate evaluation of lymph involvement and reduced stage migration.

*Baseline characteristics*

Propensity score matching was performed to improve component comparability across variables and reduce

| | |
|---|---|
| RNP | |
| Mean (SD) | 2.58 (3.29) |
| Median [Min, Max] | 2.00 [0, 32.0] |
| LNR | |
| Mean (SD) | 0.169 (0.198) |
| Median [Min, Max] | 0.105 [0, 1.00] |
| Survival | |
| Mean (SD) | 30.4 (31.1) |
| Median [Min, Max] | 19.0 [0, 167] |

multiple biases between patients in <75 and ≥75 years groups, and the distribution of propensity scores was shown in **Figure 5**. The propensity score refers to the conditional probability of dividing any individual into ≥75 years group under a given set of variables. After calculation, each individual can obtain a propensity score, and the covariates of individuals with similar propensity scores among <75 and ≥75 years groups are balanced. The baseline characteristics data of the two groups before and after PSM operation were sorted, as shown in **Table 2**. Before PSM, 5061 cases of age <75 (non-elderly group) and 1562 cases of age ≥75 (elderly group) were identified. Compared with the non-elderly group, the elderly group tended to have more female patients (56.9% vs. 46.6%), a higher proportion of white (85% vs. 79.9%), fewer patients with PDAC located at the head of the pancreas (81.8% vs. 84.9%). Considering the staging of AJCC 8th edition, the proportion of elderly patients with stage N0 was higher than that in the non-elderly group (35.7% vs. 30.9%). However, the survival of the elderly group was poorer than that of the patients <75 years old (mean [Standard Deviation, SD], 25.7 [27.7] months vs. 31.8 [32.0] months). In terms of neoadjuvant therapy, the proportion of patients receiving radiotherapy, chemotherapy and systemic treatment in the non-elderly group was more than that in the elderly group (35.9% vs. 19.1%, 72.6% vs. 50.3%, and 72.7% vs. 50.4%). There was no statistical significance of grade, size, and pT staging between the two groups. After 1:1 PSM, 1551 well-matched patients in the elderly group and the non-elderly group were enrolled. As expected, the baseline characteristics between the two groups were no longer statistically significant, implying that the imbalance between the two groups was eliminated.

*Survival analysis*

The Kaplan-Meier survival analyses of PSM-matched PDAC patients (≥75 years old) were performed and depicted in multiple conditions. For both OS and CSS, the survival of the elderly patients was poorer in the more-advanced N stage ($P$<0.0001) (**Figure 6A**, **6B**). The analysis showed that even in the same lymphatic staging (pN0, pN1 and pN2), the survival of the elderly was also poorer (all $P$<0.05), except for CSS in N2 (**Figure 6C-H**). Combined with the fewer pLNs, smaller LNR and the stage migration of elderly patients mentioned above, these significant differences in survival once again suggested that the current ELN number for elderly patients was too limited to obtain intrinsic staging of lymph nodes.

*Determination of ELN number*

Among the 1551 elderly patients (≥75 years old) after PSM matching, the global LNR was 0.146. According to the formula of binomial probability law: $P=1 - (1 - p)^n$, the ELN threshold (n) for detecting at least one positive lymph node with 95% confidence was 19. Therefore, we identified the minimum number of ELN (MNELN) for accurate lymphatic staging as 19. Meanwhile, MNELNs of subgroups divided by tumor location were calculated in the same way. As a result, MNELNs for accurate nodal evaluation of pancreatic head and body/tail adenocarcinoma were 25 and 18, respectively.

Furthermore, through the ranking statistics of the maximum selection of 1551 matched elderly patients, the cutting points of OS and CSS were defined as 16, and the statistics were 4.05 and 3.54, respectively (**Figure 7A**, **7C**). It indicated a statistically significant difference in survival between the ELN≥17 and ELN≤16 patient groups ($P$<0.001), hence the optimal ELN number was 17 in this case. Then, Kaplan-Meier survival curves of patients grouped by calculated ELN for OS and CSS were depicted (**Figure 7B**, **7D**). In addition, the optimal ELN numbers of the pancreatic head and body/tail adenocarcinoma subgroups were determined and summarized in **Tables 3**, **4**.

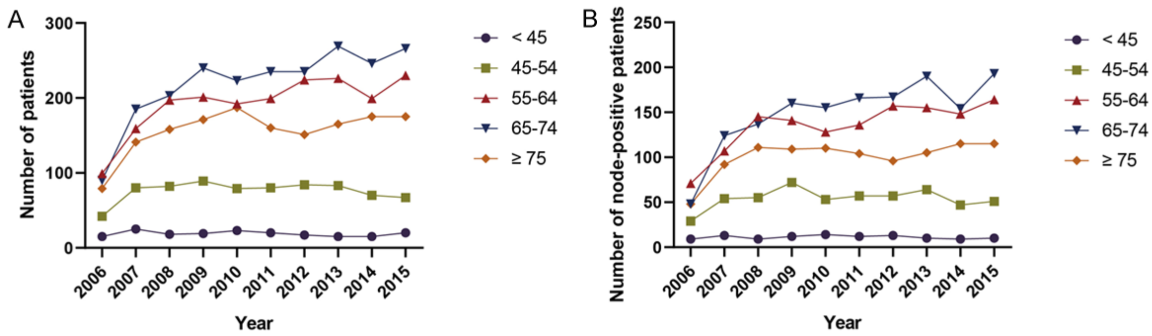


Figure 2. Epidemiological trends for PDAC patients in various age groups. A. Trends for the number of patients. B. Trends for the number of patients with nodal metastasis.

