Clinical-Testis cancer

Adherence to guideline recommendations for lymph node dissection in squamous cell carcinoma of the penis: Effect on survival and complication rates

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Abstract

Introduction: We analyzed adherence rates to contemporary guidelines regarding inguinal lymph node dissection (ILND) for squamous cell carcinoma of the penis, as well as ILND association with cancer specific mortality (CSM), and complication rates.

Materials and methods: Within the Surveillance, Epidemiology, and End Results and the National Inpatient Sample databases, 943 and 317 nonmetastatic penile cancer patients (1998−2015) were respectively identified. Multivariable analyses focused on ILND rates, CSM, and complication rates. Inverse probability of treatment weighting adjustment was used in CSM analyses.

Results: Within the Surveillance, Epidemiology, and End Results database, ILND was performed in 233 (24.7%) patients. ILND rates did not vary over time ($P = 0.2$). In the overall cohort ($n = 943$), ILND was an independent predictor of lower CSM (hazards ratio [HR]: 0.42; $P < 0.001$). In Multivariable CSM analyses stratified according to N-stage, ILND was associated with lower CSM in N1 (HR: 0.25; $P < 0.001$) and N2-3 (HR: 0.42; $P = 0.01$), but not in N0 patients. Within the National Inpatient Sample database, presence of LN invasion (LNI) was associated with longer hospitalization (odds ratio: 1.27, $P = 0.01$), but not with higher complications or in-hospital mortality.

Conclusions: The adherence to guidelines for ILND was low (24.7%), and did not change over time. Nonetheless, a CSM benefit related to ILND was observed in N1, N2, and N3 patients. Complication rates and in-hospital mortality did not differ according to LNI. However, hospital stay may be longer in LNI patients. Finally, it should be noted that lack of distinction between clinical and pathological N-stage represents an important limitation. © 2019 Elsevier Inc. All rights reserved.

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1. Introduction

Inguinal lymph node dissection (ILND) occupies a central role in the management of nonmetastatic penile cancer [1−3], and is used either for diagnostic [4,5], therapeutic, or palliative purposes [6,7]. The National Comprehensive Cancer Network and the European Association of Urology guidelines recommend ILND or dynamic sentinel lymph node excision in patients with squamous cell carcinoma of the penis (SCCP) starting from high-grade T1 stage and beyond [6,7]. Despite clear ILND recommendations, previous studies suggested low guideline adherence [8−11]. This observation might be explained by anticipated ILND complications, evidenced by historic rates ranging from 40% to 70% [12−14].

Accordingly, we hypothesized that contemporary ILND adherence rates are higher and have increased over time, due to greater familiarity with ILND and potentially lower contemporary complication rates. Moreover, we postulated that ILND might be associated with lower cancer specific mortality (CSM), relative to no ILND. We tested these hypotheses within the Surveillance, Epidemiology, and End Results (SEER) database.

To the best of our knowledge, no previous population-based studies examined the potential CSM benefits of ILND. Previous institutional studies were based on relatively small sample sizes that limited the generalizability of these reports [15,16]. This said, a recent study based on National Cancer Data Base (NCDB) reported by Woldu et al., did demonstrate a benefit in overall survival, when ILND was performed [11]. However, the Woldu et al. report did not focus on CSM. Instead, it only provided overall mortality (OM) outcomes.

Unlike previous studies, we specifically focused on CSM instead of OM. Moreover, we tested for potential ILND benefit on CSM rates, according to tumor burden, expressed as N-stages. Last but not the least, we also examined contemporary complication rates and postulated that ILND complication rates are manageable, and do not differ according to presence or absence of LN invasion (LNI). We tested this hypothesis within the National Inpatient Sample (NIS) database.

2. Materials and methods

2.1. Source of data

The SEER database that covers approximately 27.8% of the United States population [17] was used to examine all the cancer related endpoints, namely ILND and CSM rates. The NIS database is composed of longitudinal hospital inpatient databases that form the Healthcare Cost and Utilization Project family. The combined database includes 20% of the United States inpatient hospitalizations [18]. All analyses focusing on length of stay (LOS), complication rates and in-hospital mortality relied on the NIS database.

