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More lymph node dissection improves survival in patients with newly diagnosed lymph node-positive penile cancer

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Abstract

Purpose For patients with lymph node-positive (LN+) penile cancer, the optimal extent of lymph node dissection (LND) is currently not established. We aimed to reveal the potential association between survival and the number of LND in patients with newly diagnosed LN + penile cancer.

Methods Patients with LN + penile cancer diagnosed between 2004 and 2015 were identified using the SEER database. The relationships between the number of removed lymph nodes and overall survival (OS), all-cause mortality (ACM), cancer-specific mortality (CSM), and 5-year mortality were tested. Kaplan–Meier curves as well as univariate and multivariable cox regression were used to further analyze disparities in mortality and survival.

Results Among 599 eligible patients with LN + penile cancer, 527 (88.0%) received surgery and 72 (12.0%) did not. Compared with those who had not received surgery, patients receiving surgery had longer overall survival (28.31 ± 30.84 versus 16.69 ± 21.68 months) and longer median survival (15.00 versus 8.00 months) times. Univariate analyses demonstrated the number of LND to be an independent factor. Multivariable Cox regression analyses suggested that the ≥ 8 removed lymph nodes predicted a lower ACM rate (hazard ratio (HR) = 0.48, 95% CI 0.38–0.61, $p < 0.001$), penile CSM rate (HR = 0.42, 95% CI 0.30–0.57, $p < 0.001$), and lower 5-year mortality (HR = 0.58, 95% CI 0.47–0.71, $p < 0.001$).

Conclusions In patients with newly diagnosed LN + penile cancer, more LND during lymphadenectomy was associated with an improvement in ACM, CSM rate, and 5-year mortality. Therefore, patients with preoperatively LN + penile cancer should undergo LND to have more lymph nodes removed.

Keywords Penile cancer · Lymph node dissection · Lymph node-positive · Survival benefits · SEER

Abbreviations

LN+	Lymph node-positive
LND	Lymph node dissection
OS	Overall survival
ACM	All-cause mortality
CSM	Cancer-specific mortality
SEER	Surveillance, Epidemiology, and End Results

Introduction

Penile cancer among male is rare and usually occurs in the elderly, its incidence increases with age [1]. In developed Western countries, it accounts for about 0.5% of male malignancies and has a prevalence rate of approximately 1/100,000 males in Europe and the United States [1–3]. However, in some other parts of the World, such as in South America, Africa, and parts of South East Asia, the incidence is significantly higher, accounting for 1–2% of

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malignant diseases in men [4]. Squamous cell carcinoma, the main pathological type of penile cancer, usually arises from the epithelium of the inner prepuce or the glans [5].

Patients with penile cancer without lymphocyte metastasis have a better prognosis, with a 5-year survival rate of about 96% [6], but in patients with lymph node metastasis, the survival rate gradually decreases (5-year penile cancer-specific survival [CSS] pN1 = 79–89%, pN2 = 17–60%, pN3 = 0–17%) [7, 8]. Lymph node involvement is the most important prognostic factor, and the presence of lymph node metastasis is associated with a high mortality rate in patients with penile squamous cell carcinoma [2, 9].

Surgery is the main treatment for penile cancer patients with lymph nodes metastasis. Lymph node dissection (LND) includes inguinal lymphadenectomy and pelvic lymphadenectomy. However, LND is associated with significant morbidity largely due to severe complications [10]. Therefore, accurate preoperative evaluation, including count of dissected nodes, is critical in the selection of surgical patients.

To better guide the scope and extent of LND, we explored the potential correlations between the number of removed lymph nodes in patients with lymph node-positive (LN+) penile cancer and their overall survival (OS), all-cause mortality (ACM), cancer-specific mortality (CSM), and 5-year mortality. Differences in survival outcomes were evaluated for patients who received LND (surgery versus no surgery), as well as in patients who had more lymph nodes removed (≥ 8 versus < 8).

Patients and methods

Data source and patients

A total of 3 983 patients with penile cancer diagnosed between 2004 and 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. SEER*Stat (version 8.3.5) software was used to access the SEER 18 Regs Custom Data (with additional treatment field), Nov 2017 Sub (1973–2015 varying) database using the client–server mode of SEER*Stat. Patients with non-LN+, unknown AJCC stage, unknown T/M stage, or unknown survival time, as well as those diagnosed at autopsy, under 18 years of age or having a non-initial visit to hospital were excluded thus leaving 599 eligible patients diagnosed with penile cancer between January 1, 2004 and December 31, 2015. The national cancer institute's SEER database covers about 30% of the American population and collects information including basic demographics, tumor site, histology, grade, TNM stage, treatment, and survival time from 17 tumor registries [11, 12].

Study variables

Patients with penile cancer were identified in the SEER database based on *International Classification of Diseases for Oncology, Third Edition (ICD-O-3)* site codes. According to whether the patients received surgery, the patients were divided into either a surgery group or a no surgery group. Clinicopathological characteristics including year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2015), age at diagnosis (18–40, 41–60, 61–80, > 80), race (white, black, others), marital status (married, unmarried, unknown), area of diagnosis (West, Northeast, South, Midwest), urban–rural residence (metropolitan, non-metropolitan), and median household income (<$35,000, $35,000–$45,000, $45,001–$55,000, >$55,000) were recorded [13].

Variables about tumor phenotypes including tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, unknown), histology type (squamous cell carcinoma, verrucous carcinoma, others), American Joint Committee on Cancer (AJCC 2nd Edition staging [14]) Cancer Stage (II, III, IV), T stage (T0, T1, T2, T3, T4), N stage (N1, N2, N3), M stage (M0, M1), and tumor size (< 3 cm, ≥ 3 cm, unknown) were recorded. Removal of lymph nodes was treated as a categorical variable, and the numbers of LND were divided into three ranges (< 8 nodes, ≥ 8 nodes, and number of nodes unknown). OS, ACM, and CSM were the primary study end points, and 5-year mortality was also an outcome of interest in this study.

Statistical analysis

Univariate analysis as well as univariate and multivariable cox regression were used to evaluate factors related to ACM, cancer-specific mortality, and 5-year mortality. Kaplan–Meier analyses with log-rank tests were used to analyze the OS and cumulative incidence of penile CSM rate of patients with different treatments or different N stages. Statistical Package for the Social Sciences software (version 20.0; SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. A p value ≤ 0.05 was considered statistically significant.

