The prognostic value of lymph node ratio in comparison to positive lymph node count in penile squamous cell carcinoma

Jiajie Yu1 · Qian Long2 · Zhiqiang Zhang1 · Shufen Liao1 · Fufu Zheng1

Received: 20 July 2021 / Accepted: 12 September 2021 / Published online: 28 September 2021
© The Author(s) 2021

Abstract
Purpose Penile cancer is a rare male neoplasm with a wide variation in its global incidence. In this study, the prognostic value of lymph node ratio (LNR) was compared to that of positive lymph node count (PLNC) in penile squamous cell carcinoma.

Methods A total of 249 patients with penile squamous cell carcinoma were enrolled from The Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. The X-tile program was used to calculate the optimal cut-off values of LNR and PLNC that discriminate survival. We used the $\chi^2$ or the Fisher exact probability test to assess the association between clinical-pathological characteristics and LNR or PLNC. Univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors for survival. Spearman correlation analysis was used to determine the correlation between LNR and PLNC.

Results We found that patients with high LNR tended to have advanced N stage, the 7th AJCC stage, and higher pathological grade, while patients with high PLNC had advanced N stage and the 7th AJCC stage. Univariate Cox regression analysis revealed that the N stage, M stage, the 7th AJCC stage, lymph-vascular invasion, LNR, and PLNC were significantly associated with prognosis. Multivariate Cox regression analysis demonstrated that LNR rather than PLNC was an independent prognostic factor for cancer-specific survival. Subgroup analysis of node-positive patients showed that LNR was associated with CSS, while PLNC was not.

Conclusion LNR was a better predictor for long-term prognosis than PLNC in patients with penile squamous cell carcinoma.

Keywords LNR · Positive lymph node count · Penile squamous cell carcinoma · SEER

Introduction
Penile cancer (PC) is a relatively rare disease in developed countries, with approximately 2200 new cases of PC reported in 2020 in the US [1]. However, PC remains a significant public health concern since it has a considerably higher incidence in developing countries [2, 3]. Besides, PC is most common in men aged between 50 and 70 [4]. Pathologically, squamous cell carcinoma (SCC) is the most common type of penile cancer, accounting for approximately 95% of malignant neoplasms of the penis, although other histological types have also been reported [5]. Patients with early-stage PC generally have a favorable prognosis; however, the 5-year cancer-specific survival precipitously declines with lymph node metastasis [6]. Therefore, more effective therapeutic strategies and better prognostic predictors are needed for PSCC patients.

The TNM staging system is one of the most important prognostic factors for survival, associated with tumor (T)/lymph node metastasis (N)/distant metastasis (M) in cancers. Recently, the lymph node ratio (LNR, the ratio of metastatic to total examined lymph nodes) and positive lymph node count (PLNC, the number of metastatic lymph nodes) have been considered as powerful prognostic factors in various tumors [7–12]. However, the prognostic value of LNR versus PLNC in penile squamous cell carcinoma (PSCC) has not been well established.
Therefore, this study aimed to compare the prognostic impact of PLNC versus LNR in PSCC patients.

**Methods**

**Patients and variables**

A total of 249 men diagnosed with PSCC between 2010 and 2015 were retrospectively identified using the SEER*Stat software program. The inclusion criteria was as follows: (1) ICD-O-3 topography code of primary tumor site: C60.0, C60.1, C60.2, C60.8, C60.9; (2) ICD-O-3 histology code of malignant squamous cell carcinoma: 8051, 8052, 8070–8076, 8081, 8083 and 8084; (3) Complete survival time information; (4) Active follow-up; (5) Diagnostic period: 2010–2015. The exclusion criteria were as follows: (1) AJCC stage: Unknown; (2) SEER cause-specific death classification: NA/Unknown; (3) Regional nodes examined: 0–1 OR Unknown; (4) Regional nodes positive: Unknown; (5) Grade: Unknown. The screening process is as presented in Fig. 1.

The following variables were assessed: age, marital status, the 7th AJCC/TNM stages, histology, grade, primary site, lymph-vascular invasion, PLNC, and LNR. The age was grouped by patients’ median age at diagnosis. Detailed information is as shown in Table 1. The endpoints of this study were overall survival (OS) and cancer-specific survival.

**Table 1** Characteristics of patients recruited from SEER

| Characteristic                              | Patients, No. (%) |
|--------------------------------------------|-------------------|
| **Age, y**                                 |                   |
| Median (SD)                                | 62(12.3)          |
| ≤ 62                                       | 126(50.6)         |
| > 62                                       | 123(49.4)         |
| **Marital status**                         |                   |
| Married                                    | 149(59.8)         |
| Single                                     | 52(20.9)          |
| Unknown                                    | 10(4.0)           |
| Divorced/Separated/Widowed                 | 38(15.3)          |
| **T stage**                                |                   |
| T1a, T1b, T1NOS                            | 54(21.6)          |
| T2                                         | 107(43.0)         |
| T3                                         | 83(33.3)          |
| T4                                         | 5(2.0)            |
| **N stage**                                |                   |
| N0                                         | 116(46.6)         |
| N1                                         | 39(15.7)          |
| N2                                         | 37(14.9)          |
| N3                                         | 57(22.9)          |
| **M stage**                                |                   |
| M0                                         | 240(96.4)         |
| M1                                         | 9(3.6)            |
| **The 7th AJCC stage**                     |                   |
| I                                          | 11(4.4)           |
| II                                         | 101(40.6)         |
| IIIA                                       | 36(14.5)          |
| IIIB                                       | 35(14.1)          |
| IV                                         | 66(26.5)          |
| **Histology**                              |                   |
| Verrucous carcinoma                        | 6(2.4)            |
| Papillary squamous cell carcinoma          | 2(0.8)            |
| Squamous cell carcinoma, NOS               | 150(60.2)         |
| Squamous cell carcinoma, keratinizing       | 69(27.7)          |
| Squamous cell carcinoma, large cell, nonkeratinizing | 6(2.4)          |
| Squamous cell carcinoma, spindle cell      | 5(2.0)            |
| Basaloid squamous cell carcinoma           | 11(4.4)           |
| **Grade**                                  |                   |
| I-II                                       | 175(70.3)         |
| III-IV                                     | 74(29.7)          |
| **Primary site**                           |                   |
| Prepuce                                    | 18(7.2)           |
| Glans penis                                | 101(40.6)         |
| Body of penis                              | 16(6.4)           |
| Overlapping lesion of penis                | 14(5.6)           |
| Penis, NOS                                 | 100(40.2)         |

**Fig. 1** Flow diagram indicating patients from the SEER database
survival (CSS), which were determined by vital status and SEER cause-specific death classification, respectively.

**Statistical analysis**

The lymph node ratio was calculated as the ratio of the number of positive lymph nodes to the total number of lymph nodes examined. The optimal cut-off value was determined using the X-tile program. For OS, the optimal cut-off value of LNR was 0.23, with values ≤ 0.23 considered low and values > 0.23 considered high. The optimal cut-off value of PLNC was 3, with values ≤ 3 regarded as low while those > 3 were high. For CSS, the optimal cut-off value of LNR was identical to OS. The optimal cut-off value of PLNC was 1, with PLNC ≤ 1 considered low, and PLNC > 1 high. The χ² test or the Fisher exact probability test was used to assess the association between the clinical-pathological characteristics and LNR or PLNC. Kaplan–Meier method was used to determine the survival analysis and the Log-rank test was used to examine the statistical differences between LNR or PLNC groups in terms of overall survival and cancer-specific survival. Spearman correlation analysis was used to determine the correlation between LNR and PLNC. Cox regression analysis was used to compute the hazard ratios (HRs) and 95% confidence intervals (95%CIs) for the identification of the prognostic factors in the survival of PSCC patients. All statistical analyses were performed using IBM SPSS Statistics 25. P values < 0.05 were considered statistically significant in the χ² test, the Fisher exact probability test, the Log-rank test, and multivariate Cox regression analysis, while P values < 0.1 were considered significant in univariate Cox regression analysis.