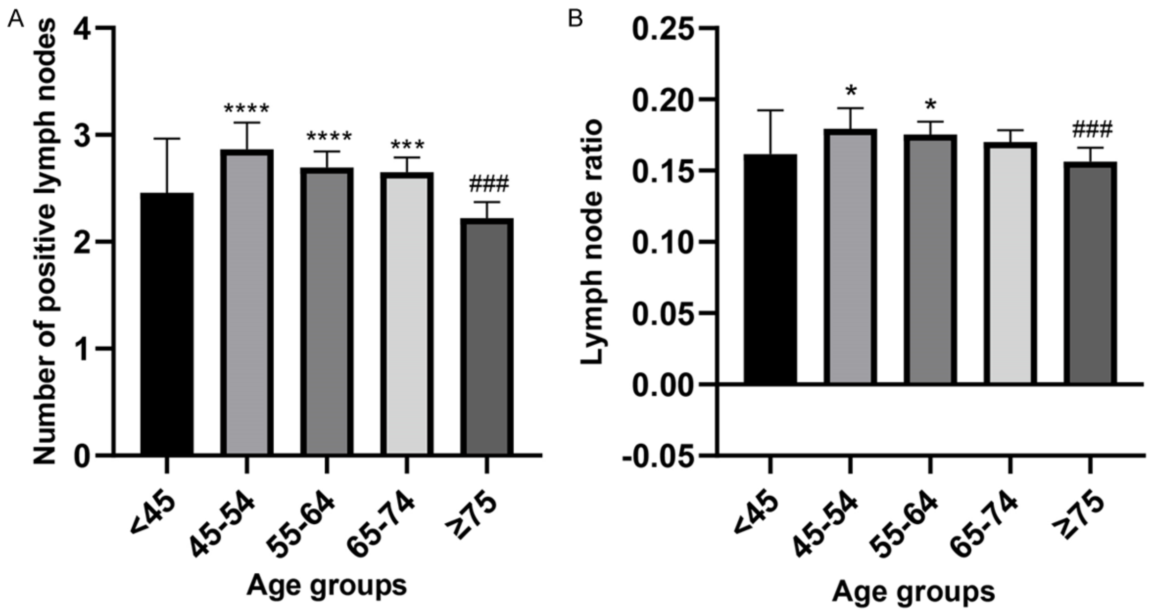


Figure 3. The status of nodal involvement for PDAC patients in different age groups. A. Number of positive nodes in various age groups. B. Lymph node ratio in various age groups.

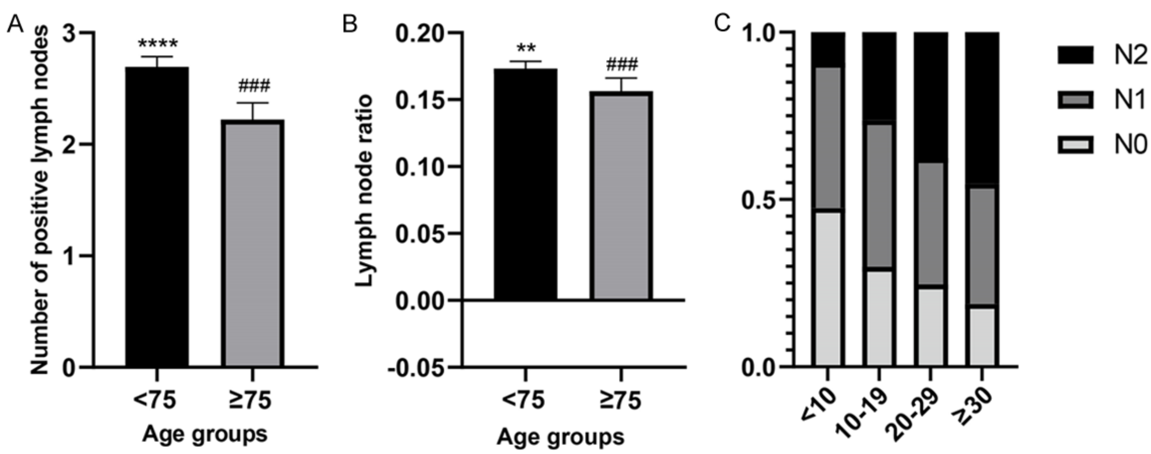


Figure 4. The status of nodal involvement for PDAC patients. A. Number of positive nodes in patients with ages of <75 and ≥75 years. B. Lymph node ratio of patients in the two age groups. C. Proportions of pN0, pN1, pN2 for patients in different ELN groups.

