The value of the lymph node ratio and total number of lymph nodes examined for resected pancreatic signet ring cell carcinoma: a retrospective cohort study

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Abstract

Background: Pancreatic signet ring cell carcinoma (SRCC) is an exceedingly rare histological subtype of pancreatic cancer. Previous studies have focused on the trends of incidence and independent predictors of pancreatic SRCC. Our objectives of the study were to analyze the prognostic value of the lymph node ratio (LNR) and to explore the minimal number of lymph nodes examined to accurately evaluate the N stage in resected pancreatic SRCC.

Method: We analyzed 120 patients diagnosed from January 1, 1990, to December 31, 2016, constituted the study cohort from the Surveillance, Epidemiology, and End Results (SEER) registry. We calculated the overall survival (OS) of these patients by using a Kaplan–Meier analysis. The Kaplan–Meier analysis was used to analyze the influence of various factors on the prognosis of patients in the univariate analysis. The multivariate Cox analysis were applied to find independent prognostic factors of patients with pancreatic SRCC. Receiver-operating characteristic curve (ROC) analysis to investigate the discriminatory ability of the total number of lymph nodes examined (TNLE) relative to whether lymph node metastasis was present.

Results: The median number of lymph nodes examined among 120 patients with resected pancreatic SRCC was 14 (interquartile range: 6.25–20.0). According to the univariate analysis of OS, age, grade, chemotherapy, LNR, and TNLE were significantly different (P < .05). We demonstrated the prognostic benefit of chemotherapy in resected pancreatic SRCC, whereas radiotherapy was not associated with improved survival. The multivariate survival analysis showed that LNR and grade were independent prognostic indicators after pancreatic SRCC resection for OS. TNLE ≥ 8 showed the highest discriminatory power for evaluating lymph node metastasis (Area under curve (AUC): 0.656, 95% confidence interval: 0.564–0.741, Youden index:0.2533, sensitivity: 78.67%, specificity: 46.67%, P = .003).

Conclusion: Our study indicated that the LNR was a valuable independent prognostic factor for resected pancreatic SRCC. Regional lymphadenectomy of at least 8 lymph nodes was necessary to accurately stage patients. An adequate number of lymph nodes examined are necessary for clinicians to accurately predict the significance of the LNR in resected pancreatic SRCC.

Keywords: Independent factor; Lymph node ratio; Pancreatic signet ring cell carcinoma; SEER database; Total number of lymph nodes examined

Introduction

Pancreatic signet ring cell carcinoma (SRCC) is a mucin-secreting adenocarcinoma that contains abundant intracytoplasmic mucin and pushes the nucleus to one side of the cell.[9] SRCC mostly occurs in the digestive system, and the most common occurrence site is the stomach, which accounts for 15.1% to 28.2% of primary gastric cancers,[2–5] and occasionally occurs in colorectal, bile, cysts, breast, bladder, prostate, and lung cancers, whereas primary pancreatic SRCC is extremely rare. Currently, 12 case reports have been published in the English literature concerning primary SRCC of the pancreas.[5–16] Previously, Patel et al searched 497 pancreatic SRCC patients diagnosed between January 1, 1973, and December 31, 2013, SEER database and focused on determining the predictive effects of epidemiological factors and treatment interventions, with 1-, 2-, and 5-year overall survival (OS) rates of 17%, 9%, and 4%, respectively, which demonstrated very poor survival.[17] And Wu et al[18] identified 24,171 SRCC patients of different tumor locations from the SEER database (1988–2012) and 441 pancreatic SRCC accounts for just 1.8%.