**Results**

**Patients’ characteristics**

A total of 249 patients with PSCC were recruited from the SEER database. Of these, 132 (53%) patients were confirmed to have lymph node metastasis, whereas 117 (47%) patients were free of lymph node metastasis. The median follow-up time was 30 months (range of 0–82 months). At the end of the follow-up, 57 (22.9%) patients died from PSCC. The median number of LNR, PLNC, and lymph nodes examined was 0.04 (range of 0.00–1.00), 1 (range of 1–18), and 17 (range of 2–78), respectively. A detailed description of the clinical-pathological characteristics of the enrolled patients is shown in Table 1.

**The relationship between LNR/PLNC and clinical pathological characteristics in patients with PSCC**

We used the χ² test or the Fisher exact probability test to compare the characteristics between the LNR/PLNC groups and clinical-pathological characteristics of PSCC patients. Our results revealed that high LNR patients tended to have advanced N stage (P < 0.001), the 7th AJCC stage (P < 0.001), and higher pathological grade (P = 0.048) while no significant association was found with other characteristics. PLNC was significantly associated with the N stage (P < 0.001) and the 7th AJCC stage (P < 0.001) based on the cut-off value of 1 and 3, while a significant association was observed between the M stage and PLNC grouping based on the cut-off value of 1 (P = 0.010) (Table 2). These findings suggested that both high LNR and PLNC were associated with poor clinical-pathological characteristics in PSCC. Consequently, LNR and PLNC can serve as potential prognostic factors guiding clinical decisions.

**The prognostic value of LNR and PLNC for survival in patients with PSCC**

To further explore the role of LNR and PLNC in predicting the survival of PSCC patients, Kaplan–Meier analysis and the Log-rank test were used to estimate the overall survival and cancer-specific survival based on the LNR and PLNC status. There were significant differences in overall survival analysis between the LNR (Fig. 2A) and PLNC groups (Fig. 2B). Patients with LNR ≤ 0.23 had a significantly higher 5-year overall survival rate than those with LNR > 0.23 (67.5 vs. 27.3%). The 5-year overall survival rate of patients with PLNC ≤ 3 and > 3 were 67.4 and 25.8%, respectively. A similar trend was observed in cancer-specific survival analysis (Fig. 2C and Fig. 2D). The 5-year
Table 2 The relationship between LNR/PLNC and clinical pathological characteristics in PSCC

| Characteristic                | LNR | P value | PLNC | P value | PLNC | P value |
|------------------------------|-----|---------|------|---------|------|---------|
|                              | ≤ 0.23 | > 0.23 |      | ≤ 1     | > 1  |        |
| Age                          |       |         |      |         |      |         |
| ≤ 62                         | 113 (89.7%) | 13 (10.3%) | 2.409 | 81 (64.3%) | 45 (35.7%) | 0.067 | 0.795 |
| > 62                         | 102 (82.9%) | 21 (17.1%) |      | 81 (65.9%) | 42 (34.1%) |      |      |
| Marital status               |       |         |      |         |      |         |
| Married                      | 125 (83.9%) | 24 (16.1%) | 0.498 | 96 (64.4%) | 53 (35.6%) | 0.299 | 0.795 |
| Single                       | 47 (90.4%) | 5 (9.6%) |      | 35 (67.3%) | 17 (32.7%) |      |      |
| Unknown                      | 10 (100.0%) | 0 (0.0%) |      | 9 (90.0%) | 1 (10.0%) |      |      |
| Divorced/Separated/Widowed   | 33 (86.8%) | 5 (13.2%) |      | 22 (57.9%) | 16 (42.1%) |      |      |
| T stage                      |       |         |      |         |      |         |
| T1a, T1b, T1NOS              | 49 (90.7%) | 5 (9.3%) |      | 38 (70.4%) | 16 (29.6%) | 0.263 | 0.795 |
| T2                           | 94 (87.9%) | 13 (12.1%) |      | 73 (68.2%) | 34 (31.8%) |      |      |
| T3                           | 67 (80.7%) | 16 (19.3%) |      | 47 (56.6%) | 36 (43.4%) |      |      |
| T4                           | 5 (100.0%) | 0 (0.0%) |      | 4 (80.0%) | 1 (20.0%) |      |      |
| N stage                      |       |         |      |         |      |         |
| N0                           | 116 (100.0%) | 0 (0.0%) |      | 116 (100.0%) | 0 (0.0%) | 179.292 | 0.001* |
| N1                           | 33 (84.6%) | 6 (15.4%) |      | 33 (84.6%) | 6 (15.4%) |      |      |
| N2                           | 29 (78.4%) | 8 (21.6%) |      | 2 (5.4%) | 35 (94.6%) |      |      |
| N3                           | 37 (64.9%) | 20 (35.1%) |      | 11 (19.3%) | 46 (80.7%) |      |      |
| M stage                      |       |         |      |         |      |         |
| M0                           | 209 (87.1%) | 31 (12.9%) |      | 160 (66.7%) | 80 (33.3%) | 0.010* | 0.795 |
| M1                           | 6 (66.7%) | 3 (33.3%) |      | 2 (22.2%) | 7 (77.8%) |      |      |
| The 7th AJCC stage           |       |         |      |         |      |         |
| I                             | 11 (100.0%) | 0 (0.0%) |      | 11 (100.0%) | 0 (0.0%) | 11 (100.0%) | 0 (0.0%) | 0.001* |
| II                            | 101 (100.0%) | 0 (0.0%) |      | 101 (100.0%) | 0 (0.0%) |      |      |
| IIIA                          | 31 (86.1%) | 5 (13.9%) |      | 31 (86.1%) | 5 (13.9%) |      |      |
| IIIB                          | 27 (77.1%) | 8 (22.9%) |      | 2 (5.7%) | 33 (94.3%) |      |      |
| IV                            | 45 (68.2%) | 21 (31.8%) |      | 17 (25.8%) | 49 (74.2%) |      |      |
| Characteristic                                      | LNR     | \( \chi^2 \) | \( P \) value | PLNC    | \( \chi^2 \) | \( P \) value | PLNC    | \( \chi^2 \) | \( P \) value |
|---------------------------------------------------|---------|---------------|----------------|---------|---------------|----------------|---------|---------------|----------------|
|                                                   | \( \leq 0.23 \) | > 0.23 |                  | \( \leq 1 \) | > 1            |                  | \( \leq 3 \) | > 3            |                  |
| Histology                                         |         |               |                 |         |               |                 |         |               |                 |
| Verrucous carcinoma                                | 6 (100.0%) | 0 (0.0%) | 0.330           | 6 (100.0%) | 0 (0.0%) | 0.078           | 6 (100.0%) | 0 (0.0%) | 0.332          |
| Papillary squamous cell carcinoma                  | 1 (50.0%) | 1 (50.0%) |                 | 1 (50.0%) | 1 (50.0%) |                 | 1 (50.0%) | 1 (50.0%) |                 |
| Squamous cell carcinoma, NOS                       | 131 (87.3%) | 19 (12.7%) |                 | 93 (62.0%) | 57 (38.0%) | 130 (86.7%) | 20 (13.3%) |                 |                 |
| Squamous cell carcinoma, keratinizing              | 57 (82.6%) | 12 (17.4%) |                 | 47 (68.1%) | 22 (31.9%) | 56 (81.2%) | 13 (18.8%) |                 |                 |
| Squamous cell carcinoma, large cell, nonkeratinizing | 5 (83.3%) | 1 (16.7%) |                 | 2 (33.3%) | 4 (66.7%) | 5 (83.3%) | 1 (16.7%) |                 |                 |
| Squamous cell carcinoma, spindle cell              | 4 (80.0%) | 1 (20.0%) |                 | 3 (60.0%) | 2 (40.0%) |                 | 5 (100.0%) | 0 (0.0%) |                 |
| Basaloid squamous cell carcinoma                   | 11 (100.0%) | 0 (0.0%) |                 | 10 (90.9%) | 1 (9.1%) |                 | 11 (100.0%) | 0 (0.0%) |                 |
| Grade                                             |         |               |                 |         |               |                 |         |               |                 |
| I-II                                              | 156 (89.1%) | 19 (10.9%) | 3.909           | 120 (68.6%) | 55 (31.4%) | 3.194           | 149 (85.1%) | 26 (14.9%) | 0.313           | 0.576          |
| III-IV                                            | 59 (79.7%) | 15 (20.3%) |                 | 42 (56.8%) | 32 (43.2%) |                 | 65 (87.8%) | 9 (12.2%) |                 |                 |
| Primary site                                       |         |               |                 |         |               |                 |         |               |                 |
| Prepuce                                           | 16 (88.9%) | 2 (11.1%) | 0.606           | 10 (55.6%) | 8 (44.4%) | 0.635           | 16 (88.9%) | 2 (11.1%) | 0.451           |                 |
| Glans penis                                       | 83 (82.2%) | 18 (17.8%) |                 | 63 (62.4%) | 38 (37.6%) | 83 (82.2%) | 18 (17.8%) |                 |                 |
| Body of penis                                      | 14 (87.5%) | 2 (12.5%) |                 | 10 (62.5%) | 6 (37.5%) | 15 (93.8%) | 1 (6.3%) |                 |                 |
| Overlapping lesion of penis                       | 12 (85.7%) | 2 (14.3%) |                 | 11 (78.6%) | 3 (21.4%) | 14 (100.0%) | 0 (0.0%) |                 |                 |
| Penis, NOS                                         | 90 (90.0%) | 10 (10.0%) |                 | 68 (68.0%) | 32 (32.0%) | 86 (86.0%) | 14 (14.0%) |                 |                 |
| Lymph-vascular invasion                            |         |               |                 |         |               |                 |         |               |                 |
| Unknown                                           | 28 (80.0%) | 7 (20.0%) | 0.123           | 24 (68.6%) | 11 (31.4%) | 5.278           | 32 (91.4%) | 3 (8.6%) | 0.462           |                 |
| Negative                                          | 121 (90.3%) | 13 (9.7%) |                 | 94 (70.1%) | 40 (29.9%) | 116 (86.6%) | 18 (13.4%) |                 |                 |
| Positive                                          | 66 (82.5%) | 14 (17.5%) |                 | 44 (55.0%) | 36 (45.0%) | 56 (82.5%) | 14 (17.5%) |                 |                 |