2.2. Study population

Within the SEER database (1998−2014), we identified 943 patients with primary histologically proven SCCP (International Classification of Disease for Oncology 2 [ICD-O-2] site codes C60.0−60.9 used to identify primary site; ICD-O-3 site codes 8070−8076 used to identify histological subtypes). All patients underwent primary tumor excision (excisional biopsy, partial, or total penectomy). Exclusion criteria consisted of unknown ILND status, low-grade T1 stage, or presence of distant metastases. Within the SEER database, presence or absence of ILND represented the predictor variable of interest. The outcome variables of interest were ILND and CSM rates. Covariates consisted of T-stage, tumor grade, year of surgery, age at surgery (younger vs. older than 70 yrs.), race (Caucasian, African-American or other), SEER registry (Alaska and Rural Georgia SEER registries were excluded because of the rarity of observations), marital status (married, never married, previously married, and unknown) and socioeconomic status (SES, 1st quartile vs. 2nd to 4th quartile). According to the SEER coding, the California registry provides information from the State of California with the exception of: Los Angeles, San Francisco-Oakland and San Jose-Monterey. According to the consensus stage assignment, nodal status was reported as pathological N-stage for patients who underwent ILND, but represented clinical N-stage for those who did not undergo ILND.

In the NIS database (1998−2015), 321 patients treated with ILND for primary penile cancer were identified (ICD-9 codes 403, 4050, 4024, 4054). Exclusion criteria consisted of presence of distant metastases. Patients who received a lymph node dissection different from the regional ILND were excluded. Within NIS database, presence or absence of LNI represented the risk variable of interest. The outcome variables of interest were LOS, complication rates, and in-hospital mortality. The 12 specific complication categories considered were intraoperative, medical miscellaneous, surgical miscellaneous, genitourinary, vascular, cardiac, pulmonary, gastrointestinal, infectious, wound, lymphadenitis, and lymphedema [19].

2.3. Statistical analysis

Within the SEER database, we first evaluated ILND rates. Subsequently, estimated annual percentage changes
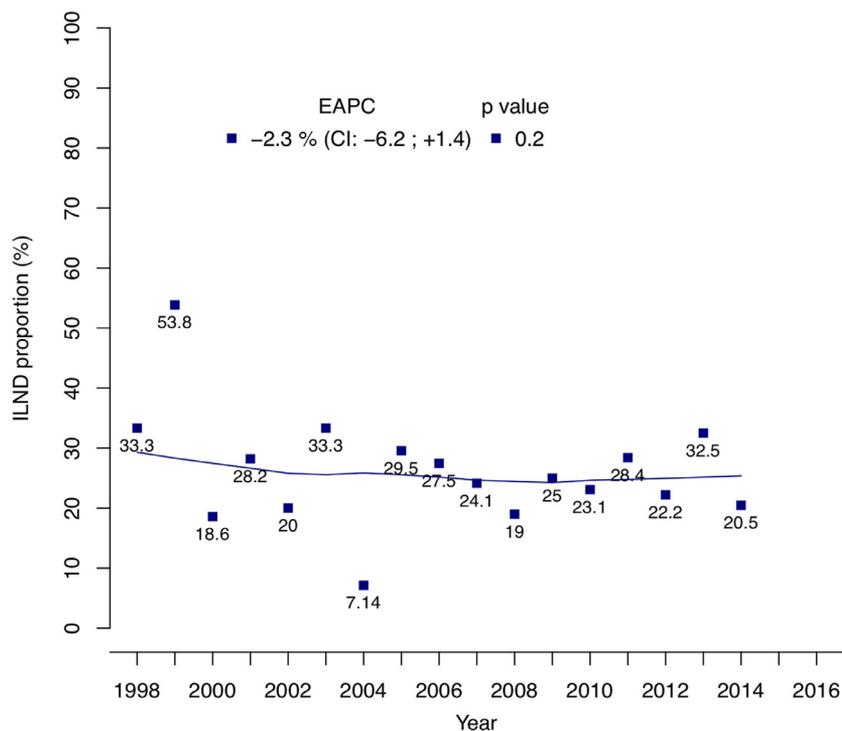
Fig. 1. Annual trends (1998−2014) of inguinal lymph node dissection (ILND) for squamous cell carcinoma of the penis, within the SEER database. Each square represents the annual proportion of ILND. The estimated annual proportion change (EAPC) was −2.3% for the entire study span, but failed to reach statistically significance ($P = 0.2$).

tested for statistically significant annual ILND rate differences. Univariable and multivariable logistic regression models focused on predictors of ILND rates. Subsequently, we performed CSM analyses. Inverse probability of treatment weighting (IPTW) was used to minimize potential differences that might exist in patient's characteristics according ILND vs. no-ILND status (Supplementary Figure 1) [20]. First, IPTW-adjusted Kaplan-Meier plots graphically depicted the effect of ILND on CSM. Second, IPTW-adjusted univariable and multivariable Cox regression models focused on CSM rates. All CSM analyses were repeated after stratification according to N0 vs. N1 vs. N2-3 stages. In all multivariable models (logistic and Cox regression) covariates consisted of age, race, marital status, T-stage, N-stage, and tumor grade.