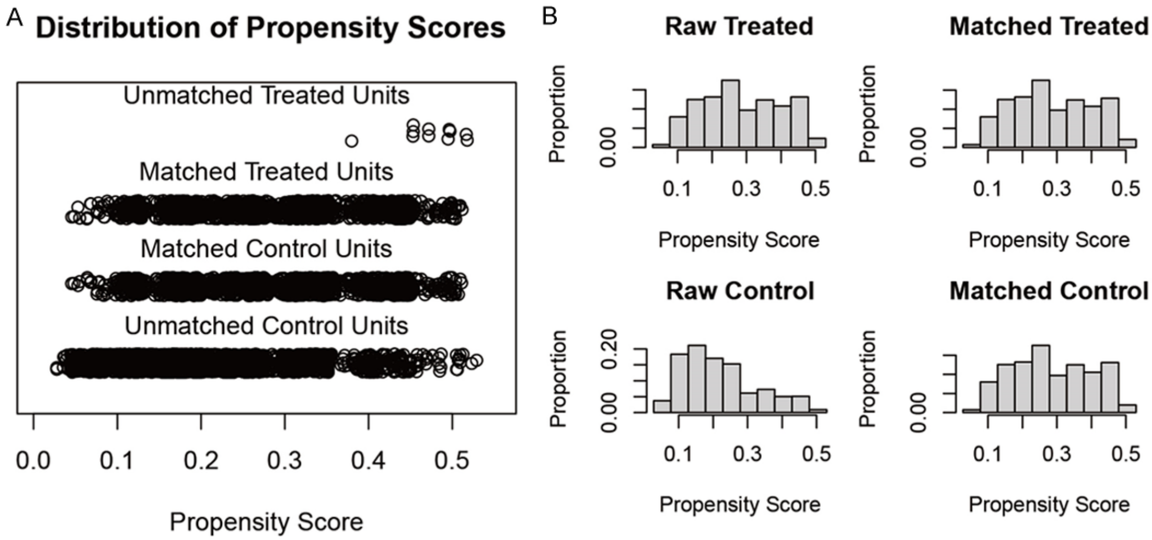


**Figure 5.** The distribution of propensity scores. A. Distribution of propensity scores. B. The proportion of propensity scores before and after matching.

*Prognostic predictor of elderly PDAC patients*

In the multivariate Cox proportional hazard regression model, all significant factors in univariate model with $P<0.1$ were included. According to the results of analysis, tumor grade (differentiation), pT staging, pN staging, radiation history, examined lymph node (ELN) ≥17 vs. <17, and lymph node ratio (LNR) were identified to be predictors of elderly patients' OS, whereas tumor location replaced radiotherapy as a prognostic factor of CSS (all $P<0.05$) (**Tables 5**, **6**). It was noteworthy that ELN grouped by optimal number aforementioned served as a strong prognostic predictor of survival (OS: HR=0.74, 95% CI: 0.65-0.83, $P<$ 0.001; CSS: HR=0.75, 95% CI: 0.66-0.85, $P<0.001$).

## Discussions

Pancreatic ductal adenocarcinoma (PDAC) mainly develops in the elderly with a peak incidence of 60 to 80 years old, and the status of nodal involvement was identified as a strong predictor for long-term prognosis of the patients [5, 25]. This analysis determined a threshold for the number of ELNs to accurately access node status. Moreover, the optimal number of ELNs for significantly better survival was defined as well. These useful insights were provided into the significance of extended lymphadenectomy for elderly PDAC patients, which can yet be regarded as an option for surgeons. Additionally, the obtained ELN number in the study can also be utilized as a criterion for evaluating the quality of LN resection for patients aforementioned in the future.

Regarding accurate assessment of nodal status, it was demonstrated that 19 ELNs provided the guarantee for accurate lymphatic staging of elderly PDAC patients with a confidence of 95%. However, the preliminary evidence appeared to be different from ours. A threshold of 10 or 15 ELNs is recommended by the guidelines including AJCC, UICC, ESMO, and ISGPS [6, 12, 13]. Nevertheless, a minimum ELN number ranging from 11 to 18 was identified as appropriate according to previous studies [7-10]. Considering the reasons for the discrepancy, the specific situation named stage migration should be taken into consideration. In recent years, accumulative evidence demonstrated that young age increased the risk for LN metastasis in patients with various cancer types [16, 17, 19, 20]. A consistent result was drawn from our analysis that PDAC patients ≥75 years old had significantly fewer metastatic LNs and smaller LNR than those <75 years old, indicating that it was difficult to obtain authentic positive nodes for accurate lymphatic staging. According to recent studies, smaller LNR was proved to be a valuable predictor for better long-term survival [8, 26-28]. However, elderly patients with smaller LNR in this study