LNR lymph node ratio, PLNC positive lymph node count
*Two-sided \( P \) value < 0.05
The cancer-specific survival rate of patients with LNR ≤ 0.23 was higher than LNR > 0.23 (76.9 vs. 36.4%), whereas the 5-year cancer-specific survival rate of patients with PLNC ≤ 1 and > 1 were 81.7 and 51.1%, respectively. Even for the P values < 0.001, the χ² values of LNR were higher than PLNC, indicating that LNR may be a more promising prognostic factor for PSCC patients.

Considering that the lymph nodes harvested from lymphadenectomy comprise positive and negative lymph nodes, PLNC is theoretically correlated with LNR. Thus, we analyzed the correlation between LNR and PLNC by performing a Spearman correlation analysis. The results (rs = 0.926, P < 0.001) suggested that LNR and PLNC were significantly correlated (Fig. 3).

Next, univariate and multivariate Cox regression analyses were performed to investigate the independent prognostic factors influencing overall survival and cancer-specific survival. N stage, M stage, the 7th AJCC stage, lymph-vascular invasion, LNR, and PLNC (all P < 0.1) were found to have a significant impact on both overall survival and cancer-specific survival while age and T stage (both P < 0.1) only influenced overall survival (Table 3). Interestingly, no prognostic significance of pathological grade in PSCC was found, which was inconsistent with our general cognition of malignant tumors. A possible reason for this inconsistency is the limited sample size, hence the lack of adequate representation of the population.

Multivariate Cox regression models for survival were used to compare the effects of LNR and PLNC. Considering that the 7th AJCC stage contains information on the N stage and M stage, several multivariate Cox regression models incorporating lymph-vascular invasion, the 7th AJCC stage, and LNR/PLNC were constructed (Table 4). We found that LNR (Model 1: HR = 2.788, 95% CI = (1.638, 4.745), P < 0.001; Model 2: HR = 3.122, 95% CI = (1.725, 5.651), P < 0.001) and lymph-vascular invasion (Positive vs Unknown: Model 1: HR = 3.023, 95% CI = (1.340, 6.817), P = 0.008; Model 2: HR = 2.721, 95% CI = (1.031, 7.183), P = 0.043) were independent prognostic factors for both overall survival and cancer-specific survival in both Model 1 and 2. Patients with LNR > 0.23 had a 3.122 fold higher probability of dying from PSCC than patients with LNR ≤ 0.23. Surprisingly, the 7th AJCC stage did not correlate with either overall survival or cancer-specific survival in both models. In Model 3, PLNC (HR = 2.298, 95% CI = (1.332,
3.963), \( P = 0.003 \) and lymph-vascular invasion (Positive vs Unknown: \( HR = 2.731, 95\% \text{ CI} = (1.208, 6.177), P = 0.016 \)) were associated with overall survival, while the 7th AJCC stage was found to have no prognostic significance. However, all the three variables included in Model 4 exhibited no prognostic significance for cancer-specific survival. Therefore, LNR was found to be a more reliable prognostic factor for PSCC.

Although the superior prognostic value of LNR over PLNC was demonstrated, it was highly unlikely that patients with similar LNR/PLNC distributed on both sides of the cut-off value exhibited significantly different survival rate. The prognostic value of LNR and PLNC was further validated in univariate Cox regression analysis as continuous variables. Both LNR (continuous; For overall survival: \( HR = 22.315, 95\% \text{ CI} = (9.865, 50.474), P < 0.001 \); For cancer-specific survival: \( HR = 28.274, 95\% \text{ CI} = (11.329, 70.565), P < 0.001 \)) and PLNC (continuous; For overall survival: \( HR = 1.165, 95\% \text{ CI} = (1.109, 1.224), P < 0.001 \); For cancer-specific survival: \( HR = 1.187, 95\% \text{ CI} = (1.126, 1.251), P < 0.001 \)) exhibited influence on survival (Table 3). In multivariate Cox regression analysis, LNR (continuous; For overall survival: \( HR = 22.538, 95\% \text{ CI} = (7.818, 64.971), P < 0.001 \); For cancer-specific survival: \( HR = 24.255, 95\% \text{ CI} = (7.194, 81.778), P < 0.001 \)) and PLNC (continuous; For overall survival: \( HR = 1.133, 95\% \text{ CI} = (1.055, 1.216), P = 0.001 \); For cancer-specific survival: \( HR = 1.133, 95\% \text{ CI} = (1.050, 1.224), P = 0.001 \)) were found to be significantly associated with overall survival and cancer-specific survival (Table 4).