Within the NIS database, separate univariable and multivariable logistic regression models focused on the association between LNI and the following endpoints: (1) LOS, (2) in-hospital mortality, (3) overall complications, and (4) twelve specific complications (intraoperative, medical miscellaneous, surgical miscellaneous, genitourinary, gastrointestinal, vascular, cardiac, pulmonary, infectious, wound, lymphadenitis, and lymphedema). Power analysis was performed according to LNI status to address the potential under-power of our analysis on complication rates. All statistical tests were 2-sided with a level of significance set at $P < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version3.4.1; http://www.r-project.org/).

3. Results

Within the SEER database, 943 patients with primary SCCP were identified. Of those, 233 patients (24.7%) underwent ILND. ILND patients (Table 1) were younger ($P < 0.001$), had higher T-stages ($P < 0.001$), and lower SES ($P < 0.01$). No significant differences were identified according to tumor grade, year of surgery, race, and marital status. The annual ILND rates ranged from 7.1% to 53.8% (Fig. 1). However, no statistically significant increase in ILND rates was identified over the study span ($P = 0.2$). Conversely, ILND rates varied within the 16 SEER registries and ranged from 16% to 50%. Similarly, the absolute numbers of patients with primary SCCP also varied according to the 16 examined SEER registries and ranged from 15 to 177 (Supplementary Figure 2). With the only exception of San Jose-Monterey, in SEER registries where ILND was performed more frequently, higher proportions of T3-T4 stages were recorded, relative to proportions recorded in other registries (Supplementary Figure 3).

In multivariable logistic regression models predicting ILND rate, stages T2, T3, and T4 were independent predictors of ILND (odds ratio [OR]: 4.03, $P < 0.001$; OR: 5.42, $P < 0.001$; OR: 3.29, $P < 0.001$, respectively). Conversely, age older than 70 years (OR: 0.39, $P < 0.001$), and higher SES quartiles (OR: 0.59, $P = 0.05$), also represented independent predictors of lower ILND rate. Finally, no significant associations were identified between ILND status and year of surgery, marital status, and race (Supplementary Table 1).

Table 1

Descriptive characteristics of 943 nonmetastatic penile cancer patients treated or not treated with inguinal lymph node dissection (ILND) between 1998 and 2014, focusing on cancer control outcomes, from within Surveillance, Epidemiology, and End Results (SEER) database

		Overall cohort (n 943)*	Patients not treated with ILND (n 710)*	Patients treated with ILND (n 233)*	Statistical significance of group differences expressed according to *t*-test or Chi-square test (*P* value)
Age at diagnosis	Mean	66.5	68.3	61.0	**<0.001**
	Median	68.0	69.0	61.0	
	Interquartile range	57−78	59−79	53−71	
Age groups	≤70	544 (57.7)	375 (68.9)	169 (31.1)	**<0.001**
	>70	399 (42.3)	335 (84.0)	64 (16.0)	
T-stage	T1	490 (52)	425 (59.9)	65 (27.9)	**<0.001**
	T2	243 (25.8)	158 (22.3)	85 (36.5)	
	T3	172 (18.2)	101 (14.2)	71 (30.5)	
	T4	37 (3.9)	25 (3.5)	12 (5.2)	
Nodal status[†]	Negative nodal status	752 (79.7)	656 (92.4)	96 (41.2)	**<0.001**
	Positive nodal status	191 (20.3)	54 (7.6)	137 (58.8)	
SEER registry of origin	California	177 (18.8)	138 (19.4)	39 (16.7)	**<0.01**
	New Jersey	113 (12)	88 (12.4)	25 (10.7)	
	Louisiana	84 (8.9)	65 (9.2)	19 (8.2)	
	Los Angeles	76 (8.1)	49 (6.9)	27 (11.6)	
	Greater Georgia	64 (6.8)	54 (7.6)	10 (4.3)	
	Seattle (Puget Sound)	64 (6.8)	39 (5.5)	25 (10.7)	
	Kentucky	58 (6.2)	47 (6.6)	11 (4.7)	
	Metropolitan Detroit	56 (5.9)	46 (6.5)	10 (4.3)	
	Connecticut	51 (5.4)	43 (6.1)	8 (3.4)	
	Iowa	47 (5)	29 (4.1)	18 (7.7)	
	San Francisco-Oakland	46 (4.9)	34 (4.8)	12 (5.2)	
	New Mexico	37 (3.9)	30 (4.2)	7 (3)	
	Metropolitan Atlanta	20 (2.1)	10 (1.4)	10 (4.3)	
	Hawaii	18 (1.9)	15 (2.1)	3 (1.3)	
	Utah	17 (1.8)	14 (2)	3 (1.3)	
	San Jose-Monterey	15 (1.6)	9 (1.3)	6 (2.6)	
Socio-economic status Low vs. High	1st quartile	246 (26.1)	168 (23.7)	78 (33.5)	**<0.01**
	2nd to 4th quartile	697 (73.9)	542 (76.3)	155 (66.5)	
Race	Caucasian	786 (83.4)	591 (83.2)	195 (83.7)	0.4
	African-American	109 (11.6)	86 (12.1)	23 (9.9)	
	Other	48 (5.1)	33 (4.6)	15 (6.4)	
Marital status	Married	486 (51.5)	356 (50.1)	130 (55.8)	0.08
	Never married	174 (18.5)	126 (17.7)	48 (20.6)	
	Previously married	219 (23.2)	174 (24.5)	45 (19.3)	
	Unknown	64 (6.8)	54 (7.6)	10 (4.3)	
Year intervals of surgery groups	1998-2002	159 (16.9)	119 (74.8)[‡]	40 (25.2)[‡]	0.8
	2003-2006	194 (20.6)	145 (74.7)[‡]	49 (25.3)[‡]	
	2007-2010	278 (29.5)	215 (77.3)[‡]	63 (22.7)[‡]	
	2011-2014	312 (33.1)	231 (74.1)[‡]	81 (25.9)[‡]	