The lymph node ratio (LNR) is defined as the ratio of the number of metastatic lymph nodes relative to the total number of LNs examined (TNLE). In the 8th edition of the TNM staging guidelines,[19,20] the N stage was further classified as N0 (no nodal metastasis), N1 (1–3 LNM), and N2 (≥4 LNM), whereas the N stage was classified as N0 (no nodal metastasis), or N1(≥1
LNM) in the 6th edition of the TNM staging guidelines. Several studies have demonstrated that the LNR is a more powerful predictor of survival in patients, compared to the use of positive lymph nodes.\textsuperscript{21–23} However, it remains unclear as to whether it is useful to determine LNR segmentation points and to elaborate the role of LNR in evaluating the survival and prognosis of patients with pancreatic SRCC. TNLE is necessary to accurately evaluate the N stage; however, until now, no study has reported the minimal number of TNLE of resected pancreatic SRCC.

In this study, we analyzed the significance of the LNR and TNLE by extracting a large sample of patients with resected pancreatic SRCC from the Surveillance, Epidemiology, and End Results (SEER) database registry of the National Cancer Institute. The aim was to retrospectively study the relationship between the LNR and the prognosis of pancreatic SRCC, to identify the independent factors of pancreatic SRCC, and to explore the minimal number of TNLEs required to accurately evaluate the N stage.

Methods

Patients

The data used in this study were retrieved from the SEER database registry of the National Cancer Institute. Permission was obtained to access the research data files (reference number 10918-Nov2019). To identify all of the eligible cases, the following inclusion criteria were applied: all patients who were included in the SEER database registry of the National Cancer Institute. The exclusion criteria were as follows: patients with active follow-up (diagnosis not obtained from autopsy or death certificate); patients with positive histology confirmation, surgical resection, and no distant metastases (M0 stage); and patients with complete data of the number of lymph nodes examined and positive lymph nodes. TNM stage was recorded according to the 6th edition of American Joint Committee on Cancer. The exclusion criteria were as follows: incomplete data of the number of lymph nodes examined and positive lymph nodes; patients with no surgical resection; and patients with distant metastases. Based on the above criteria, a total of 120 patients with pancreatic SRCC diagnosed from January 1, 1990, to December 31, 2016, were enrolled in our study cohort. The flowchart of the patient selection process was shown in Figure 1.

Data collection

In our study, the following demographic and clinicopathologic characteristics were reviewed: age, race, sex, tumor location, grade, TNM staging, T stage, N stage (6th), nodal status, radiotherapy, chemotherapy, total number of lymph nodes examined, LNR, survival months, and vital status. The age at diagnosis was divided into 2 groups (<75 and at least 75 years). The outcome was OS, which was defined as the interval from the date of diagnosis to the date of death (due to all causes) or the last follow-up. Moreover, X-tile is a bioinformatics tool that is used for biomarker assessment and outcome-based cut-point optimization.\textsuperscript{24} X-tile has been widely used to decide the cutoff values of the biomarkers and prognostic factors.\textsuperscript{25–28} The optimal cutoff value of the LNR was 0.20, and the optimal cutoff value of TNLE was 8, which were both analyzed by using X-tile software (Yale University, New Haven, CT).

Statistical analysis

All of the statistical analyses were performed by using the SPSS 25.0 statistical package (IBM Corporation, Armonk, NY). The continuous data are expressed as medians with interquartile ranges (IQRs). Categorical data were compared by using x\(^2\) tests to analyze clinicopathologic characteristics of pancreatic SRCC according to different groups of LNR. The OS was compared via Kaplan–Meier curves in the univariate analysis by using the log-rank test via SPSS and GraphPad Prism 8.0 Software (GraphPad Software Inc., San Diego, CA). Multivariate analyses and hazard ratios (HRs) were used with a Cox proportional hazards regression model to identify independent prognostic risks. The cutoff value of the variable was determined by using X-tile software. A receiver-operating characteristic (ROC) curve analysis was used to investigate the discriminatory ability of TNLE relative to lymph node metastasis.\textsuperscripts{29,30} The HRs and 95% confidential intervals (95% CIs) are presented. All of the tests were two-sided, and a P value <.05 was considered to be statistically significant.