Results

Surgery of LND is associated with more favorable survival in patients with newly diagnosed LN + penile cancer

A total of 3 983 penile cancer patients were included in the study cohort and 599 patients with newly diagnosed

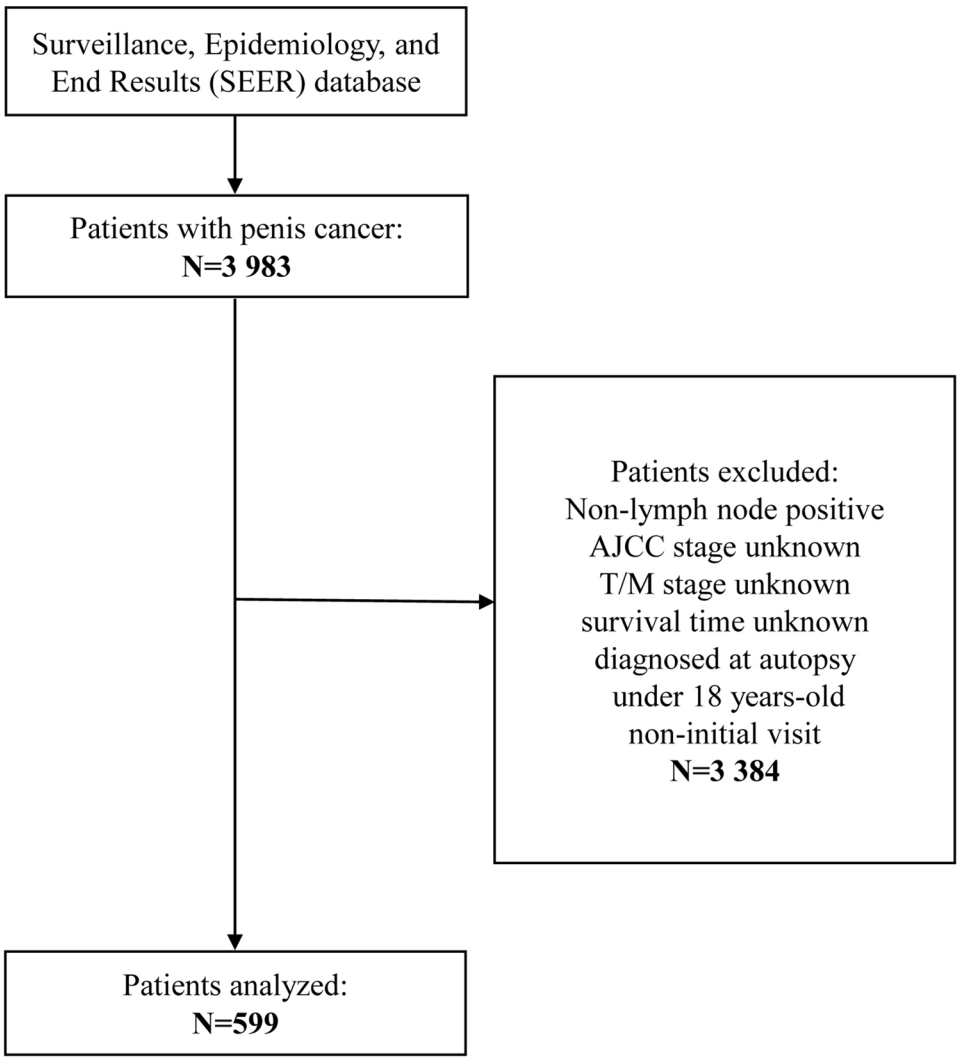

Fig. 1 Flow chart of selection of patients with newly diagnosed LN + penile cancer in this study. A total of 3 983 penile cancer patients were included in the study cohort and 599 patients with newly diagnosed LN + penile cancer were eligible for further evaluation

LN + patients were eligible for further evaluation (Fig. 1). Patients were divided into surgery and no surgery groups according to the availability of surgical treatment, and the variables associated with surgery including the demographic and clinical characteristics were described (Table 1).

The estimated OS of all patients with newly diagnosed LN + penile cancer is shown in Fig. 2a. Among them, 527 (88.0%) patients received surgery, and the use of surgery increased from the years 2004–2006 to 2013–2015 (95 patients [18.0%] versus 169 patients [32.1%]). The OS and cumulative incidence of penis CSM in patients with surgery or no surgery are shown in Fig. 2b. As shown in Table 1, the majority of patients in our cohort were age 61–80 years (49.2%), white (84.1%), married (54.8%), metropolitan (83.1%), diagnosed in the west (54.3%), and with a median household income of ≥$55 000 (55.4%). Furthermore, most of the tumors were AJCC III stage, T2N2M0 moderately differentiated squamous cell carcinoma. For the LN + patients at different N stages, 193 (91.5%) of the 211 patients at N1 stage underwent surgery, while 203 (91.0%) of 223 patients at N2 stage underwent surgery, and 131 (79.4%) of 165 patients at N3 stage underwent surgery.

Patients undergoing surgery at earlier N stage or with ≥ 8 LND have more survival benefits

Of the 527 penile cancer patients who underwent surgery, 299 (56.7%) died of all cause, while 182 (44.4%) died of penile cancer (Table 2). Apart from 31 patients with unknown numbers of removed lymph nodes, the average number of removed lymph nodes was 12.1 (median: 7; interquartile range 0–20). Considering the overall numbers of LND for each individual, 8 was the most informative cut-off value for the number of removed lymph nodes. Our univariate analyses demonstrated that urban–rural residence, median household income, AJCC stage, M stage, tumor size, and removed lymph nodes were associated with ACM, while urban–rural residence, AJCC stage, N stage, M stage, tumor

Table 1 Characteristics for penile cancer patients stratified by surgery or no surgery