ILND = inguinal lymph node dissection; SEER = Surveillance, Epidemiology, and End Results.

* Column percentage.

[†] Nodal status represents clinical staging in patients who did not undergo ILND, pathological staging in patients who undergo ILND.

[‡] Row percentage.

In IPTW adjusted Kaplan-Meier analyses depicting CSM, 5-year CSM rates were 19.8% and 28.6% (log-rank $P < 0.001$), respectively, when ILND was or was not performed (Fig. 2). When Kaplan-Meier analyses were performed after stratification according to N0 vs. N1 vs. N2-3 stages, the following 5-year CSM rates was recorded, when ILND was or was not performed: 10.8% vs. 16.6% (log-rank $P = 0.1$) for N0, 43.7% vs. 83.4% (log-rank $P = 0.04$) for N1, and 54.4% vs. 68.1% (log-rank $P = 0.04$) for N2-3 stages.

In IPTW adjusted multivariable Cox regression models predicting CSM, ILND represented an independent predictor of lower CSM (hazards ratio [HR]: 0.42, $P < 0.001$). When multivariable Cox regression models predicting CSM with IPTW adjustment were applied after stratification according to N0 vs. N1 vs. N2-3 stages, independent
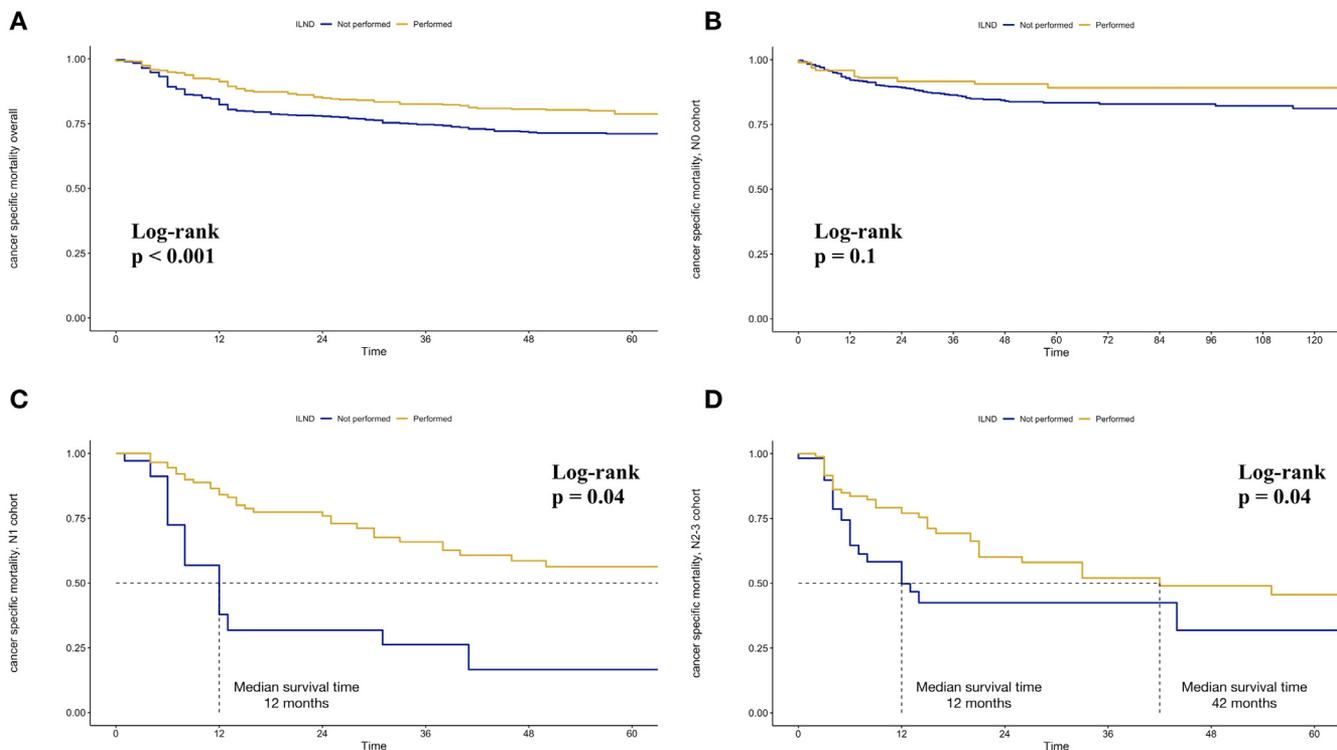
Fig. 2. Kaplan-Meier plots illustrating cancer specific mortality (CSM) according to inguinal lymph node dissection (ILND) status: performed (yellow) vs. not performed (blue). All figures represent data after matching for inverse probability treatment weight. Panel A represents the entire cohort regardless of N-stage (*n* 943). Panel B represents patients with N0 stage (*n* 752). Panel C represents patients with N1 stage (*n* 105). Panel D represents patients with N2-3 stages (*n* 86).