Subgroup and survival analysis in node-positive patients

Subgroup analysis was carried out to assess the association between clinical factors and survival in 132 patients with positive lymph nodes (Tables 5 and 6). Univariate analysis revealed that the N stage, M stage, the 7th AJCC stage, lymph-vascular invasion, LNR, and PLNC (all \( P < 0.1 \)) were associated with both overall survival and cancer-specific survival whereas age and T stage (both \( P < 0.1 \)) were only associated with overall survival. Multivariate analysis demonstrated that, LNR was an independent prognostic factor for both overall survival and cancer-specific survival (Model 1: \( HR = 2.612, 95\% \text{ CI} = (1.529, 4.461), P < 0.001 \); Model 2: \( HR = 2.994, 95\% \text{ CI} = (1.647, 5.440), P < 0.001 \)) while PLNC (Model 4: \( HR = 1.447, 95\% \text{ CI} = (0.645, 3.248), P = 0.370 \)) was not significantly associated with cancer-specific survival. These results suggested that LNR exhibited better prognostic value compared with PLNC in node-positive patients.

However, the absence of the 7th AJCC stage in all multivariate Cox proportional hazards regression models indicated that there were defects in our models. Large-scale analysis of complete and representative patients’ information is needed for the calibration of the Cox regression model. In conclusion, LNR exhibited a better prognostic prediction than PLNC and could thus, serve as a promising prognostic factor in PSCC.
Table 3  Univariate Cox regression analysis of overall survival and cancer-specific survival in PSCC

| Variables                                      | Overall survival | Cancer-specific survival |
|------------------------------------------------|------------------|-------------------------|
|                                                 | HR 95%CI         | $P$ value               | HR 95%CI         | $P$ value               |
| Age                                            |                  |                         |                  |                         |
| $> 62 \text{ vs } \leq 62$                      | 1.548 (0.989, 2.422) | 0.056*                  | 1.134 (0.674, 1.908) | 0.635                  |
| Marital status                                 |                  |                         |                  |                         |
| Single vs married                              | 1.333 (0.772, 2.301) | 0.302                  | 1.367 (0.733, 2.549) | 0.325                  |
| Unknown vs married                             | 0.530 (0.128, 2.186) | 0.380                  | 0.38 (0.052, 2.777) | 0.34                   |
| Divorced/separated/widowed vs married          | 1.314 (0.722, 2.394) | 0.372                  | 0.987 (0.457, 2.132) | 0.973                  |
| T stage                                        |                  |                         |                  |                         |
| T2 vs T1a, T1b, T1NOS                          | 1.243 (0.652, 2.371) | 0.509                  | 1.234 (0.593, 2.570) | 0.574                  |
| T3 vs T1a, T1b, T1NOS                          | 1.803 (0.953, 3.409) | 0.070 *                | 1.492 (0.706, 3.152) | 0.294                  |
| T4 vs T1a, T1b, T1NOS                          | 0.000 (0.000, 2.993*10^{-15}) | 0.964              | 0.000 (0.000, 1.018*10^{-26}) | 0.970                  |
| N stage                                        |                  |                         |                  |                         |
| N1 vs N0                                       | 2.067 (1.028, 4.157) | 0.042                  | 3.599 (1.462, 8.858) | 0.005                  |
| N2 vs N0                                       | 3.045 (1.531, 6.058) | 0.002                  | 5.051 (2.089, 12.215) | <0.001                 |
| N3 vs N0                                       | 4.751 (2.712, 8.323) | <0.001*                | 8.337 (3.912, 17.771) | <0.001*                |
| M stage                                        |                  |                         |                  |                         |
| M1 vs M0                                       | 8.254 (3.848, 17.705) | <0.001*                | 9.749 (4.266, 22.280) | <0.001*                |
| The 7th AJCC stage                             |                  |                         |                  |                         |
| II vs I                                        | 1.517 (0.203, 11.339) | 0.685                  | 0.670 (0.084, 5.355) | 0.705                  |
| IIIA vs I                                      | 2.297 (0.294, 17.969) | 0.428                  | 1.722 (0.212, 13.997) | 0.611                  |
| IIIB vs I                                      | 4.024 (0.526, 30.771) | 0.180                  | 3.122 (0.399, 24.403) | 0.278                  |
| IV vs I                                        | 6.199 (0.850, 45.216) | 0.072 *                | 5.409 (0.738, 39.641) | 0.097*                  |
| Histology                                      |                  |                         |                  |                         |
| Papillary squamous cell carcinoma vs Verrucous carcinoma | 13130.765 (0.000, 4.438*10^{32}) | 0.868              | 18317.704 (0.000, 2.438*10^{32}) | 0.886                  |
| Squamous cell carcinoma, NOS vs Verrucous carcinoma | 8664.636 (0.000, 2.880*10^{32}) | 0.874              | 8959.453 (0.000, 1.176*10^{32}) | 0.894                  |
| Squamous cell carcinoma, keratinizing, NOS vs Verrucous carcinoma | 9033.025 (0.000, 3.003*10^{32}) | 0.873              | 9244.140 (0.000, 1.214*10^{32}) | 0.894                  |
| Squamous cell carcinoma, large cell, nonkeratinizing, NOS vs Verrucous carcinoma | 13985.463 (0.000, 4.673*10^{32}) | 0.867              | 19733.170 (0.000, 2.601*10^{32}) | 0.885                  |
| Squamous cell carcinoma, spindle cell vs Verrucous carcinoma | 10528.488 (0.000, 3.528*10^{32}) | 0.871              | 7593.573 (0.000, 1.011*10^{32}) | 0.896                  |
| Basaloid squamous cell carcinoma vs Verrucous carcinoma | 3896.977 (0.000, 1.306*10^{32}) | 0.885              | 2927.710 (0.000, 3.896*10^{32}) | 0.907                  |
| Grade                                          |                  |                         |                  |                         |
| III–IV vs I–II                                 | 1.165 (0.726, 1.872) | 0.527                  | 1.201 (0.687, 2.100) | 0.522                  |
| Primary site                                   |                  |                         |                  |                         |
| Glans penis vs prepuce                         | 1.221 (0.477, 3.127) | 0.678                  | 1.691 (0.513, 5.579) | 0.388                  |
| Body of penis vs prepuce                       | 1.228 (0.371, 4.058) | 0.737                  | 1.544 (0.345, 6.905) | 0.57                   |
| Overlapping lesion of penis vs prepuce         | 0.462 (0.090, 2.383) | 0.356                  | 0.774 (0.129, 4.635) | 0.779                  |
| Penis, NOS vs prepuce                          | 1.205 (0.470, 3.089) | 0.698                  | 1.322 (0.394, 4.436) | 0.651                  |
| Lymph-vascular invasion                        |                  |                         |                  |                         |
| Negative vs unknown                            | 1.418 (0.630, 3.194) | 0.399                  | 1.570 (0.606, 4.068) | 0.353                  |
| Positive vs unknown                            | 3.028 (1.350, 6.792) | 0.007*                 | 2.697 (1.028, 7.078) | 0.044*                  |
| LNR                                            |                  |                         |                  |                         |
| $> 0.23 \text{ vs } \leq 0.23$                 | 4.291 (2.646, 6.959) | <0.001*                | 5.351 (3.091, 9.262) | <0.001*                 |
| PLNC                                           |                  |                         |                  |                         |
| $> 1 \text{ vs } \leq 1$                       | 4.365 (2.538, 7.504) | <0.001*                |                     | <0.001*                 |
| $> 3 \text{ vs } \leq 3$                       | 3.914 (2.425, 6.318) | <0.001*                |                     | <0.001*                 |
| PLNC(continuous)                               | 22.315 (9.865, 50.474) | <0.001*               | 28.274 (11.329, 70.565) | <0.001*                |
| PLNC(continuous)                               | 1.165 (1.109, 1.224) | <0.001*                | 1.187 (1.126, 1.251) | <0.001*                 |