Characteristic	Total	Surgery No. (%)	No surgery No. (%)	*p*
Total	599	527 (88.0)	72 (12.0)	
Year of diagnosis				0.085
2004–2006	100 (16.7)	95 (18.0)	5 (6.9)	
2007–2009	139 (23.2)	123 (23.3)	16 (22.2)	
2010–2012	161 (26.9)	140 (26.6)	21 (29.2)	
2013–2015	199 (33.2)	169 (32.1)	30 (41.7)	
Age at diagnosis				0.158
18–40	32 (5.3)	32 (6.1)	0 (0.0)	
41–60	202 (33.7)	175 (33.2)	27 (37.5)	
61–80	295 (49.2)	257 (48.8)	38 (52.8)	
> 80	70 (11.7)	63 (12.0)	7 (9.7)	
Race				0.464
White	504 (84.1)	441 (83.7)	63 (87.5)	
Black	59 (9.8)	52 (9.9)	7 (9.7)	
Other	36 (6.0)	34 (6.5)	2 (2.8)	
Marital status				0.718
Yes	328 (54.8)	288 (54.6)	40 (55.6)	
No	243 (40.6)	213 (40.4)	30 (41.7)	
Unknown	28 (4.7)	26 (4.9)	2 (2.8)	
State				0.067
West	325 (54.3)	295 (56.0)	30 (41.7)	
Northeast	70 (11.7)	60 (11.4)	10 (13.9)	
South	155 (25.9)	128 (24.3)	27 (37.5)	
Midwest	49 (8.2)	44 (8.3)	5 (6.9)	
Urban–rural residence				0.021
Metropolitan	498 (83.1)	445 (84.4)	53 (73.6)	
Non-metropolitan	101 (16.9)	82 (15.6)	19 (26.4)	
Median household income				0.530
1st quartile≤$35,000	45 (7.5)	37 (7.0)	8 (11.1)	
2nd quartile $35,000-$45,000	80 (13.4)	72 (13.7)	8 (11.1)	
3rd quartile $45,000-$55,000	142 (23.7)	123 (23.3)	19 (26.4)	
4th quartile≥$55,000	332 (55.4)	295 (56.0)	37 (51.4)	
Grade				< 0.001
Well differentiated	51 (8.5)	46 (8.7)	5 (6.9)	
Moderately differentiated	265 (44.2)	252 (47.8)	13 (18.1)	
Poorly differentiated	203 (33.9)	181 (34.2)	22 (30.6)	
Undifferentiated	6 (1.0)	6 (1.1)	0 (0.0)	
Unknown	74 (12.4)	42 (8.0)	32 (44.4)	
Histology type				0.050
Squamous cell carcinoma	573 (95.7)	508 (96.4)	65 (90.3)	
Verrucous carcinoma	5 (0.8)	4 (0.8)	1 (1.4)	
Others	21 (3.5)	15 (2.8)	6 (8.3)	
AJCC stage				< 0.001
II	136 (22.7)	125 (23.7)	11 (15.3)	
III	226 (40.1)	226 (42.9)	14 (19.4)	
IV	223 (37.2)	176 (33.4)	47 (65.3)	
T stage				< 0.001
T0	2 (0.3)	0 (0.0)	2 (2.8)	
T1	162 (27.0)	134 (25.4)	28 (38.9)	
T2	207 (34.6)	197 (37.4)	10 (13.9)	
T3	190 (31.7)	176 (33.4)	14 (19.4)	
T4	38 (6.3)	20 (3.8)	18 (25.0)	

Table 1 (continued)

Characteristic	Total	Surgery No. (%)	No surgery No. (%)	*p*
N stage				< 0.001
N1	211 (35.2)	193 (36.6)	18 (25.0)	
N2	223 (37.2)	203 (38.5)	20 (27.8)	
N3	165 (27.5)	131 (24.9)	34 (47.2)	
M stage				0.001
M0	517 (86.3)	464 (88.0)	53 (73.6)	
M1	82 (13.7)	63 (12.0)	19 (26.4)	
Tumor size				< 0.001
< 3 cm	150 (25.0)	140 (26.6)	10 (13.9)	
≥ 3 cm	331 (55.3)	310 (58.8)	21 (29.2)	
Unknown	118 (19.7)	77 (14.6)	41 (56.9)	

AJCC American Joint Committee on Cancer; percentages may not total 100 because of rounding