Results

Clinicopathologic characteristics

Of the 859 patients identified with pancreatic SRCC, 120 patients were finally included in our study. There were 64 males (53.3%) and 56 females (46.7%), with a median age of 67 years (IQR: 58.3–75.0 years). Tumors were located at the pancreatic head (79.2%) and at the body or tail (12.5%). Poor differentiation and undifferentiation (n = 95, 79.2%) was the most common tumor grade, compared with moderate differentiation (n = 18, 15.0%). More than half of the patients (n = 75, 62.5%) had lymph node metastasis, compared with 45 (37.5%) patients without metastasis. Forty-one patients (22.6%) received radiotherapy, whereas 64 patients (53.3%) received chemotherapy. A total of 1 to 7 lymph nodes were examined in 37 patients (30.8%) and at least 8 lymph nodes were examined in 83 patients (69.2%). The detailed baseline characteristics are displayed in Table 1.

Comparison of clinicopathologic characteristics according to different group of LNR

The median LNR of all of the patients was 0.106 (IQR: 0–0.273). We divided the entire cohort into the low-risk cohort (LNR < 0.20) and high-risk cohort (LNR ≥ 0.20), according to the results that were analyzed via X-tile software. Seventy-six patients were included in the low-risk cohort, whereas 44 patients constituted the high-risk cohort. The clinicopathologic
characteristics of high-risk cohort (LNR ≥ 0.20) and low-risk cohort (LNR < 0.20) were found to be significantly different in tumor grade \((P = .023)\), location \((P = .017)\), N stage (6th) \((P < .001)\), and nodal status \((P < .001)\) (Table 1).

**High LNR and low TNLE are related to poor survival**

In our study, 8 and 0.20 represented the cutoff values of TNLE and LNR, respectively. The Kaplan–Meier curves showed that there were significant differences in the OS rates of LNR and TNLE \((P < .05)\). According to the OS results, patients with resected pancreatic SRCC who had higher LNR and lower TNLE exhibited a worse survival (Fig. 2A and B). With further stratified data analysis, when TNLE was at least 8, the LNR was able to distinguish the survival differences of the patients with resected pancreatic SRCC in the OS analysis (Fig. 2C and D).

**Prognostic significance of chemotherapy**

In the total cohort, patients with resected pancreatic SRCC were more likely to receive chemotherapy (64/120 patients) than radiotherapy (41/120 patients). There were no significant differences in OS after radiotherapy \((P > .05\), Fig. 3A\). Moreover, the overall median survival time of patients with resected pancreatic SRCC who did not receive chemotherapy was just 10 months, and the overall median survival time of patients with resected pancreatic SRCC who receive chemotherapy was just 16 months. Chemotherapy significantly improved survival in OS analyses \((P < .05\), Fig. 3B\).

**Univariate and multivariate analyses**

The median OS of pancreatic SRCC was 12 months (IQR: 6–29 months), and the 1-, 3-, 5-year OS rates were 52.4%, 20.8%, and 16.6%, respectively. In the univariate analysis, age \((P = .019)\), location \((P = .001)\), chemotherapy \((P = .009)\), LNR \((P = .006)\), and TNLE \((P = .010)\) were significantly associated with OS, whereas race, sex, tumor location, TNM staging, T stage, N stage (6th), nodal status, and radiotherapy were not significantly related to OS \((P > .05)\) (Table 2). Variables that were significantly associated with the OS analyzed via multivariate analyses were selected to be prognostic indicators. After adjusting for other risk factors in the model for LNR in the multivariate survival analysis, LNR \((P = .010, HR = 1.178\), 95% confidence interval