Table 2
Univariable and multivariable Cox regression models predicting cancer specific mortality according to inguinal lymph node dissection status (performed vs. not performed) within the entire patients' cohort as well as in patients' subgroups stratified according to N0 vs. N1 vs. N2-3.   All analyses were adjusted for the following covariates: age at diagnosis, T-stage, tumor grade, socioeconomic status, race, and marital status

		Univariable HR	2.5 %	97.5 %	*P* value	Multivariable HR	2.5 %	97.5 %	*P* value
	Overall patients' cohort								
ILND									
	No ILND	Ref.				Ref.			
	ILND	0.42	0.31	0.57	**<0.001**	0.42	0.31	0.57	**<0.001**
N-stage									
	N0	Ref.				Ref.			
	N1	3.92	2.75	5.59	**<0.001**	6.31	4.31	9.24	**<0.001**
	N2	3.89	2.42	6.26	**<0.001**	10.48	6.85	16.04	**<0.001**
	N3	6.96	4.08	11.88	**<0.001**	11.14	6.8	18.27	**<0.001**
Stratified analyses according to N-stage									
	Patients with N0 stage								
ILND									
	No ILND	Ref.				Ref.			
	ILND	0.59	0.28	1.21	0.1	0.65	0.41	1.05	0.08
	Patients with N1 stage								
ILND									
	No ILND	Ref.				Ref.			
	ILND	0.50	0.26	0.98	**0.04**	0.25	0.13	0.49	**<0.001**
	Patients with N2-3 stages								
ILND									
	No ILND	Ref.				Ref.			
	ILND	0.51	0.26	0.98	**0.04**	0.42	0.22	0.83	**0.01**

CI = confidence intervals; HR = hazard ratio; ILND = inguinal lymph node dissection; Ref. = reference.

Table 3

Descriptive characteristics of 317 penile cancer patients treated with inguinal lymph node dissection, stratified according to presence or absence lymph node invasion (LNI), focusing on length of stay, postoperative complications and in hospital mortality, from within the National Inpatient Sample database (1998 −2015)