**Table 2.** Characteristic comparison of patients in the two age groups before and after PSM matching

| Characteristics | Unmatched Data | | | After Propensity Score Matching | | |
|---|---|---|---|---|---|---|
| | Age <75 (N=5061) | Age ≥75 (N=1562) | *P*-value | Age <75 (N=1551) | Age ≥75 (N=1551) | *P*-value |
| Sex, N (%) | | | | | | |
| Female | 2357 (46.6%) | 889 (56.9%) | <0.001 | 880 (56.7%) | 879 (56.7%) | 0.999 |
| Male | 2704 (53.4%) | 673 (43.1%) | | 671 (43.3%) | 672 (43.3%) | |
| Race, N (%) | | | | | | |
| American Indian/Alaska Native | 28 (0.6%) | 5 (0.3%) | <0.001 | 3 (0.2%) | 5 (0.3%) | 0.949 |
| Asian or Pacific Islander | 417 (8.2%) | 151 (9.7%) | | 136 (8.8%) | 147 (9.5%) | |
| Black | 573 (11.3%) | 79 (5.1%) | | 70 (4.5%) | 79 (5.1%) | |
| White | 4043 (79.9%) | 1327 (85.0%) | | 1342 (86.5%) | 1320 (85.1%) | |
| Location, N (%) | | | | | | |
| Body/Tail of pancreas | 762 (15.1%) | 285 (18.2%) | 0.0104 | 266 (17.2%) | 276 (17.8%) | 0.894 |
| Head of the pancreas | 4299 (84.9%) | 1277 (81.8%) | | 1285 (82.8%) | 1275 (82.2%) | |
| Grade, N (%) | | | | | | |
| Moderately differentiated; Grade II | 2551 (50.4%) | 796 (51.0%) | 0.911 | 794 (51.2%) | 787 (50.7%) | 0.937 |
| Poorly differentiated; Grade III | 1929 (38.1%) | 582 (37.3%) | | 596 (38.4%) | 580 (37.4%) | |
| Undifferentiated; anaplastic; Grade IV | 56 (1.1%) | 12 (0.8%) | | 10 (0.6%) | 12 (0.8%) | |
| Well-differentiated; Grade I | 525 (10.4%) | 172 (11.0%) | | 151 (9.7%) | 172 (11.1%) | |
| Size | | | | | | |
| Mean (SD) | 34.7 (22.6) | 33.6 (15.8) | 0.0853 | 33.4 (15.8) | 33.7 (15.9) | 0.931 |
| Median [Min, Max] | 31.0 [1.00, 700] | 30.0 [1.00, 240] | | 30.0 [1.00, 165] | 30.0 [1.00, 240] | |
| Ajcc 8th edition T, N (%) | | | | | | |
| T1 | 850 (16.8%) | 262 (16.8%) | 0.334 | 281 (18.1%) | 259 (16.7%) | 0.861 |
| T2 | 2939 (58.1%) | 953 (61.0%) | | 934 (60.2%) | 946 (61.0%) | |
| T3 | 1183 (23.4%) | 328 (21.0%) | | 324 (20.9%) | 327 (21.1%) | |
| T4 | 89 (1.8%) | 19 (1.2%) | | 12 (0.8%) | 19 (1.2%) | |
| Ajcc 8th edition N, N (%) | | | | | | |
| N0 | 1565 (30.9%) | 557 (35.7%) | <0.001 | 530 (34.2%) | 550 (35.5%) | 0.066 |
| N1 | 2097 (41.4%) | 661 (42.3%) | | 608 (39.2%) | 658 (42.4%) | |
| N2 | 1399 (27.6%) | 344 (22.0%) | | 413 (26.6%) | 343 (22.1%) | |
| Radiation, N (%) | | | | | | |
| No radiation | 3242 (64.1%) | 1264 (80.9%) | <0.001 | 1249 (80.5%) | 1253 (80.8%) | 0.984 |
| Radiation after surgery | 1819 (35.9%) | 298 (19.1%) | | 302 (19.5%) | 298 (19.2%) | |
| Chemotherapy, N (%) | | | | | | |
| No/Unknown | 1386 (27.4%) | 777 (49.7%) | <0.001 | 758 (48.9%) | 766 (49.4%) | 0.96 |
| Yes | 3675 (72.6%) | 785 (50.3%) | | 793 (51.1%) | 785 (50.6%) | |
| Systemic therapy, N (%) | | | | | | |
| No systemic therapy | 1383 (27.3%) | 775 (49.6%) | <0.001 | 758 (48.9%) | 764 (49.3%) | 0.977 |
| Systemic therapy after surgery | 3678 (72.7%) | 787 (50.4%) | | 793 (51.1%) | 787 (50.7%) | |
| Survival | | | | | | |
| Mean (SD) | 31.8 (32.0) | 25.7 (27.7) | | 30.2 (32.4) | 25.7 (27.7) | |
| Median [Min, Max] | 20.0 [0, 167] | 16.0 [0, 147] | | 18.0 [0, 167] | 16.0 [0, 147] | |

obtained significantly poorer survival, implying there was a pseudo-small LNR induced by the insufficient number of ELNs. Moreover, with the increasing number of ELN, the proportions of pN2 and pN0 had significant trends of rising and falling, respectively. It revealed that the current ELN of the elderly was too limited to accurately evaluate nodal status, thereby leading to an incorrect staging, which was the stage migration. Therefore, more ELNs are required to accurately evaluate the nodal involvement status of elderly PDAC patients.