CI confidence interval, LNR lymph node ratio, PLNC positive lymph node count
*Two-sided $P$ value < 0.1
Table 4 Multivariate Cox regression analysis of overall survival and cancer-specific survival in PSCC

| Variables                                      | Overall survival | Cancer-specific survival |
|------------------------------------------------|-----------------|-------------------------|
|                                                | HR, 95%CI, P     | HR, 95%CI, P            |
| Model 1                                        |                 |                         |
| LNR                                             |                 |                         |
| >0.23 vs ≤0.23                                 | 2.788, (1.638, 4.745) <0.001* | 3.122, (1.725, 5.651) <0.001* |
| Lymph-vascular invasion                        |                 |                         |
| Negative vs unknown                            | 1.746, (0.764, 3.989) 0.186 | 2.094, (0.794, 5.524) 0.135 |
| Positive vs unknown                            | 3.023, (1.340, 6.817) 0.008* | 2.721, (1.031, 7.183) 0.043* |
| Model 2                                        |                 |                         |
| The 7th AJCC stage                             |                 |                         |
| II vs I                                        | 1.325, (0.175, 10.026) 0.785 | 0.663, (0.082, 5.362) 0.700 |
| IIIA vs I                                      | 1.776, (0.222, 14.236) 0.589 | 1.518, (0.182, 12.694) 0.700 |
| IIIB vs I                                      | 2.548, (0.326, 19.883) 0.372 | 2.100, (0.262, 16.829) 0.485 |
| IV vs I                                        | 3.846, (0.513, 28.859) 0.190 | 3.780, (0.499, 28.634) 0.198 |
| Model 3                                        |                 |                         |
| PLNC                                           |                 |                         |
| >3 vs ≤3                                       | 2.298, (1.332, 3.963) 0.003* |                         |
| Lymph-vascular invasion                        |                 |                         |
| Negative vs unknown                            | 1.467, (0.643, 3.345) 0.362 |                         |
| Positive vs unknown                            | 2.731, (1.208, 6.177) 0.016* |                         |
| Model 4                                        |                 |                         |
| The 7th AJCC stage                             |                 |                         |
| II vs I                                        | 1.275, (0.168, 9.650) 0.814 |                         |
| IIIA vs I                                      | 1.907, (0.238, 15.266) 0.543 |                         |
| IIIB vs I                                      | 2.391, (0.303, 18.847) 0.408 |                         |
| IV vs I                                        | 3.699, (0.490, 27.894) 0.204 |                         |
| Model 5                                        |                 |                         |
| PLNC                                           |                 |                         |
| >1 vs ≤1                                       | 1.859, (0.837, 4.130) 0.128 |                         |
| Lymph-vascular invasion                        |                 |                         |
| Negative vs unknown                            | 1.719, (0.656, 4.501) 0.270 |                         |
| Positive vs unknown                            | 2.419, (0.915, 6.396) 0.075 |                         |
| Model 7                                        |                 |                         |
| The 7th AJCC stage                             |                 |                         |
| II vs I                                        | 0.636, (0.079, 5.147) 0.671 |                         |
| IIIA vs I                                      | 1.578, (0.189, 13.165) 0.673 |                         |
| IIIB vs I                                      | 1.637, (0.181, 14.832) 0.661 |                         |
| IV vs I                                        | 3.175, (0.386, 26.105) 0.283 |                         |
| Model 6                                        |                 |                         |
| LNR(continuous)                                | 22.538, (7.818, 64.971) <0.001* | 24.255, (7.194, 81.778) <0.001* |
| Lymph-vascular invasion                        |                 |                         |
| Negative vs unknown                            | 2.340, (0.988, 5.542) 0.053 | 2.943, (1.054, 8.214) 0.039 |
| Positive vs unknown                            | 4.044, (1.743, 9.379) 0.001* | 3.861, (1.399, 10.652) 0.009* |
| Model 8                                        |                 |                         |
| The 7th AJCC stage                             |                 |                         |
| II vs I                                        | 1.338, (0.177, 10.125) 0.778 | 0.671, (0.083, 5.431) 0.709 |
| IIIA vs I                                      | 1.313, (0.163, 10.612) 0.798 | 1.140, (0.135, 9.610) 0.904 |
| IIIB vs I                                      | 1.788, (0.227, 14.060) 0.581 | 1.473, (0.181, 11.962) 0.717 |
| IV vs I                                        | 2.990, (0.396, 22.571) 0.288 | 3.062, (0.402, 23.324) 0.280 |
| PLNC(continuous)                               | 1.133, (1.055, 1.216) 0.001* | 1.133, (1.050, 1.224) 0.001* |
| Lymph-vascular invasion                        |                 |                         |
| Negative vs unknown                            | 1.417, (0.620, 3.240) 0.409 | 1.563, (0.592, 4.123) 0.367 |
| Positive vs unknown                            | 2.824, (1.249, 6.384) 0.013* | 2.442, (0.924, 6.458) 0.072 |
| Model 9                                        |                 |                         |
| The 7th AJCC stage                             |                 |                         |
| II vs I                                        | 1.230, (0.162, 9.324) 0.841 | 0.607, (0.075, 4.924) 0.640 |
| IIIA vs I                                      | 1.604, (0.199, 12.913) 0.657 | 1.377, (0.164, 11.561) 0.768 |
| IIIB vs I                                      | 1.823, (0.224, 14.834) 0.575 | 1.544, (0.183, 13.019) 0.690 |
| IV vs I                                        | 3.200, (0.421, 24.318) 0.261 | 3.142, (0.408, 24.204) 0.272 |
LNR (≤ 6.7 vs. > 6.7%) was significantly associated with 45 patients between 1979 and 2007 and reported that not been well elucidated. Svatek et al. conducted a survey between LNR/PLNC and survival in patients with PSCC has variety of tumors, including salivary gland cancer [20], prostate cancer [21], non-small cell lung cancer [22, 23], breast cancer [24], and colon cancer [25]. To date, the association between LNR/PLNC and survival in patients with PSCC has not been well elucidated. Svatek et al. conducted a survey with 45 patients between 1979 and 2007 and reported that LNR (≤ 6.7 vs. > 6.7%) was significantly associated with CSS in patients with node-positive PSCC [26]. However, the small population and excessively long period limited the validity of the findings. Similarly, Lughezzani et al. observed significant differences in survival rates based on LNR [27]. The highlighted studies stratified survival outcomes using the median value, which is not very rigorous in determining the threshold. Besides, both studies did not compare the prognostic value of LNR and PLNC.

A recent study proposed that LNR was a better prognostic indicator compared to PLNC [28], however, the study population comprised only 28 penile cancer patients. Another study suggested that LNR, but not PLNC was a predictor of dismal survival outcomes in node-positive PSCC [29]. However, the study simultaneously added LNR and PLNC into the multivariate Cox regression model, which led to multicollinearity.

Compared with previous studies, the present study had a relatively large sample size, thus making it more applicable in clinical practice. Furthermore, there is still a considerable discrepancy in the threshold of LNR to discriminate between favorable and poor survival in prior studies, ranging between 0.067 and 0.33 [26–30]. This discrepancy may be explained by the use of varied surgical approaches, the extent of lymph node dissection, and the use of different statistical methods to calculate the optimal cut-off values. Unlike in previous studies where stratification of patients was done using the median, the optimal cut-off values for LNR/PLNC were determined using the X-tile program in this study. The optimal cut-off points were 0.23 for LNR (for both OS and CSS) and 3 (for OS)/1 (for CSS) for PLNC. When considered as categorical variables in both univariate and multivariate Cox regression analyses, LNR > 0.23 predicted worse survival outcomes compared with LNR ≤ 0.23 in patients with penile cancer. However, PLNC did not exhibit prognostic value in multivariate model predicting CSS. Thus, LNR was found to be a better prognostic factor for PSCC. Surprisingly, when converted to continuous variables, both LNR and PLNC were found to be independent prognostic factors of poor survival in penile cancer. The varying prognostic value exhibited by PLNC may be attributed to the loss of information contained in the raw data when converted to a categorical variable. However, a definite threshold is required by clinicians assessing prognosis in clinical practice. Therefore, investigating the prognostic value of LNR and PLNC as categorical variables makes it easier for clinical decision-making. Considering that heterogeneity may exist in patients with and without lymph node metastasis, subgroup analysis was performed in node-positive patients. LNR (P < 0.001) was found to be a better prognostic marker than PLNC (P = 0.370) for CSS. Accordingly, LNR was found to be a better predictor for survival than PLNC in patients with PSCC, and could also be used to distinguish between postoperative PSCC patients with poor prognosis requiring adjuvant therapy. The optimal cut-off value of 0.23 for LNR may not be directly used in clinical practice, and further consideration in combination with clinical information is needed.