		Overall cohort (*n* 317)	Subgroup of patients without lymph node invasion (*n* 263)	Subgroup of patients with lymph node invasion (*n* 54)	Statistical significance of group differences expressed according to t-test or Chi-square test (*P* value)
Age at diagnosis	Mean	60.6	60.3	61.9	0.4
	Median	62.0	61.0	63.0	0.4
	Interquartile range	52−70	51−70	54−71.75	
Age groups	≤70	240 (75.7)	201 (76.4)	39 (72.2)	0.6
	>70	77 (24.3)	62 (23.6)	15 (27.8)	
Length of stay	Mean	4.8	4.5	6.2	**0.03**
	Median	4	4	5	**<0.01**
	Interquartile range	3−6	2−6	3−7	
Year intervals of surgery groups	1998−2002	74 (23.3)	59 (22.4)	15 (27.8)	0.2
	2003−2007	85 (26.8)	66 (25.1)	19 (35.2)	
	2008−2011	102 (32.2)	90 (34.2)	12 (22.2)	
	2012−2015	56 (17.7)	48 (18.3)	8 (14.8)	
Overall complications	0	268 (84.5)	224 (85.2)	44 (81.5)	0.6
	1	49 (15.5)	39 (14.8)	10 (18.5)	
Intraoperative complications	0	315 (99.4)	261 (99.2)	54 (100)	1.0
	1	2 (0.6)	2 (0.8)	0 (0)	
Lymphadenitis	0	305 (96.2)	256 (97.3)	49 (90.7)	0.05
	1	12 (3.8)	7 (2.7)	5 (9.3)	
Lymphedema	0	311 (98.1)	259 (98.5)	52 (96.3)	0.6
	1	6 (1.9)	4 (1.5)	2 (3.7)	
Cardiac complications	0	305 (96.2)	252 (95.8)	53 (98.1)	0.7
	1	12 (3.8)	11 (4.2)	1 (1.9)	
Pulmonary complications	0	308 (97.2)	257 (97.7)	51 (94.4)	0.4
	1	9 (2.8)	6 (2.3)	3 (5.6)	
Genitourinary complications	0	311 (98.1)	260 (98.9)	51 (94.4)	0.1
	1	6 (1.9)	3 (1.1)	3 (5.6)	
Gastrointestinal complications	0	308 (97.2)	257 (97.7)	51 (94.4)	0.4
	1	9 (2.8)	6 (2.3)	3 (5.6)	
Infections complications	0	310 (97.8)	257 (97.7)	53 (98.1)	1.0
	1	7 (2.2)	6 (2.3)	1 (1.9)	
Vascular complications	0	314 (99.1)	260 (98.9)	54 (100)	1.0
	1	3 (0.9)	3 (1.1)	0 (0)	
Wound complications	0	308 (97.2)	256 (97.3)	52 (96.3)	1.0
	1	9 (2.8)	7 (2.7)	2 (3.7)	
Miscellaneous medical complications	0	307 (96.8)	255 (97)	52 (96.3)	1.0
	1	10 (3.2)	8 (3)	2 (3.7)	
Miscellaneous surgical complications	0	309 (97.5)	255 (97)	54 (100)	0.4
	1	8 (2.5)	8 (3)	0 (0)	
In-hospital mortality	0	316 (99.7)	262 (99.6)	54 (100)	1.0
	1	1 (0.3)	1 (0.4)	0 (0)	

predictor status of ILND was confirmed in the subgroups of N1 patients (HR: 0.25, *P* < 0.001) and N2-3 patients (HR: 0.42, *P* = 0.01), but not in N0 patients (Table 2).

All analyses were repeated after inclusion of patients from Alaska and Rural Georgia. This modification did not result in any change to the reported results.

Within the NIS population (*n* = 317), the overall complications rate after ILND was 15.5% (Table 3). The median LOS after ILND was 4 (interquartile range: 3−6) days and the in-hospital mortality rate was 0.3%. After stratification according to LNI, median LOS was higher in the LNI patients (5 vs. 4 days; interquartile range: 3−7 vs. 2−6;

P < 0.01). However, neither overall complications nor in-hospital mortality rates differed according to LNI status (*P* = 0.6 and *P* = 1.0, respectively). Similarly, LNI status did not affect any of the 12 examined specific complications: intraoperative, medical miscellaneous, surgical miscellaneous, genitourinary, gastrointestinal, vascular, cardiac, pulmonary, infectious, wound complications, lymphadenitis, and lymphedema (all *P* > 0.05; Table 3). In 15 separate multivariable logistic regression models that specifically focused on overall complications, each of 12 separate specific complications, on median LOS and on in-hospital mortality, no differences were identified according

to LNI status, except for longer LOS in LNI patients (OR: 1.27, $P = 0.01$). Power analysis showed that to achieve 80% power with the same proportions of complications (14.8% vs. 18.5% in respectively LNI present vs. absent groups) as recorded in our analyses, 945 individuals would have been required per arm. Our sample size provided very limited power of only 15% instead of the customarily required 80%.