The study disclosed that insufficient ELNs could lead to incorrect nodal staging. However, ELN cannot be increased infinitely, and it should be limited within an appropriate range. Excessive ELN is associated with a longer length of operating time and increased mortality [29]. The optimal ELN number in this study was defined

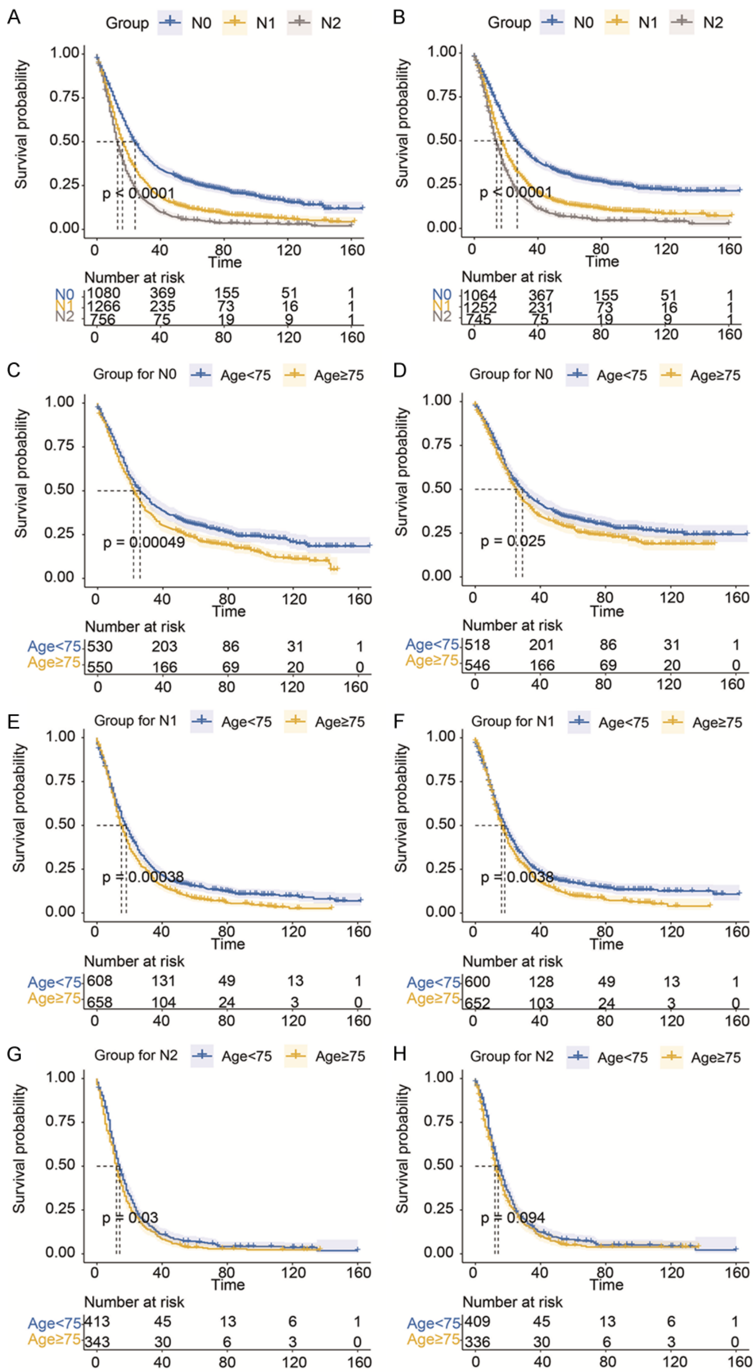


**Figure 6.** OS and CSS for patients in various groups. A, B. OS and CSS for patients with different pN, respectively. C, D. OS and CSS for pN0 patients of the two age groups. E, F. OS and CSS for pN1 patients of the two age groups. G, H. OS and CSS for pN2 patients of the two age groups.

as 17 for elderly patients to obtain a significantly better long-term prognosis. With 17 ELNs, the patients achieve an optimal balance of benefits to improve survival with adequate LN examination, as well as a balance of risk of harmful effects from excessive resection. Nevertheless, it has also been suggested that lymph node resection is associated with an increased long-term prognosis, suggesting that the more LNs examined, the better the survival of patients [27, 30]. The reasons reflecting such divergence were listed hereafter. For one thing, the unfavorable impact on survival caused by excessive ELNs was not considered in the earlier studies. The ELN number was separated and divided by different cutoff values. In the previous analysis, the maximum cutoff of the ELN number used for the grouping was 15, meaning the maximum ELN grouping was ELN≥15, which was not sufficient to reach the standard of excessive LN resection. For another, through maximizing selection of ranking statistics, the present study accurately obtained the complete trend of significant change with the continuous change of ELN number. While previous studies could only investigate the relationship between the number of ELNs and long-term prognosis by comparing the survival of patients with a range of ELN intervals.