### Table 1

| Variables                              | No. of patients | LNR < 0.20 (n = 76) | LNR ≥ 0.20 (n = 44) | P value |
|-----------------------------------------|-----------------|---------------------|---------------------|---------|
| Age at diagnosis (y)                    |                 |                     |                     |         |
| <75                                     | 88 (73.3%)      | 56 (63.6%)          | 32 (36.4%)          | .909    |
| ≥75                                     | 32 (26.7%)      | 20 (62.5%)          | 12 (37.5%)          |         |
| Race                                    |                 |                     |                     |         |
| Black                                   | 13 (10.8%)      | 11 (84.6%)          | 2 (15.4%)           | .241    |
| White                                   | 102 (85.0%)     | 62 (60.8%)          | 40 (39.2%)          |         |
| Other                                   | 5 (4.2%)        | 3 (60.0%)           | 2 (40.0%)           |         |
| Sex                                     |                 |                     |                     | .085    |
| Male                                    | 64 (53.3%)      | 36 (56.2%)          | 28 (43.8%)          |         |
| Female                                  | 56 (46.7%)      | 40 (71.4%)          | 16 (28.6%)          |         |
| Location                                |                 |                     |                     |         |
| Pancreas head                           | 95 (79.2%)      | 66 (69.5%)          | 29 (30.5%)          | .017    |
| Pancreas body/tail                      | 15 (12.5%)      | 7 (46.7%)           | 8 (53.3%)           |         |
| Pancreas other                          | 10 (8.3%)       | 3 (30.0%)           | 7 (70.0%)           |         |
| Grade (n = 113)                         |                 |                     |                     | .023    |
| Moderately differentiated               | 18 (15.9%)      | 16 (88.9%)          | 2 (11.1%)           |         |
| Poorly differentiated/undifferentiated  | 95 (84.1%)      | 58 (61.1%)          | 37 (38.9%)          |         |
| TNM staging system (6th) (n = 72)       |                 |                     |                     |         |
| I                                       | 3 (4.2%)        | 3 (100%)            | 0 (0%)              | .202    |
| II                                      | 64 (88.9%)      | 36 (56.2%)          | 28 (43.8%)          |         |
| III                                     | 5 (6.9%)        | 4 (80.0%)           | 1 (20.0%)           |         |
| T stage (6th) (n = 72)                  |                 |                     |                     |         |
| T1                                      | 3 (4.2%)        | 2 (66.7%)           | 1 (33.3%)           | .305    |
| T2                                      | 9 (12.5%)       | 3 (33.3%)           | 6 (66.7%)           |         |
| T3                                      | 55 (76.4%)      | 34 (61.8%)          | 21 (38.2%)          |         |
| T4                                      | 5 (6.9%)        | 4 (80.0%)           | 1 (20.0%)           |         |
| N stage (6th)                           |                 |                     |                     | .001    |
| N0                                      | 45 (37.5%)      | 45 (100%)           | 0 (0%)              |         |
| N1                                      | 75 (62.5%)      | 31 (41.3%)          | 44 (58.7%)          |         |
| Nodal n                                 |                 |                     |                     | <.001   |
| N0                                      | 45 (37.5%)      | 45 (100%)           | 0 (0%)              |         |
| ≥4 positive nodes                       | 27 (22.5%)      | 46 (58.2%)          | 33 (41.8%)          | .107    |
| Radiotherapy                            |                 |                     |                     | .107    |
| No                                      | 79 (77.4%)      | 46 (58.2%)          | 33 (41.8%)          |         |
| Yes                                     | 41 (22.6%)      | 30 (73.2%)          | 11 (26.8%)          |         |
| Chemotherapy                            |                 |                     |                     | .349    |
| No                                      | 56 (46.7%)      | 33 (58.9%)          | 23 (41.1%)          |         |
| Yes                                     | 64 (53.3%)      | 43 (67.2%)          | 21 (32.8%)          |         |
| Total lymph nodes examined              |                 |                     |                     | .557    |
| 1–7                                     | 37 (30.8%)      | 22 (59.5%)          | 15 (40.5%)          |         |
| ≥8                                      | 83 (69.2%)      | 54 (65.1%)          | 29 (34.9%)          |         |

Bold figures indicate statistical significant \(P < .05\).
Figure 2. Kaplan–Meier survival curves for patients with resected pancreatic signet ring cell carcinoma according to LNR and the TNLE. LNR = lymph node ratio, TNLE = total number of lymph nodes examined.