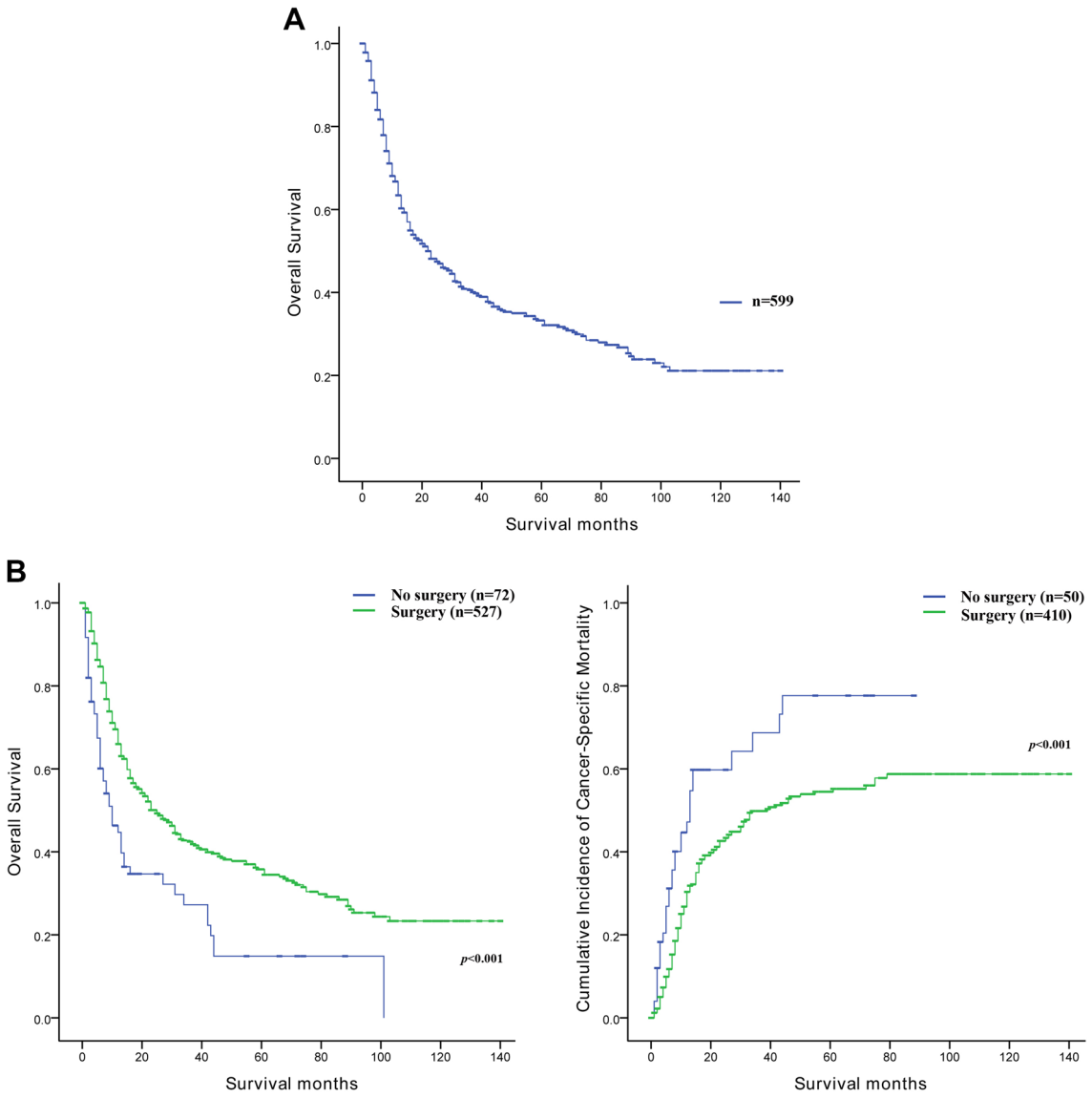

Fig. 2 Surgery of LND is associated with more favorable survival in patients with newly diagnosed LN + penile cancer. **a** The estimated OS of all patients with newly diagnosed LN + penile cancer. **b** The OS and cumulative incidence of penis CSM in patients with surgery or without surgery

Table 2 Univariate survival analyses of penile cancer patients according to various clinicopathological variables

Characteristic	All-cause		*p*	Penile cancer cause		*p*
	Dead	Alive		Dead	Alive	
	No. (%)	No. (%)		No. (%)	No. (%)	
Total	299 (56.7)	228 (43.3)		182 (44.4)	228 (55.6)	
Age at diagnosis			0.558			0.624
18–40	17 (53.1)	15 (46.9)		13 (46.4)	15 (53.6)	
41–60	94 (53.7)	81 (46.3)		66 (44.9)	81 (55.1)	
61–80	148 (57.6)	109 (42.4)		78 (41.7)	109 (47.8)	
> 80	40 (63.5)	23 (36.5)		25 (52.1)	23 (47.9)	
Race			0.449			0.433
White	249 (56.5)	192 (43.5)		151 (44.0)	192 (56.0)	
Black	33 (63.5)	19 (36.5)		21 (52.5)	19 (47.5)	
Other	17 (50.0)	17 (50.0)		10 (37.0)	17 (63.0)	
Marital status			0.295			0.863
Yes	159 (55.2)	129 (44.8)		103 (44.4)	129 (55.6)	
No	128 (60.1)	85 (39.9)		70 (45.2)	85 (54.8)	
Unknown	12 (46.2)	14 (53.8)		9 (39.1)	14 (60.9)	
State			0.948			0.500
West	167 (56.6)	128 (43.4)		114 (47.1)	128 (52.9)	
Northeast	36 (60.0)	24 (40.0)		16 (40.0)	24 (60.0)	
South	72 (56.2)	56 (43.8)		35 (38.5)	56 (61.5)	
Midwest	24 (54.5)	20 (45.5)		17 (45.9)	20 (54.1)	
Urban–rural residence			0.040			0.027
Metropolitan	244 (54.8)	201 (45.2)		146 (42.1)	201 (57.9)	
Non-metropolitan	55 (67.1)	27 (32.9)		36 (57.1)	27 (42.9)	
Median household income			0.046			0.186
1st quartile≤$35,000	29 (78.4)	8 (21.6)		15 (65.2)	8 (34.8)	
2nd quartile $35,000-$45,000	42 (58.3)	30 (41.7)		27 (47.4)	30 (52.6)	
3rd quartile $45,000-$55,000	68 (55.3)	55 (44.7)		39 (41.5)	55 (58.5)	
4th quartile≥$55,000	160 (54.2)	135 (45.8)		101 (42.8)	135 (57.2)	
Grade			0.292			0.479
Well differentiated	31 (67.4)	15 (32.6)		17 (53.1)	15 (46.9)	
Moderately differentiated	132 (52.4)	120 (47.6)		81 (40.3)	120 (59.7)	
Poorly differentiated	108 (59.7)	73 (40.3)		69 (48.6)	73 (51.4)	
Undifferentiated	4 (66.7)	2 (33.3)		2 (50.0)	2 (50.0)	
Unknown	24 (57.1)	18 (42.9)		13 (41.9)	18 (58.1)	
Histology type			0.425			0.581
Squamous cell carcinoma	289 (56.9)	219 (43.1)		178 (44.8)	219 (55.2)	
Verrucous carcinoma	1 (25.0)	3 (75.0)		1 (25.0)	3 (75.0)	
Others	9 (60.0)	6 (40.0)		3 (33.3)	6 (66.7)	
AJCC stage			0.004			0.002
II	61 (48.8)	64 (51.2)		32 (33.3)	64 (66.7)	
III	121 (53.5)	105 (46.5)		76 (42.0)	105 (58.0)	
IV	117 (66.5)	59 (33.5)		74 (55.6)	59 (44.4)	
T stage			0.276			0.197
T1	73 (54.5)	61 (45.5)		42 (40.8)	61 (59.2)	
T2	107 (54.3)	90 (45.7)		61 (40.4)	90 (59.6)	
T3	104 (59.1)	72 (40.9)		71 (49.7)	72 (50.3)	
T4	15 (75.0)	5 (25.0)		8 (61.5)	5 (38.5)	
N stage			0.135			0.042
N1	103 (53.4)	90 (46.6)		56 (38.4)	90 (61.6)	

Table 2 (continued)

Characteristic	All-cause		*p*	Penile cancer cause		*p*
	Dead	Alive		Dead	Alive	
	No. (%)	No. (%)		No. (%)	No. (%)	
N2	112 (55.2)	91 (44.8)		70 (43.5)	91 (56.5)	
N3	84 (64.1)	47 (35.9)		56 (54.4)	47 (45.6)	
M stage			0.005			0.003
M0	253 (54.5)	211 (45.5)		151 (41.7)	211 (58.3)	
M1	46 (73.0)	17 (27.0)		31 (64.6)	17 (35.4)	
Tumor size			0.002			0.001
< 3 cm	62 (44.3)	78 (55.7)		33 (29.7)	78 (70.3)	
≥ 3 cm	192 (61.9)	118 (38.1)		121 (50.6)	118 (49.4)	
Unknown	45 (58.4)	32 (41.6)		28 (46.7)	32 (53.3)	
Removed lymph nodes			< 0.001			< 0.001
< 8 nodes	168 (65.6)	88 (34.4)		109 (55.3)	88 (44.7)	
≥ 8 nodes	112 (46.7)	128 (53.3)		64 (33.3)	128 (66.7)	
Unknown	19 (61.3)	12 (38.7)		9 (42.9)	12 (57.1)	

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size, and number of removed lymph nodes were associated with CSM (all $p < 0.05$; Table 2). Additionally, the patient's age at diagnosis, race, marital status, living state, tumor grade, histology type, and T stage were unrelated factors.