Integrating the appropriate number of ELNs for accurate staging and greater survival benefit, we tended to prioritize that of survival. According to further analysis, 93% of the patients with 17 LNs detected could be accurate in nodal status assessment, which was extremely close to 95% of those with 19 LNs detected. Resection of 17 LNs is more achievable and produces less surgical trauma in patients compared with 19 ELNs, which may lead to a better prognosis. Considering these factors, 17 ELNs are recommended for elderly patients with

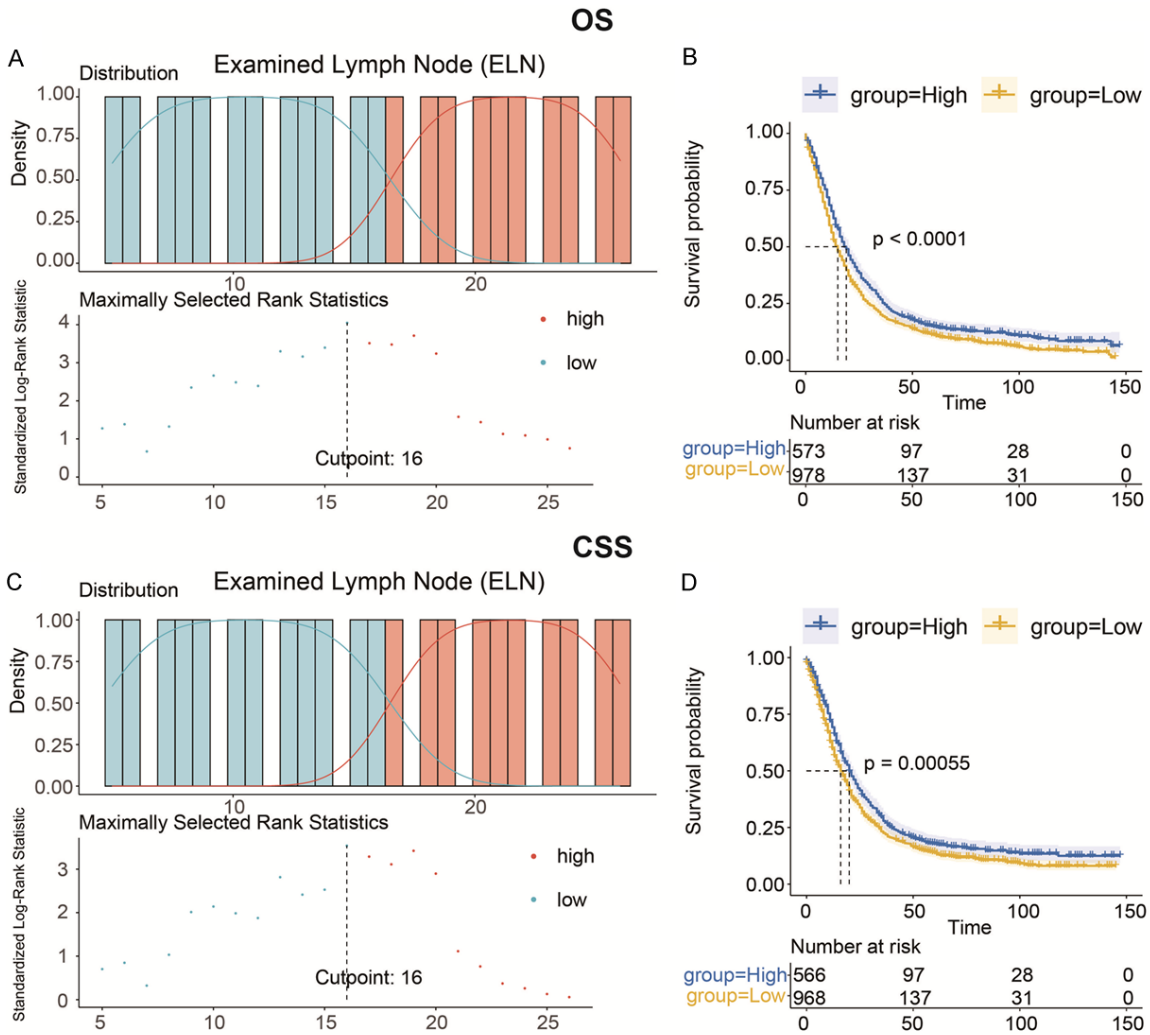


**Figure 7.** Analysis for optimal ELN number for significantly better survival. A, C. The appropriate ELN number for better OS and CSS. B, D. OS and CSS for patients with ELNs<17 and ≥17.