Figure 3. Kaplan–Meier survival curves of chemotherapy and radiotherapy for patients with resected pancreatic signet ring cell carcinoma.
[CI]: 1.149–2.756) and grade (P = .011, HR = 2.481, 95% CI: 1.230–5.002) were considered independent prognostic indicators. In the model for TNLE of the multivariate analysis, grade (P = .010, HR = 2.512, 95% CI: 1.246–5.064) was considered as the independent prognostic indicator, whereas TNLE (P = .060, HR = 0.643, 95% CI: 0.406–1.019) was not considered as the independent prognostic indicator (Table 3).

**Total number of lymph nodes examined and nodal status**

The total number of lymph nodes examined and nodal status are important in identifying the N stage. To further clarify the optimal value of TNLE, an ROC analysis was used to investigate the discriminatory ability of the total number of lymph nodes examined among the patients who had no LNM (N0), and patients who had at least 1 LNM (N1 6th). As shown in the Figure 4, TNLE 8 showed the highest discriminatory power (AUC: 0.656, 95% CI: 0.564–0.741, Youden index: 0.253, sensitivity: 78.67%, specificity: 46.67%, P = .003). Although N stage (6th) and nodal status were not prognostic factors

**Table 2**

Univariate analysis of prognostic factors associated with overall survival of patients with resected pancreatic signet ring cell carcinoma

| Variables                              | N  | Median survival (mo) | 1-y survival (%) | 3-y survival (%) | P value |
|----------------------------------------|----|----------------------|------------------|------------------|---------|
| Age at diagnosis, y                    |    |                      |                  |                  |         |
| <75                                    | 88 | 15                   | 56.9             | 22.3             | .019    |
| ≥75                                    | 32 | 8                    | 40.2             | 12.6             |         |
| Race                                   |    |                      |                  |                  |         |
| Black                                  | 13 | 17                   | 0                | 0                | .695    |
| White                                  | 102| 13                   | 52.3             | 19.3             |         |
| Other                                  | 5  | 12                   | 40.0             | 20.0             |         |
| Sex                                     |    |                      |                  |                  |         |
| Male                                   | 64 | 14                   | 50.8             | 22.4             | .860    |
| Female                                 | 56 | 13                   | 53.7             | 17.0             |         |
| Location                               |    |                      |                  |                  |         |
| Body/tail                              | 15 | 11                   | 36.1             | 21.7             | .995    |
| Head                                   | 95 | 14                   | 55.4             | 19.0             |         |
| Other                                  | 10 | 12                   | 48.0             | 12.0             |         |
| Grade                                  |    |                      |                  |                  |         |
| Moderately differentiated              | 18 | 53                   | 80.4             | 51.0             | .001    |
| Poorly differentiated/undifferentiated | 95 | 12                   | 48.3             | 14.8             |         |
| TNM staging system (6th)               |    |                      |                  |                  |         |
| I                                      | 3  | 38                   | 66.7             | 33.3             | .496    |
| II                                     | 64 | 13                   | 52.9             | 25.1             |         |
| III                                    | 5  | 12                   | 40.0             | 0                |         |
| T stage (6th)                          |    |                      |                  |                  |         |
| T1                                     | 3  | 32                   | 66.7             | 33.3             | .802    |
| T2                                     | 9  | 26                   | 66.7             | 21.5             |         |
| T3                                     | 55 | 13                   | 50.6             | 23.8             |         |
| T4                                     | 5  | 12                   | 40.0             | 20.0             |         |
| N stage (6th)                          |    |                      |                  |                  |         |
| N0                                     | 45 | 18                   | 65.2             | 22.6             | .206    |
| N1                                     | 75 | 11                   | 44.8             | 17.8             |         |
| Nodal status                           |    |                      |                  |                  |         |
| N0                                     | 45 | 18                   | 65.2             | 22.6             | .254    |
| 1–3 positive nodes                     | 48 | 11                   | 47.1             | 20.9             |         |
| ≥4 positive nodes                      | 27 | 11                   | 40.1             | 8.9              |         |
| Radiotherapy                           |    |                      |                  |                  |         |
| No                                     | 79 | 12                   | 50.0             | 19.3             | .556    |
| Yes                                    | 41 | 15                   | 57.2             | 23.4             |         |
| Chemotherapy                           |    |                      |                  |                  |         |
| No                                     | 56 | 10                   | 41.3             | 11.8             | .009    |
| Yes                                    | 64 | 16                   | 62.0             | 28.7             |         |
| Total lymph nodes examined             |    |                      |                  |                  |         |
| 1–7                                    | 37 | 10                   | 40.9             | 5.8              | .058    |
| ≥8                                     | 83 | 14                   | 54.8             | 27.5             |         |
| Lymph node ratio                       |    |                      |                  |                  |         |
| <0.20                                  | 76 | 17                   | 63.3             | 26.9             | .006    |
| ≥0.20                                  | 44 | 9                    | 32.9             | 10.1             |         |