Patients who were non-metropolitan unmarried black patients aged over 80 years with lower income had both higher ACM and higher CSM. In contrast, patients whose number of removed lymph nodes was ≥ 8 had significantly lower ACM (46.7% vs 65.6%, $p < 0.001$) and lower CSM (33.3% vs 55.3%, $p < 0.001$) than those who had < 8 lymph nodes removed (Table 2). Moreover, patients with node categories N1 and N2 had much improved OS (left) and cumulative incidence of CSM (right) than patients with node category N3 (Fig. 3a). Furthermore, patients with more removed lymph nodes (≥ 8) had more survival benefits than patients with fewer removed lymph nodes (< 8) in terms of OS (left) and cumulative incidence of CSM (right) (Fig. 3b).

Multivariate analyses of factors associated with ACM, CSM, and 5-year mortality in patients with newly diagnosed LN + penile cancer

Stratified univariate and multivariate cox regression were used to analyze the factors associated with ACM and CSM. As shown in Table 3, tumor AJCC stage, N stage, M stage, tumor size, and number of removed lymph nodes were factors that affected ACM and CSM (all $p < 0.05$), while T stage was not an influential factor in both ACM and CSM. According to the multivariate cox regression among patients with LN + penile cancer, AJCC stage III (vs AJCC stage II; HR = 1.23, 95% CI 0.91–1.68, $p = 0.185$) and AJCC stage IV (vs AJCC stage II; HR = 1.90, 95% CI 1.39–2.60, $p < 0.001$), tumor size ≥ 3 cm (vs tumor size < 3 cm; HR = 1.71, 95% CI 1.28–2.28, $p < 0.001$) were associated with significantly greater odds of ACM. A higher number of removed lymph nodes ≥ 8 was obviously associated with lower odds of ACM (HR = 0.48, 95% CI 0.38–0.61, $p < 0.001$) and CSM (HR = 0.42, 95% CI 0.30–0.57, $p < 0.001$).

In addition, we also used univariate and multivariate cox regression to analyze the factors associated with 5-year mortality. As shown in Table 4, tumor N stage, M stage, tumor size, and number of removed lymph node all correlated with 5-year mortality (all $p < 0.05$). Notably, a significant protective effect of more (≥ 8) removed lymph node (HR = 0.56, 95% CI 0.46–0.68, $p < 0.001$; HR = 0.58, 95% CI 0.47–0.71, $p < 0.001$) in terms of 5-year mortality was observed among patients with penile cancers (Table 4).

Identification of the correlation between more LND and better survival benefits in patients with different N stages

We further stratified all the 599 patients according to different numbers of removed lymph nodes (≥ 8 vs < 8), different N stages (N1, N2, and N3), and whether surgical treatment was performed (surgery versus no surgery).

The median survival months and survival months of patients are shown in Table 5. Among these LN + patients, surgery improved the median survival months (surgery versus no surgery; 15.0 months versus 8.0 months) and survival months (28.31 ± 30.84 versus 16.69 ± 21.68). Moreover, surgery was associated with lower ACM and lower CSM (Table 5). In addition, the median survival months (for patients with ≥ 8 LND and < 8 LND, 23.0 months and 11.0