The prognostic value of PLNC depends to a great extent on surgical and pathological procedures. In conditions of inadequate lymph node dissection, this can lead to the phenomenon of “stage migration” [31]. The superior prognostic value of LNR can be explained by the incorporation of disease burden and quality pathologic examination (PLNC), and the extent of lymphadenectomy (the number of examined nodes), which would reduce bias due to insufficient lymph node evaluation [32, 33]. Thus, in the case of sufficient lymph node retrieval, the prognostic value of LNR may

### Table 4 (continued)

| Table 4 | CI confidence interval, LNR lymph node ratio, PLNC positive lymph node count |
|---------|--------------------------------------------------------------------------------|
| *Two-sided P value < 0.05* | **Note** |

### Discussion

Penile cancer is a relatively rare disease worldwide, it accounts for only 1% of all male malignancies, but causes considerable psychological and physiological trauma [1]. Squamous cell carcinoma is the most common histological type of penile cancer, with approximately 80% of cases localized in the glans penis and prepuce [13]. The diagnosis, treatment, and prognosis of PSCC are greatly correlated with lymph node status. The diagnosis of PSCC is mainly based on physical examination and regional lymph nodes evaluation [14]. Surgical resection with regional lymph node dissection remains the standard therapeutic modality for locally advanced cases [15] and an important prognostic values [16, 17]. However, apart from metastasis, lymphadenopathy may also be caused by infection [18]. Thus, antibiotic treatment can prevent unnecessary lymph node biopsy. Besides, the lymphatic nodal metastasis status is the most significant prognostic factor in patients with penile squamous cell carcinoma [19]. Although men with less severe disease exhibit prolonged survival, the prognosis of advanced or metastatic PSCC remains poor, thus requiring a more robust prognostic index than the traditional AJCC TNM staging system.

LNR and PLNC have exhibited prognostic value in a variety of tumors, including salivary gland cancer [20], prostate cancer [21], non-small cell lung cancer [22, 23], breast cancer [24], and colon cancer [25]. To date, the association between LNR/PLNC and survival in patients with PSCC has not been well elucidated. Svatek et al. conducted a survey with 45 patients between 1979 and 2007 and reported that LNR (≤ 6.7 vs. > 6.7%) was significantly associated with CSS in patients with node-positive PSCC [26]. However, the small population and excessively long period limited the validity of the findings. Similarly, Lughezzani et al. observed significant differences in survival rates based on LNR [27]. The highlighted studies stratified survival outcomes using the median value, which is not very rigorous in determining the threshold. Besides, both studies did not compare the prognostic value of LNR and PLNC.

A recent study proposed that LNR was a better prognostic indicator compared to PLNC [28], however, the study population comprised only 28 penile cancer patients. Another study suggested that LNR, but not PLNC was a predictor of dismal survival outcomes in node-positive PSCC [29]. However, the study simultaneously added LNR and PLNC into the multivariate Cox regression model, which led to multicollinearity.

Compared with previous studies, the present study had a relatively large sample size, thus making it more applicable in clinical practice. Furthermore, there is still a considerable discrepancy in the threshold of LNR to discriminate between favorable and poor survival in prior studies, ranging between 0.067 and 0.33 [26–30]. This discrepancy may be explained by the use of varied surgical approaches, the extent of lymph node dissection, and the use of different statistical methods to calculate the optimal cut-off values. Unlike in previous studies where stratification of patients was done using the median, the optimal cut-off values for LNR/PLNC were determined using the X-tile program in this study. The optimal cut-off points were 0.23 for LNR (for both OS and CSS) and 3 (for OS)/1 (for CSS) for PLNC. When considered as categorical variables in both univariate and multivariate Cox regression analyses, LNR > 0.23 predicted worse survival outcomes compared with LNR ≤ 0.23 in patients with penile cancer. However, PLNC did not exhibit prognostic value in multivariate model predicting CSS. Thus, LNR was found to be a better prognostic factor for PSCC. Surprisingly, when converted to continuous variables, both LNR and PLNC were found to be independent prognostic factors of poor survival in penile cancer. The varying prognostic value exhibited by PLNC may be attributed to the loss of information contained in the raw data when converted to a categorical variable. However, a definite threshold is required by clinicians assessing prognosis in clinical practice. Therefore, investigating the prognostic value of LNR and PLNC as categorical variables makes it easier for clinical decision-making. Considering that heterogeneity may exist in patients with and without lymph node metastasis, subgroup analysis was performed in node-positive patients. LNR (P < 0.001) was found to be a better prognostic marker than PLNC (P = 0.370) for CSS. Accordingly, LNR was found to be a better predictor for survival than PLNC in patients with PSCC, and could also be used to distinguish between postoperative PSCC patients with poor prognosis requiring adjuvant therapy. The optimal cut-off value of 0.23 for LNR may not be directly used in clinical practice, and further consideration in combination with clinical information is needed.

The prognostic value of PLNC depends to a great extent on surgical and pathological procedures. In conditions of inadequate lymph node dissection, this can lead to the phenomenon of “stage migration” [31]. The superior prognostic value of LNR can be explained by the incorporation of disease burden and quality pathologic examination (PLNC), and the extent of lymphadenectomy (the number of examined nodes), which would reduce bias due to insufficient lymph node evaluation [32, 33]. Thus, in the case of sufficient lymph node retrieval, the prognostic value of LNR may

© Springer
Table 5  Univariate Cox regression analysis of overall survival and cancer-specific survival in patients with positive lymph nodes