Bold figures indicate statistical significant P < .05.

**Table 3**

Multivariate analysis of prognostic factors associated with overall survival of patients with resected pancreatic signet ring cell carcinoma

| Variables                              | HR  | 95% CI       | P value |
|----------------------------------------|-----|--------------|---------|
| Model 1 with TNLE                      |     |              |         |
| Age, y (<75 vs ≥75)                    | 1.586| 0.983–2.323  | .061    |
| Grade (G2 vs G3/4)                     | 2.512| 1.246–5.064  | .010    |
| TNLE (<8 vs ≥8)                        | 0.643| 0.406–1.019  | .060    |
| Model 2 with LNR                       |     |              |         |
| Age, y (<75 vs ≥75)                    | 1.570| 0.978–2.522  | .062    |
| Grade (G2 vs G3/4)                     | 2.481| 1.230–5.002  | .011    |
| Chemotherapy (yes/no)                  | 1.485| 0.970–2.276  | .069    |
| LNR (<0.20 vs ≥0.20)                   | 1.780| 1.149–2.756  | .010    |

Bold figures indicate statistical significant P < .05.

CI = confidence interval, HR = hazard risk, LNR = lymph node ratio, TNLE = total lymph nodes examined.
improve the outcomes of patients with resectable pancreatic SRCC. Moreover, their studies did not reveal the significance of chemotherapy. In a case report of pancreatic SRCC, a good response to neoadjuvant gemcitabine monotherapy was demonstrated. For pancreatic SRCC, Kaji et al.[12] reported that borderline resectable disease should still be considered for neoadjuvant chemotherapy to facilitate potential resectability. Based on previous studies,[12,14,17] we believed that chemotherapy based on gemcitabine could be used as a beneficial attempt for the treatment of patients if patients could tolerate chemotherapy. In our study cohort, we demonstrated the prognostic benefit of chemotherapy in resected pancreatic SRCC, whereas radiotherapy was not associated with improved survival. However, the choice of chemotherapy before or after surgery, as well as the type of program of chemotherapy should be further studied.

According to the epidemiological report of pancreatic cancer,[12] pancreatic cancer is mostly diagnosed in elderly individuals aged >70 years. Wang et al.[33] proposed that the age at diagnosis is a negative independent factor in pancreatic cancer patients, as well as the fact that an early diagnosis indicates a very important significance for improving the survival of pancreatic cancer patients. In one case report, Yepuri et al.[15] found that poorly differentiated SRCC of the pancreas was delayed because of an incorrect diagnosis as chronic pancreatitis, and patients died 8 weeks after the diagnosis, which indicates that early diagnosis is important to the physician and to the patient. In our analysis, the median age of pancreatic SRCC was 67 years (IQR: 58.3–75.0 years), which was similar to the previous literature. The age at diagnosis is also a negative risk factor for pancreatic SRCC, which demonstrates that the 1-year OS and 3-year OS of patients over 75-years-old were 40.2% and 12.6%, respectively, whereas the 1-year OS and 3-year OS of patients younger than 75-years-old were 56.9% and 22.3%, respectively.