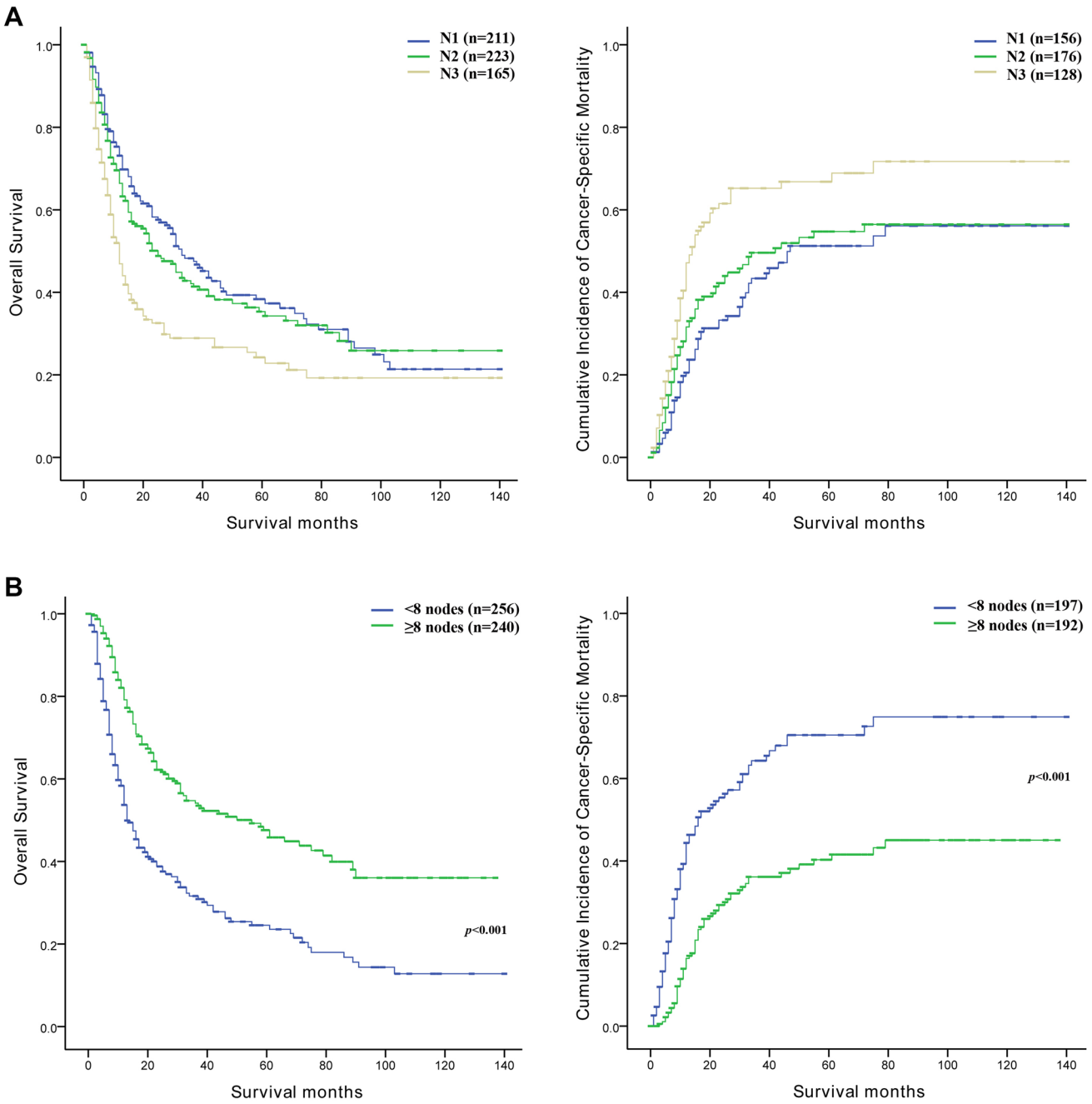


Fig. 3 Patients underwent surgery at earlier N stage or with ≥8 removed lymph nodes have better survival benefits. **a** Patients with node categories N1 and N2 had much improved OS (left) and cumulative incidence of CSM (right) than patients with node category N3. **b** Patients with more removed lymph nodes (≥8) had better survival benefits than patients with fewer removed lymph nodes (<8) in terms of OS (left) and cumulative incidence of CSM (right)

months, respectively) and survival months (35.82 ± 32.40 and 21.53 ± 27.85, respectively) of patients with LN + surgical patients were significantly improved when the number of LND was ≥8. Moreover, the higher number of LND (≥8) was associated with lower ACM (HR = 0.46, 95% CI 0.32–0.66, $p < 0.001$) and lower CSM (HR = 0.40, 95% CI 0.27–0.61, $p < 0.001$). Furthermore, the correlation between larger number of LND and better survival benefits was also found in patients with N1 stage (Fig. 4a), N2 stage (Fig. 4b), and N3 stage (Fig. 4c).

Table 3 Risk factors for survival: outcome is all-cause mortality and penis cancer-specific mortality

Characteristic	All-cause mortality				Cancer-specific mortality			
	Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Urban–rural residence								
Metropolitan	Reference		Reference		Reference		Reference	
Non-metropolitan	1.38 (1.03–1.84)	0.033	NA	0.138	1.53 (1.06–2.20)	0.023	NA	0.078
AJCC stage								
II	Reference		Reference		Reference		Reference	
III	1.21 (0.89–1.64)	0.234	1.23 (0.91–1.68)	0.185	1.45 (0.96–2.20)	0.077	1.51 (0.99–2.29)	0.054
IV	1.97 (1.45–2.69)	< 0.001	1.90 (1.39–2.60)	< 0.001	2.34 (1.54–3.55)	< 0.001	1.86 (1.17–2.95)	0.009
T stage								
T1	Reference		Reference		Reference		Reference	
T2	NA	0.767	NA	0.480	NA	0.819	NA	0.424
T3	NA	0.155	NA	0.171	NA	0.102	NA	0.120
T4	NA	0.230	NA	0.433	NA	0.252	NA	0.821
N stage								
N1	Reference		Reference		Reference		Reference	
N2	1.13 (0.87–1.48)	0.357	NA	0.846	1.25 (0.88–1.78)	0.210	NA	0.416
N3	1.63 (1.22–2.18)	0.001	NA	0.789	1.79 (1.24–2.59)	0.002	NA	0.367
M stage								
M0	Reference		Reference		Reference		Reference	
M1	2.42 (1.76–3.33)	< 0.001	NA	0.082	2.92 (1.97–4.32)	< 0.001	1.61 (0.99–2.59)	0.053
Tumor size								
< 3 cm	Reference		Reference		Reference		Reference	
≥ 3 cm	1.88 (1.41–2.50)	< 0.001	1.71 (1.28–2.28)	< 0.001	2.25 (1.53–3.30)	< 0.001	1.89 (1.28–2.81)	0.002
Unknown	1.46 (0.99–2.14)	0.055	1.22 (0.83–1.80)	0.320	1.74 (1.05–2.89)	0.031	1.51 (0.90–2.52)	0.116
Removed lymph nodes								
< 8 nodes	Reference		Reference		Reference		Reference	
≥ 8 nodes	0.47 (0.37–0.60)	< 0.001	0.48 (0.38–0.61)	< 0.001	0.39 (0.29–0.53)	< 0.001	0.42 (0.30–0.57)	< 0.001
Unknown	0.79 (0.49–1.27)	0.337	0.77 (0.48–1.24)	0.279	0.65 (0.33–1.27)	0.206	0.57 (0.28–1.12)	0.104

AJCC American Joint Committee on Cancer, *NA* not applicable

Discussion

Penile cancer is a rare urogenital tumor. In the United States, the overall age-adjusted incidence per 100,100 persons dropped from 0.84 in 1973–1982 to 0.58 in 1993–2002 [15]. But its incidence remained high in countries with poorer hygiene practices and lower levels of economic development overall, such as in India, Brazil, and Uganda [16].

Surgical treatment is still the main method to treat the primary tumor of penile cancer, and lymph node involvement is the most important factor for the survival of penile cancer patients [17, 18]. However, how the extent of LND impacts the outcome of survival in patients with newly diagnosed LN + penile cancer is largely unknown. Here, we showed that surgical removal of more lymph nodes was associated with lower ACM, CSM, and 5-year mortality in these patients. Specifically, we found that when the number of removed lymph nodes after LND was ≥ 8, there were lower ACM (HR = 0.48, 95% CI 0.38–0.61; $p < 0.001$), CSM (HR = 0.42, 95% CI 0.30–0.57; $p < 0.001$), and 5-year mortality (HR = 0.58, 95% CI 0.47–0.71; $p < 0.001$) in the patients.