| Variables                              | Overall survival | Cancer-specific survival |
|----------------------------------------|------------------|-------------------------|
|                                        | HR   | 95%CI       | P     | HR   | 95%CI       | P     |
| Age                                    |      |             |      |      |             |      |
| > 62 vs ≤ 62                           | 1.652 | (0.984, 2.774) | 0.058* | 1.223 | (0.694, 2.155) | 0.487 |
| Marital status                         |      |             |      |      |             |      |
| Single vs married                      | 1.254 | (0.673, 2.336) | 0.476 | 1.258 | (0.642, 2.468) | 0.504 |
| Unknown vs married                     | 0.331 | (0.045, 2.428) | 0.277 | 0.437 | (0.059, 3.207) | 0.415 |
| Divorced/separated/widowed vs married  | 0.996 | (0.493, 2.012) | 0.990 | 0.717 | (0.298, 1.727) | 0.458 |
| T stage                                |      |             |      |      |             |      |
| T2 vs T1a, T1b, T1NOS                  | 1.364 | (0.610, 3.051) | 0.450 | 1.422 | (0.605, 3.347) | 0.420 |
| T3 vs T1a, T1b, T1NOS                  | 2.257 | (1.030, 4.945) | 0.042* | 1.810 | (0.765, 4.287) | 0.177 |
| T4 vs T1a, T1b, T1NOS                  | <0.001 | (0.000, 2.707*10256) | 0.972 | 0.000 | (0.000, 7.307*10277) | 0.974 |
| N stage                                |      |             |      |      |             |      |
| N2 vs N1                               | 1.361 | (0.637, 2.907) | 0.427 | 1.336 | (0.566, 3.149) | 0.509 |
| N3 vs N1                               | 2.103 | (1.104, 4.004) | 0.024* | 2.193 | (1.060, 4.539) | 0.034* |
| M stage                                |      |             |      |      |             |      |
| M1 vs M0                               | 4.925 | (2.268, 10.695) | <0.001* | 5.274 | (2.292, 12.134) | <0.001* |
| The 7th AJCC stage                     |      |             |      |      |             |      |
| IIIB vs IIIA                           | 1.641 | (0.716, 3.758) | 0.242 | 1.728 | (0.657, 4.548) | 0.268 |
| IV vs IIIA                             | 2.853 | (1.414, 5.755) | 0.003* | 3.338 | (1.466, 7.597) | 0.004* |
| Histology                              |      |             |      |      |             |      |
| Squamous cell carcinoma, NOS vs Papillar squamous cell carcinoma | 0.330 | (0.045, 2.435) | 0.277 | 0.280 | (0.038, 2.084) | 0.214 |
| Squamous cell carcinoma, keratinizing, NOS vs Papillary squamous cell carcinoma | 0.415 | (0.055, 3.123) | 0.393 | 0.333 | (0.044, 2.551) | 0.290 |
| Squamous cell carcinoma, large cell, nonkeratinizing, NOS vs Papillary squamous cell carcinoma | 0.490 | (0.051, 4.746) | 0.538 | 0.513 | (0.053, 4.980) | 0.565 |
| Squamous cell carcinoma, spindle cell vs Papillary squamous cell carcinoma | 0.237 | (0.015, 3.843) | 0.311 | 0.257 | (0.016, 4.163) | 0.339 |
| Basaloid squamous cell carcinoma vs Papillary squamous cell carcinoma | 0.203 | (0.013, 3.275) | 0.261 | 0.213 | (0.013, 3.436) | 0.276 |
| Grade                                  |      |             |      |      |             |      |
| Grade III, Grade IV vs Grade I, Grade II | 1.023 | (0.601, 1.741) | 0.934 | 1.062 | (0.587, 1.920) | 0.842 |
| Primary site                           |      |             |      |      |             |      |
| Glans penis vs prepuce                 | 2.164 | (0.656, 7.139) | 0.205 | 2.791 | (0.658, 11.850) | 0.164 |
| Body of penis vs prepuce               | 1.364 | (0.274, 6.777) | 0.704 | 2.152 | (0.359, 12.885) | 0.401 |
| Overlapping lesion of penis vs prepuce | 0.926 | (0.155, 5.543) | 0.933 | 1.409 | (0.198, 10.006) | 0.732 |
| Penis, NOS vs prepuce                  | 1.945 | (0.586, 6.464) | 0.277 | 2.208 | (0.512, 9.517) | 0.288 |
| Lymph-vascular invasion                |      |             |      |      |             |      |
| Negative vs unknown                    | 1.499 | (0.615, 3.656) | 0.373 | 2.126 | (0.738, 6.129) | 0.163 |
| Positive vs unknown                    | 2.665 | (1.105, 6.425) | 0.029* | 2.771 | (0.946, 8.111) | 0.063* |
| LNR                                    |      |             |      |      |             |      |
| > 0.23 vs ≤ 0.23                       | 2.769 | (1.647, 4.656) | <0.001* | 2.988 | (1.678, 5.321) | <0.001* |
| PLNC                                   |      |             |      |      |             |      |
| > 1 vs ≤ 1                             | 1.980 | (1.027, 3.818) | 0.041* |
| > 3 vs ≤ 3                             | 2.476 | (1.472, 4.163) | 0.001* |

CI confidence interval, LNR lymph node ratio, PLNC positive lymph node count

*Two-sided P value < 0.1
decline and PLNC would more precisely reflect the nodal status. In the present study, LNR was found to be a better predictor for long-term survival compared with PLNC in PSCC, thus, reflecting insufficient clinical lymph node dissection. Therefore, standardization of lymphadenectomy is needed in clinical practice.

Despite the advantages of the present study, there were several potential limitations. First, this was a retrospective study based on a public database, and the study population was highly selected, which may result in selection bias. Second, the data obtained from the SEER database involved multiple centers. Thus, standardization of the surgical approach, especially the extent of lymphadenectomy, could not be implemented due to the multicentre nature of the study. Third, several important variables were not included in the SEER database, such as the size of lymph nodes, the region of lymph node metastasis (inguinal/pelvic lymph nodes), extranodal extension, tumor recurrence, and adjuvant therapy. These confounding factors influence survival but could not adjusted in our study. Finally, some common prognostic factors such as T stage and pathological grade were not associated with CSS in this study, possibly because the sample size of some stratified patients was too small.

Conclusion

In summary, we demonstrated that LNR is associated with the long-term survival of postoperative PSCC patients and is a better prognostic marker than PLNC. Besides, LNR can be used to stratify patients for adjuvant therapy in the case of inadequate lymph node dissection.

Acknowledgements We thank the contribution of the SEER database and the 18 registries supplying cancer research information.

Author contributions Conception and design: FZ, JY, QL; administrative support: FZ; provision of study materials or patients: SL; collection and assembly of data: ZZ; data analysis and interpretation: JY,

| Variables | Overall survival | Cancer-specific survival |
|-----------|------------------|--------------------------|
|           | HR 95%CI P       | HR 95%CI P               |
| LNR       |                  |                          |
| > 0.23 vs ≤ 0.23 | 2.612 (1.529, 4.461) <0.001* | 2.994 (1.647, 5.440) <0.001* |
| Lymph-vascular invasion |                  |                          |
| Negative vs unknown | 1.598 (0.641, 3.983) 0.315 | 2.333 (0.790, 6.890) 0.125 |
| Positive vs unknown | 2.440 (0.994, 5.986) 0.051 | 2.545 (0.856, 7.570) 0.093 |
| The 7th AJCC stage |                  |                          |
| IIIB vs IIIA | 1.319 (0.567, 3.069) 0.520 | 1.281 (0.475, 3.449) 0.625 |
| IV vs IIIA | 2.178 (1.060, 4.477) 0.034* | 2.513 (1.083, 5.835) 0.032* |
| PLNC       |                  |                          |
| > 3 vs ≤ 3 | 2.092 (1.2309, 3.620) 0.008* |                  |
| Lymph-vascular invasion |                  |                          |
| Negative vs Unknown | 1.232 (0.497, 3.053) 0.653 |                  |
| Positive vs Unknown | 2.067 (0.841, 5.081) 0.113 |                  |
| The 7th AJCC stage |                  |                          |
| IIIB vs IIIA | 1.189 (0.496, 2.854) 0.698 |                  |
| IV vs IIIA | 2.000 (0.945, 4.233) 0.070 |                  |
| PLNC       |                  |                          |
| > 1 vs ≤ 1 | 1.447 (0.645, 3.248) 0.370 |                  |
| Lymph-vascular invasion |                  |                          |
| Negative vs Unknown | 1.831 (0.628, 5.342) 0.268 |                  |
| Positive vs Unknown | 2.207 (0.745, 6.543) 0.153 |                  |
| The 7th AJCC stage |                  |                          |
| IIIB vs IIIA | 1.182 (0.365, 3.832) 0.780 |                  |
| IV vs IIIA | 2.373 (0.885, 6.366) 0.086 |                  |