4. Discussion

Although, United States and European guidelines recommend ILND in SCCP patients with high-grade T1 or higher stages, [6,7] lack of adherence to these guidelines has been reported in previous population-based studies that relied either on NCDB or SEER databases. [8−11] Based on these observations, we hypothesized that ILND rates may have increased within the SEER database and postulated that ILND may have a beneficial role on CSM and not only on OM, as was previously reported in NCDB-based analyses by Chipollini et al. [10] and Woldu et al. [11]. Last but not least, we also relied on a second population-based database to examine LOS, complication rates and in-hospital mortality, according to presence or absence of LNI. Based on these considerations, we focused on 3 specific objectives: (1) rates of ILND, (2) effect of ILND on CSM, and (3) effect of LNI on LOS, complications, and in-hospital mortality after ILND. Our analyses revealed several noteworthy findings.

First, the rate of ILND within the SEER database was only 24.7% and it did not increase over time. Younger patients and patients with higher T-stage were more likely to undergo ILND, while race and marital status did not represent ILND access barriers. Our findings regarding the overall ILND rate were similar to the latest NCDB publication by Woldu et al. [11], but higher than those reported in other NCDB-based reports, for example in the study of Chipollini et al., where ILND rate was as low as 19.6% [10]. Interestingly, a previous SEER database analysis (1988−2006) showed a higher ILND rate (27.6%) than in the current study [8]. Taken together, our findings showed that approximately 1 of 4, or even fewer, patients in whom ILND is recommended will undergo of this surgery. This observation warrants efforts aimed at improving awareness about the importance of ILND in the context of SCCP, in accordance with contemporary North American and European guidelines.

Second, we and others examined temporal ILND rates. The most recent NCDB analysis by Woldu et al. is in accordance with our observations, where no increase in ILND rates over time could be documented [11]. In their analyses Woldu et al. performed detailed analyses that demonstrated higher nonadherence rates to ILND at nonacademic institutions [11]. Similarly within the NCDB, Chipollini et al. also demonstrated a higher rate of ILND at academic institutions [10]. Taken together, it is possible that maximum efforts aimed at sensitizing clinicians about the importance of ILND may be warranted at nonacademic institutions.

Moreover, despite historic reports suggesting an increase in annual rates of ILND [8], the most contemporary SEER and NCDB databases analyses [11] cannot be used to justify this enthusiasm. Lastly, in another recent NCDB-based study, Campbell at al. reported higher ILND rates, with an increasing trend over time (from 46.2% in 2004 to 69.4% in 2013, $P = 0.034$) [21]. However, the findings of Campbell et al. exclusively focused on patients with clinically positive lymph nodes. Our analyses could not stratify the rates of ILND according to cN status, since only consensus N stage that combines clinical and pathological information is available in the SEER database. In consequence, our study cannot be directly compared to that of Campbell et al. Additionally, it should be emphasized that the study of Chipollini et al. and Woldu et al. focused on patients with clinically negative lymph nodes. In those reports, an increase in ILND rates over time was recorded by Chipollini et al., but not by Woldu et al.

Third, we and others examined the effect of ILND on mortality. In previous NCDB based analyses, reported by Chipollini et al. and by Woldu et al. [10,11] the outcome of interest exclusively consisted of OM. The most recent NCDB analysis focused on all SCCP patients, regardless of N-stage that was reported by Woldu et al., showed a 1.43-fold higher OM rate, when ILND was omitted [11]. In the second NCDB based analysis that relied on all SCCP patients, regardless of N-stage that was reported by Chipollini et al., the effect of early ILND resulted in a protective effect on OM, as evidenced by a HR of 0.67, relative to delayed ILND [10]. In the current analysis we focused on CSM, which represents a more specific cancer control outcome than OM. This statement is particularly important, when analyses include elderly patients, who are at a significant risk of other cause mortality. Our CSM analyses corroborated a protective effect of ILND in the overall cohort, regardless of N-stage (HR: 0.42, $P < 0.001$). Moreover, in our study, ILND showed a protective effect on CSM in patients with N1 (HR: 0.25, $P < 0.001$) and N2-3 stages (HR: 0.42, $P = 0.01$). These findings are in agreement with a recent study reported by Joshi et al., where overall survival was examined exclusively in SCCP patients with pathologically established LNI, within the NCDB database (2004−2014) [22]. In their study, Joshi et al. recorded an overall survival benefit of noILND vs. ILND (HR: 0.64; $P < 0.001$). Differently, our study provides also observations on patients without LNI. In this specific subgroup no CSM benefit was recorded. It should be noted that lack of distinction between clinical and pathological N stage represents an important limitation. Specifically, our analyses of ILND vs. no ILND in N0 patients did not demonstrate statistical significance regarding the CSM benefit that was recorded after ILND vs. no ILND (5-year CSM 10% vs. 16%). Several explanations may be proposed. First, a smaller proportion of patients benefitted from ILND in the N0 than in the N1-3 group (40% vs. 58%). In consequence, a weaker effect size and consequently lack of statistical significance may have resulted. Second, it may also be postulated that the Will