In patients with penile cancer, the lymph node metastasis of cancer cells follows the anatomical structure of human lymphatic drainage. The first affected part is the sentinel inguinal lymph nodes, followed by the central inguinal lymph node, and finally the pelvic lymph node [8, 19]. Liu et al. [20] have found that the number and density of metastatic inguinal lymph nodes were predictors of pathological pelvic lymph node involvement. As penile cancer typically

Table 4 Risk factors for 5-year mortality

Characteristic	5-year mortality			
	Univariate Cox regression		Multivariate Cox regression	
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Urban–rural residence				
Metropolitan	Reference		Reference	
Non-metropolitan	NA	0.218	NA	0.584
AJCC stage				
II	Reference		Reference	
III	1.18 (0.92–1.50)	0.195	NA	0.584
IV	1.62 (1.26–2.09)	< 0.001	NA	0.984
T stage				
T1	Reference		Reference	
T2	NA	0.985	NA	0.374
T3	NA	0.082	NA	0.065
T4	NA	0.983	NA	0.465
N stage				
N1	Reference		Reference	
N2	1.14 (0.92–1.42)	0.229	1.17 (0.94–2.45)	0.167
N3	1.45 (1.14–1.85)	0.002	1.37 (1.07–1.76)	0.014
M stage				
M0	Reference		Reference	
M1	2.18 (1.66–2.86)	< 0.001	1.65 (1.24–2.21)	0.001
Tumor size				
< 3 cm	Reference		Reference	
≥ 3 cm	1.52 (1.22–1.90)	< 0.001	1.38 (1.10–1.74)	0.005
Unknown	1.07 (0.78–1.47)	0.671	0.95 (0.69–1.32)	0.773
Removed lymph nodes				
< 8 nodes	Reference		Reference	
≥ 8 nodes	0.56 (0.46–0.68)	< 0.001	0.58 (0.47–0.71)	< 0.001
Unknown	0.81 (0.54–1.21)	0.296	0.82 (0.55–1.23)	0.338

AJCC American Joint Committee on Cancer, *NA* not applicable

has long-term local lymph node metastasis before the distant spread, it is curable by dissection of local metastatic lymph nodes. Even when the metastasis into sentinel lymph nodes occurs, LND can also achieve a high cure rate [21].

As mentioned earlier, LND includes inguinal lymphadenectomy and pelvic lymphadenectomy. For enlarged lymph nodes in the N1 and N2 inguinal regions, inguinal LND should be performed and analyzed through pathology. If findings are positive, radical inguinal lymphadenectomy should be performed. For patients with two or more inguinal lymph node metastases on one side and as well as N3 stage patients, an ipsilateral pelvic lymphadenectomy is required, and postoperative adjuvant chemotherapy or radiotherapy is used to prolong survival [22–24]. However, the postoperative complication rate of LND is relatively high [21, 25, 26]. In the study by Yao et al. [27], the complication rate of developing inguinal LND was about 35–88%, and the commonly the complications were lymphoedema (13.9%), skin necrosis (4.7%), lymphocele formation (2.0%), seroma (2.0%), and wound infections (1.4%). Moreover, if pelvic LND and radiotherapy were combined, the complication rate was higher. However, therapeutic lymphadenectomy can be effective and should not be underutilized because of concerns about related complications. Since different (in location and type) lymph nodes might function differently in terms of metastasis and complications, further stratification of lymph node characteristics (i.e., not only by numbers) might more accurately delineate the impact of the extent of LND on survival benefits of patients with newly diagnosed LN + penile cancer.

The significance of the number of dissected lymph nodes was not reported in earlier studies investigating penile cancer treatment. However, the extent and number of lymphadenectomies were recently reported to be important in the prognosis of bladder cancer and prostate cancer. In these cancers, there was conclusive evidence that the more lymph

Table 5 Median survival months and survival months of penile cancer patients

Subtype	Patients no.	Median survival months	Survival months	All-cause mortality		Cancer-specific mortality	
				Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
No surgery	72	8.0	16.69 ± 21.68	Reference		Reference	
Surgery	527	15.0	28.31 ± 30.84	0.52 (0.39–0.69)	< 0.001	0.51 (0.35–0.75)	0.001
N+							
Lymph nodes removed < 8 nodes	256	11.0	21.53 ± 27.85	Reference		Reference	
Lymph nodes removed ≥ 8 nodes	240	23.0	35.82 ± 32.40	0.47 (0.37–0.60)	< 0.001	0.39 (0.28–0.53)	< 0.001
N1 stage							
Lymph nodes removed < 8 nodes	105	13.0	25.15 ± 30.20	Reference		Reference	
Lymph nodes removed ≥ 8 nodes	76	30.5	41.32 ± 33.12	0.42 (0.27–0.64)	< 0.001	0.36 (0.20–0.65)	0.001
N2 stage							
Lymph nodes removed < 8 nodes	86	12.0	21.92 ± 27.58	Reference		Reference	
Lymph nodes removed ≥ 8 nodes	107	22.0	33.71 ± 30.36	0.51 (0.35–0.74)	< 0.001	0.42 (0.26–0.67)	< 0.001
N3 stage							
Lymph nodes removed < 8 nodes	65	7.0	15.15 ± 23.09	Reference		Reference	
Lymph nodes removed ≥ 8 nodes	57	15.0	32.44 ± 34.74	0.45 (0.28–0.71)	0.001	0.34 (0.19–0.60)	< 0.001