CI confidence interval, LNR lymph node ratio, PLNC positive lymph node count
*Two-sided P value < 0.05
1. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70(1):7–30. https://doi.org/10.3322/caac.21590
2. Pow-Sang MR, Ferreira U, Pow-Sang JM, Nardi AC, Destefano V (2010) Epidemiology and natural history of penile cancer. Urol 76(2 Suppl 1):S2-6. https://doi.org/10.1016/j.urology.2010.03.003
3. Christodoulidou M, Sahdev V, Housein S, Muneer A (2015) Epidemiology of penile cancer. Curr Probl Cancer 39(3):126–136. https://doi.org/10.1016/j.currcancerbl.2015.03.010
4. Clark PE, Spiess PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, Inman BA, Kuhan DA, Kuzel TM et al (2013) Penile cancer: clinical practice guidelines in oncology. J Natl Compr Canc Netw 11(5):594–615. https://doi.org/10.6004/jnccn.2013.0075
5. Downes MR (2015) Review of in situ and invasive penile squamous cell carcinoma and associated non-neoplastic dermatological conditions. J Clin Pathol 68(5):333–340. https://doi.org/10.1136/jclinpath-2015-202911
6. Hakenberg OW, Comper EM, Minhas S, Necchi A, Protzel C, Watkin N (2015) EAU guidelines on penile cancer: 2014 update. Eur Urol 67(1):142–150. https://doi.org/10.1016/j.eururo.2014.10.017
7. Deng J, Liang H, Wang D, Sun D, Ding X, Pan Y, Liu X (2010) Enhancement the prediction of postoperative survival in gastric cancer by combining the negative lymph node count with ratio between positive and examined lymph nodes. Ann Surg Oncol 17(4):1043–1051. https://doi.org/10.1245/s10434-009-0863-0
8. Yang J, Long Q, Li H, Lv Q, Tan Q, Yang X (2017) The value of positive lymph nodes ratio combined with negative lymph node count in prediction of breast cancer survival. J Thorac Dis 9(6):1531–1537. https://doi.org/10.21037/jtd.2017.05.30
9. Lowder CY, Metkus J, Epstein J, Kozak GM, Lavu H, Yeo CJ, Winter JM (2018) Clinical implications of extensive lymph node metastases for resected pancreatic cancer. Ann Surg Oncol 25(13):4004–4011. https://doi.org/10.1245/s10434-018-6763-4
10. Bhanvadia RR, RodriguezBagrodia JA, Eggener SE (2019) Lymph node count impacts survival following post-chemotherapy retropertioneal lymphadenectomy for non-seninomatous testicular cancer: a population-based analysis. BJU Int 124(5):792–800. https://doi.org/10.1111/bju.14798
11. Li X, Lin H, Sun Y, Gong J, Feng H, Tu J (2019) Prognostic significance of the lymph node ratio in surgical patients with distal cholangiocarcinoma. J Surg Res 236:2–11. https://doi.org/10.1016/j.sjs.2018.10.044
12. Liu GJ, Li XH, Chen YX, Sun HD, Zhao GM, Hu SY (2013) Radical lymph node dissection and assessment: impact on gallbladder cancer prognosis. World J Gastroenterol 19(31):5150–5158. https://doi.org/10.3748/wjg.v19.i31.5150
13. Chipollini J, Tang DH, Sharma P, Spiess PE (2018) National trends and predictors of organ-sparing for invasive penile tumors: expanding the therapeutic window. Clin Genitourin Cancer 16(2):e383–e389. https://doi.org/10.1016/j.clgc.2017.09.004
14. Marchioni M, Berardinelli F, De Nunzio C, Spiess P, Porpiglia F, Schips L, Cindolo L (2018) New insight in penile cancer. Minerva Urol Nefrol 70(6):559–569. https://doi.org/10.23736/S0393-2249.18.03215-0
15. Peyraud F, Allenet C, Gross-Goupil M, DombliCes L, Lefort F, Daste A, Yacoub M, Haaser T, Ferretti L, Robert G et al (2020) Current management and future perspectives of penile cancer: an updated review. Cancer Treat Rev 90:102087. https://doi.org/10.1016/j.ctrv.2020.102087
16. Cindolo L, Spiess PE, Bada M, Chipollini JJ, Nyirady P, Chiodoni P, Varga J, Ditonno P, Battaglia M, De Nunzio C et al (2019) Adherence to EAU guidelines on penile cancer translates into better outcomes: a multicenter international study. World J Urol 37(8):1649–1657. https://doi.org/10.1007/s00345-018-2549-3
17. Ghahhari J, Marchioni M, Spiess PE, Chipollini JJ, Nyirady P, Varga J, Ditonno P, Boccasile S, Primiceri G, De Nunzio C et al (2020) Radical penectomy, a compromise for life: results from the PEcad study. Transl Androl Urol 9(3):1306–1313. https://doi.org/10.21037/tau.2020.04.04
18. Zheng FF, Liang YY, Guo YS, Dai YP, Zheng KL (2008) Diagnosis and therapy for penile cancer: a report of 46 cases with literature review. Ai zheng = Aizheng = Chin J Cancer 27(9):962–965
19. Srinivas V, Morse MJ, Herr HW, Sogani PC, Whitmore WF (1987) Penile cancer: relation of extent of nodal metastasis to survival. J Urol 137(5):880–881. https://doi.org/10.1016/s0022-5347(17)44281-9
20. Elhusseiny KM, Abd-Elhay FA, Kamel MG, El Hamid A, Hassan HH, El Tanany HHM, Hieu TH, Tieu TM, Low SK, Hou V, Dibas M et al (2019) Examined and positive lymph nodes counts and lymph nodes ratio are associated with survival in major salivary
25. Bui L, Rempel E, Reeson D, Simunovic M (2006) Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. J Surg Oncol 93(6):439–445. https://doi.org/10.1002/jso.20499

26. Svatek RS, Munsell M, Kincaid JM, Hegarty P, Slaton JW, Busby JE, Gaston KE, Spiess PE, Pagliaro LC, Tamboli P et al (2009) Association between lymph node density and disease specific survival in patients with penile cancer. J Urol 182(6):2721–2727. https://doi.org/10.1016/j.juro.2009.08.029

27. Lughezzani G, Catanaro M, Torelli T, Piva L, Biasoni D, Stagni S, Necchi A, Giannatempo P, Raggi D, Fare E et al (2015) Relationship between lymph node ratio and cancer-specific survival in a contemporary series of patients with penile cancer and lymph node metastases. BJU Int 116(5):727–733. https://doi.org/10.1111/bju.12510

28. Ball MW, Schwen ZR, Ko JS, Meyer A, Netto GJ, Burnett AL, Bivalacqua TJ (2017) Lymph node density predicts recurrence and death after inguinal lymph node dissection for penile cancer. Invest Clin Urol 58(1):20–26. https://doi.org/10.4111/icu.2017.58.1.20

29. Zhu Y, Gu CY, Ye DW (2013) Validation of the prognostic value of lymph node ratio in patients with penile squamous cell carcinoma: a population-based study. Int Urol Nephrol 45(5):1263–1271. https://doi.org/10.1007/s11255-013-0502-3

30. Li ZS, Yao K, Chen P, Wang B, Mi QW, Chen JP, Li YH, Deng CZ, Liu ZW, Qin ZK et al (2016) Development of a new classification method for penile squamous cell carcinoma based on lymph node density and standard pathological risk factors: the ND staging system. J Cancer 7(3):262–267. https://doi.org/10.7150/jca.13171

31. Negi SS, Singh A, Chaudhary A (2011) Lymph nodal involvement as prognostic factor in gallbladder cancer: location, count or ratio? J Gastrointest Surg 15(6):1017–1025. https://doi.org/10.1007/s11605-011-1528-4

32. Spillane AJ, Winstanley J, Thompson JF (2009) Lymph node ratio in melanoma: a marker of variation in surgical quality? Cancer 115(11):2384–2387. https://doi.org/10.1002/cncr.24295

33. Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM (2008) 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 15(1):165–174. https://doi.org/10.1245/s10434-007-9587-1

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.