In recent years, the LNR has been considered to be a better independent prognostic predictor of survival in pancreatic adenocarcinoma (PDAC) patients than positive lymph nodes for patients after they receive resection of pancreatic cancer.[34–36] It is not surprising that the LNR could be used to assess the survival of resected pancreatic SRCC. However, at present, the role of the LNR in predicting the survival of resected pancreatic SRCC is unclear. It is worth establishing the standard best cutoff value for the LNR and confirming whether the LNR is correlated with the OS of resected pancreatic SRCC. Our study is the first population-based analysis to describe the value of the LNR in resected pancreatic SRCC. In our study, the LNR was confirmed as an independent prognostic risk factor in the univariate and multivariate analyses. By using X-tile software, 0.20 was found to be the optimal cutoff value to assess OS.

In the consensus statement by the International Study Group on Pancreatic Surgery, standard lymphadenectomy for PDAC should regularly provide at least 15 lymph nodes to ensure adequate pathological staging of the disease.[37] The mean number of LNs resected in patients with pancreatic cancer who underwent standard lymphadenectomy in randomized controlled trials (RCTs) has been shown to be 13 to 17.[38–41] These guidelines focus on the study of pancreatic adenocarcinoma. However, there is no previous evidence to determine the optimal cutoff value of the total lymph nodes examined in patients with resected pancreatic SRCC. X-tile software succeeded in identifying 8 as the optimal cutoff value of the number of lymph nodes examined. Zhang et al.[29,30] used an ROC analysis to investigate the minimal number of lymph nodes for evaluating the N stage and found that regional lymphadenectomy of at least 8 lymph nodes was necessary to accurately stage patients. By using a similar method, our study found that TNLE 8 showed the highest discriminatory power for evaluating lymph node metastasis (AUC: 0.656, \( P = .003 \)). We successfully
concluded that the minimal TNLE to evaluate the N stage is at least 8 lymph nodes of resected pancreatic SRCC. Furthermore, our study demonstrated that the minimum TNLE was at least 8, which indicates that once the threshold is crossed, the LNR was not only able to distinguish the survival difference of patients with resected pancreatic SRCC, but also allowed for accurate nodal staging. We believe that a sufficient number of lymph nodes examined was necessary for clinicians to accurately predict the significance of the LNR in resected pancreatic SRCC.

In the present study, several limitations should be taken into account. First, our study had a small sample size and was retrospective. Thus, our conclusions could be further proven with more prospective, randomized, and standard studies. In addition, the SEER database only provides information on whether radiotherapy and chemotherapy were performed, without mention of any data relating to aim (palliative or curative), doses, and schemes. These incomplete data limit further research on chemoradiotherapy in pancreatic SRCC. Furthermore, the missing data of surgical margins and stations of lymph node metastasis may seriously affect the number of lymph nodes examined, which could confuse the surgeon on how to use these data.

**Conclusion**

To our knowledge, this is the first study to describe the value of the LNR in resected pancreatic SRCC. Our analysis showed that age, grade, chemotherapy, LNR, and TNLE were risk factors for OS, whereas grade and LNR were independent adverse prognostic factors in patients with pancreatic SRCC. Furthermore, we demonstrated that regional lymphadenectomy of at least 8 lymph nodes is necessary to accurately stage patients, and a sufficient number of lymph nodes examined was necessary for clinicians to accurately predict the significance of the LNR in resected pancreatic SRCC. Our analysis may be helpful to determine the N stage and the decisions of clinicians regarding how to perform regional lymphadenectomy.

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**Author contributions**

Data curation: CR; Methodology: CR, FX, YW; Formal analysis: CR, FX, YW; Writing – original draft: CR; Supervision: ZW; Writing – review and editing: FX, YW, ZW. All authors approved the final manuscript for publication.

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Conflicts of interest
The authors declare no conflicts of interest.

Ethics approval
All the data accessed from the SEER database were freely available. Therefore, this study does not require institutional review board approval for use of the SEER database.

Declaration of participant consent
The authors certify that they have obtained the participant consent forms. In the forms, participants have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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