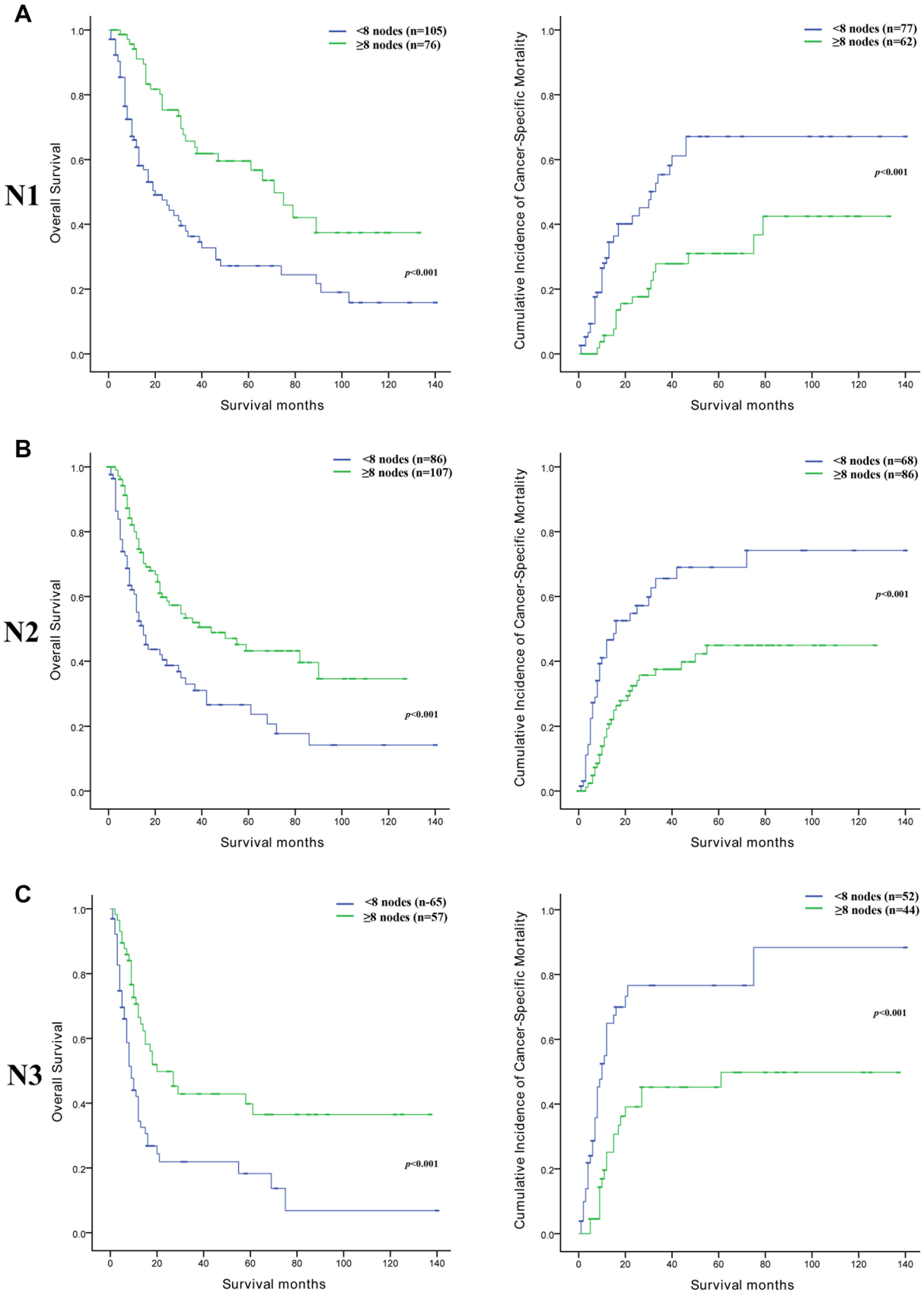
nodes were dissected, the lower the probability of local tumor recurrence. Additionally, the more lymph nodes were removed, the lower the resulting risk of distant metastasis [28–30]. Similarly, Herr et al. [31] reported that patients with more LND had longer disease-free survival and higher OS rates than those with less LND. They found the 5-year OS rates of 33% at 0–5 nodes, 44% at 6–10 nodes, 73% at 11–14 nodes, and 79% at more than 14 nodes. Leissner et al. [30] evaluated 447 patients with radical cystectomy and found that when more lymph nodes were removed, patient survival increased.

In addition, Abdollah et al. [32] investigated 315 cases of pN1-stage prostate cancer patients treated with radical prostatectomy and anatomically extended pelvic LND, and found that removing more lymph nodes during surgery can significantly improve the cancer-specific survival rate of patients (HR = 0.93, 95% CI 0.88–0.99, $p = 0.02$). Moreover, Poulsen et al. [33] pointed out that expanding the scope of pelvic lymphadenectomy was beneficial for patients with organ-limited tumors and lymph node-negative bladder cancer. The 5-year OS rate of patients with expanded dissection was 85%, while the survival rate of patients with standard dissection was only 64%. Besides, they found that extended cleaning can also reduce the transfer of pelvic organs [33].

Taken together, our and other researchers' results imply that the number of dissected lymph nodes might be an independent prognostic factor for multiple cancers. However, this hypothesis needs to be validated through larger epidemiological studies with long-time follow-up periods.

Limitations

Our study has some limitations. Firstly, the SEER database is a retrospective dataset, which has its own limitations of retrospective studies. In our multivariate analyses, many factors were irrelevant possibly due to the small sample sizes. Therefore, further prospective clinical trials are needed to assess the role of LND number in survival benefits of patients with penile cancer. Secondly, the SEER database lacks detailed information on the LND site of the patients, such as the location of infiltrated LN, margin clear or not. Thirdly, the patient's physical condition was unclear, patients with much comorbidities might pursue more conservative treatment. Moreover, more surgical patients were treated with simple/partial surgical (Supplementary Fig. S1), and the choice of surgery bias also affected the patient's prognosis. Besides, the number of LND ranged from 0 to 82 in this study. The wide range of fluctuation might also affect the outcomes, which are associated with individual differences


A
N1
<8 nodes (n=105)
≥8 nodes (n=76)
Overall Survival
Survival months
p<0.001
<8 nodes (n=77)
≥8 nodes (n=62)
Cumulative Incidence of Cancer-Specific Mortality
Survival months
p<0.001
B
N2
<8 nodes (n=86)
≥8 nodes (n=107)
Overall Survival
Survival months
p<0.001
<8 nodes (n=68)
≥8 nodes (n=86)
Cumulative Incidence of Cancer-Specific Mortality
Survival months
p<0.001
C
N3
<8 nodes (n-65)
≥8 nodes (n=57)
Overall Survival
Survival months
p<0.001
<8 nodes (n=52)
≥8 nodes (n=44)
Cumulative Incidence of Cancer-Specific Mortality
Survival months
p<0.001

◂**Fig. 4** More LND is correlated with prolonged survival in patients with different N stages. **a–c** Among patients with N1 stage (**a**), N2 stage (**b**), and N3 stage (**c**) of newly diagnosed LN + penile cancer, patients with more removed lymph nodes (≥ 8) had better survival benefits than patients with fewer removed lymph nodes (< 8) in terms of OS (left) and cumulative incidence of CSM (right)

of patients. In addition, we did not include other adjuvant treatments, such as chemotherapy or radiotherapy, whether adjuvant or neoadjuvant therapy, which may also affect the patient's survival time.

Conclusions

In summary, we showed that removing more lymph nodes during LND was associated with lower mortality and higher OS rates in patients with newly diagnosed LN + penile cancer. The extent of LND might represent an independent prognostic factor for these patients, although further studies with larger sample sizes and longer follow-up periods are required to validate this hypothesis.

Author contributions WM, JF, and JG were involved in the study conception and design. WM, JG collected and assembled data. WM, JF, and JG were involved in data analysis and interpretation WM, XH, and MK wrote the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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