**Table 3.** Threshold of ELN number for accurate staging

| Group | Global *p* | ELN |
|---|---|---|
| Pancreatic adenocarcinoma | 0.146 | 19 |
| Pancreatic head adenocarcinoma | 0.153 | 25 |
| Pancreatic body/tail adenocarcinoma | 0.11 | 18 |

**Table 4.** Optimal number of ELN for significantly better survival

| Group | Statistic | ELN |
|---|---|---|
| Pancreatic adenocarcinoma | | |
| for OS | 4.05 | 17 |
| for CSS | 3.54 | 17 |
| Pancreatic head adenocarcinoma | | |
| for OS | 4 | 17 |
| for CSS | 3.51 | 11 |
| Pancreatic body/tail adenocarcinoma | | |
| for OS | 1.63 | 17 |
| for CSS | 2.05 | 17 |

PDAC. Nevertheless, whether 17 or 19 LNs are resected, they belong to extended lymphadenectomy due to the greater ELN number than the recommendations of the guidelines above-mentioned. Perspectives on extended and standard lymphadenectomy have been discussed for a long time. The first prospective, randomized, multicenter study regarding this discussion was published by Pedrazzoli and colleagues in 1988 [31]. 83 patients with pancreatic tumors were divided into the standard lymphadenectomy group (N=42, mean ELN=13.3) and the extended lymphadenectomy group (N=41, mean ELN=19.8). It

**Table 5.** Cox regression analysis for OS of elderly PDAC patients

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Sex (Male vs. Female) | 1.11 (1-1.23) | 0.056 | 1.1 (0.99-1.23) | 0.068 |
| Race (reference American Indian/Alaska Native) | | | | |
| Asian or Pacific Islander | 0.89 (0.33-2.41) | 0.819 | | |
| Black | 0.9 (0.33-2.47) | 0.836 | | |
| White | 0.9 (0.34-2.4) | 0.83 | | |
| Location (reference Body/Tail of pancreas) | | | | |
| Head of the pancreas | 1.14 (1-1.31) | 0.055 | 1.16 (1-1.34) | 0.051 |
| Grade (reference Moderately differentiated; Grade II) | | | | |
| Poorly differentiated; Grade III | 1.39 (1.24-1.56) | <0.001 | 1.37 (1.23-1.54) | <0.001 |
| Undifferentiated; anaplastic; Grade IV | 1.62 (0.91-2.86) | 0.099 | 1.33 (0.75-2.37) | 0.329 |
| Well-differentiated; Grade I | 0.7 (0.58-0.83) | <0.001 | 0.64 (0.53-0.77) | <0.001 |
| Ajcc 8th edition T (reference T1) | | | | |
| T2 | 1.48 (1.28-1.72) | <0.001 | 1.34 (1.13-1.57) | <0.001 |
| T3 | 1.86 (1.56-2.21) | <0.001 | 1.66 (1.29-2.13) | <0.001 |
| T4 | 3.36 (2.1-5.38) | <0.001 | 2.83 (1.75-4.56) | <0.001 |
| Ajcc 8th edition N (reference N0) | | | | |
| N1 | 1.56 (1.38-1.76) | <0.001 | 1.48 (1.28-1.72) | <0.001 |
| N2 | 2.06 (1.78-2.38) | <0.001 | 1.81 (1.45-2.26) | <0.001 |
| Radiation (Yes vs. No) | 0.75 (0.66-0.85) | <0.001 | 0.84 (0.73-0.98) | 0.022 |
| Chemotherapy (Yes vs. No) | 0.63 (0.56-0.7) | <0.001 | 0.55 (0.13-2.23) | 0.4 |
| Systemic therapy (Yes vs. No) | 0.63 (0.56-0.69) | <0.001 | 1 (0.25-4.06) | 1 |
| ELN (≥17 vs. <17) | 0.8 (0.72-0.89) | <0.001 | 0.74 (0.65-0.83) | <0.001 |
| LNR | 4.67 (3.63-6.02) | <0.001 | 1.81 (1.22-2.68) | 0.003 |

demonstrated that the mean survival of patients with extended lymphadenectomy was better than those with standard lymphadenectomy (500 days vs. 335 days), but there was no statistical significance. Several subsequent studies showed that data did not support a more extended lymphadenectomy, which herein appeared to achieve an inconsistent conclusion with ours [29]. However, several vital factors should be taken into account that will contribute to these discrepancies. To begin with, unlike previous studies, the patients enrolled into our analysis were ≥75 years old. These patients tended to have fewer metastatic LNs, emphasizing the importance of extended lymphadenectomy for more accurate nodal status assessment. Additionally, the definitions of ELN number in extended lymphadenectomy varied greatly according to some subjective decisions in different studies. For example, in Yeo's randomized trial of 299 patients undergoing resection at Johns Hopkins, the mean ELN number of patients with extended lymphadenectomy was 28.5 [32, 33], while the definition of extended lymphadenectomy in our study was the number of LN resection greater than guideline recommendations (a threshold of 15 ELNs). Too much dissection of LNs will indeed lead to prolongation of operation time and greater physical trauma, thereby resulting in unfavorable effects on the prognosis [29].

Reviewing the present research, there were still some limitations needed to be considered. Since this was a cross-sectional population-based study, we cannot avoid the existence of multiple biases. In addition, due to the limitation of SEER database, a proportion of baseline data were not available including short-term prognosis, surgical margin status, and length of hospital stay. We herein were not able to explore the maximum number of ELNs to prevent the side effects of excessive LN resection on the recovery of the body. In some cases, the number of ELN was not only determined by the decisions of surgeon, but also subject to the specific situation of the patient and the progress of the surgical procedure, which could pro-

**Table 6.** Cox regression analysis for CSS of elderly PDAC patients

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Sex (Male vs. Female) | 1.1 (0.98-1.23) | 0.096 | 1.1 (0.98-1.23) | 0.102 |
| Race (reference American Indian/Alaska Native) | | | | |
| Asian or Pacific Islander | 0.72 (0.26-1.95) | 0.516 | | |
| Black | 0.72 (0.26-1.97) | 0.518 | | |
| White | 0.74 (0.28-1.98) | 0.551 | | |
| Location (reference Body/Tail of pancreas) | | | | |
| Head of the pancreas | 1.19 (1.02-1.38) | 0.024 | 1.19 (1.02-1.39) | 0.03 |
| Grade (reference Moderately differentiated; Grade II) | | | | |
| Poorly differentiated; Grade III | 1.42 (1.26-1.6) | <0.001 | 1.39 (1.23-1.57) | <0.001 |
| Undifferentiated; anaplastic; Grade IV | 1.67 (0.92-3.03) | 0.093 | 1.33 (0.73-2.43) | 0.349 |
| Well-differentiated; Grade I | 0.68 (0.56-0.83) | <0.001 | 0.64 (0.52-0.78) | <0.001 |
| Ajcc 8th edition T (reference T1) | | | | |
| T2 | 1.53 (1.3-1.79) | <0.001 | 1.36 (1.14-1.62) | <0.001 |
| T3 | 1.89 (1.57-2.28) | <0.001 | 1.68 (1.29-2.19) | <0.001 |
| T4 | 3.47 (2.11-5.71) | <0.001 | 2.94 (1.77-4.88) | <0.001 |
| Ajcc 8th edition N (reference N0) | | | | |
| N1 | 1.65 (1.45-1.88) | <0.001 | 1.56 (1.34-1.82) | <0.001 |
| N2 | 2.17 (1.86-2.53) | <0.001 | 1.89 (1.49-2.39) | <0.001 |
| Radiation (Yes vs. No) | 0.79 (0.69-0.91) | 0.001 | 0.88 (0.75-1.02) | 0.094 |
| Chemotherapy (Yes vs. No) | 0.65 (0.58-0.73) | <0.001 | 0.46 (0.11-1.89) | 0.282 |
| Systemic therapy (Yes vs. No) | 0.65 (0.58-0.73) | <0.001 | 1.2 (0.3-4.9) | 0.795 |
| ELN (≥17 vs. <17) | 0.82 (0.73-0.92) | 0.001 | 0.75 (0.66-0.85) | <0.001 |
| LNR | 4.89 (3.75-6.39) | <0.001 | 1.78 (1.17-2.71) | 0.007 |

duce an influence on the analysis. However, the strong points also should not be ignored that our analysis firstly determined the optimal number of ELNs for elderly PDAC patients and revealed the relationship between positive-nodes and age of these patients. A relatively large scale of enrolled PDAC patients from 17 registries served as a support for the credibility of the results. Furthermore, 1 to 1 propensity score matching (PSM) was utilized to reduce the imbalance of baseline characteristics, making this cross-sectional study approximate to a prospective one.

## Conclusions

According to multiple analysis, the elderly patients with pancreatic ductal adenocarcinoma (PDAC) had fewer lymph node (LN) metastases, implying that it was more difficult to detect the authentic number of positive-LNs, thus leading to a migration of lymphatic and pathologic staging. In this study, a threshold of 19 ELNs was determined to allow accurate assessment of nodal status. An optimal ELN number of 17 was identified to achieve significantly better survival. Considering that the MNELNs obtained are greater than current guideline recommendations, extended LN resection tended to be suitable for elderly PDAC patients. However, we should explain that the study was not conducted to recommend extended lymphadenectomy for elderly patients, because prospective, randomized clinical trials are required to support this view in the future.

## Disclosure of conflict of interest

None.

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