Rogers phenomenon [23] that is operational in N0 patients may be weaker than in N1 or N2-3 subgroups. Hence, the recorded CSM rates favor ILND (5-year CSM 10% vs. 16%), but their significance is only borderline ($P = 0.1$). Finally, it is possible that the surgical selection bias for ILND among N0 patients resulted in higher than expected CSM in ILND patients or in lower than expected CSM in no ILND patients, or in both outcomes simultaneously. Regardless of the explanation for the borderline CSM benefit of ILND in N0 patients within the current analyses, it is important to base clinical decisions for ILND in N0 patients on the much more robust NCDB data that did demonstrate a survival benefit in 2 independent analyses.

Fourth, to the best of our knowledge, no previous studies examined population-based rates of complications, LOS and in-hospital mortality related to ILND. Based on the notion that patients with LNI might experience higher complication rates, we stratified our analyses according to LNI status. Our results demonstrated an overall complication rate of 15.5%. After ILND, among specific complications, wound complications, vascular complications, and infections accounted for 2.8%, 0.9%, and 2.2%, respectively. The rest of the complications ranged from 0.6% (intraoperative complications) to 3.8% (cardiac complications and lymphadenitis) (Table 3). These rates are substantially lower than historical (from 1984 to 2013) complication rates (40%−70%) that were described in institutional databases. [12,13] Such decrease might be related to patient selection, improved surgical technique, or might be related to less extensive ILND in the community than at centers of excellence. Unfortunately, neither of these explanations could be tested within our database. Finally, in multivariable logistic regression models, our findings also indicated that presence of LNI at ILND does not predispose to higher rates of complications or to higher rates of in-hospital mortality. Nonetheless, patients with LNI should be expected to require a longer hospital stay, as evidenced in our data (OR: 1.27, $P = 0.01$). These findings only illustrate differences in adverse outcomes after ILND according to presence vs. absence of LNI. LNI positive and LNI negative patients experienced rates of complications that were lower than those previously reported [12−14]. It is of note that the low rates of complications apply to both groups (LNI positive and negative) and should be interpreted as an indicator that presence or absence of LNI does not predispose to higher rates of complications. Additionally, despite the apparent presence of similar complication rates according to LNI status (14.8% vs. 18.5%), we cannot conclude with certainty that a true difference existed. Indeed, as evidenced by the power analysis, our sample size provided very limited power of only 15% instead of the customarily required 80%. In consequence, the interpretation of our results needs to account for this important power limitation. This said, to achieve 80% power with the same proportions of complications as recorded in our analyses, 945 individuals would have been required per arm. It is relatively unlikely that such large sample size will be available for analysis, even in the largest population-based databases, including the NIS, NCDB, or SEER. In consequence, the current results provide an exploratory estimate that is limited by limited power, as well as potential under-reporting of come complications such as wound infections and flap necrosis relative to prospectively gathered data.

Taken together, our study corroborates the suboptimal rate of ILND in SCCP patients. Moreover, we demonstrated no improvement in ILND rates over time. Despite these negative findings, we also showed a CSM benefit, when ILND is performed in either N1 or N2-3 stages. However, borderline significant albeit clinically meaningful CSM benefit was identified in N0 stage patients. Additionally, we also demonstrated that the presence or absence of LNI has no bearing on complication rates at ILND. Nonetheless, we also observed a modest increase in LOS in ILND patients with LNI, relative to those without LNI. This finding could be attributable to a more challenging and longer surgical procedure in LNI positive patients. These observations warrant efforts aimed at sensitizing the urologic community about the importance of ILND in SCCP patients, especially when LNI is clinically or radiologically suspected. Last but not the least, our analyses of CSM benefit after ILND that demonstrated highly clinically meaningful and highly statistically significant findings in N1 and N2-3 patients, as well as borderline significant albeit clinically meaningful in N0 patients represents the most contemporary incentive for the use of ILND across N stages.

Despite several strengths of our findings, important limitations need to be acknowledged. First, giving that SCCP is a rare malignancy, analyses from institutional, or even population-based data repositories such as the SEER or the NIS database, could be limited by sample size. Moreover, ILND is performed only in a proportion of SCCP patients, which could further limit the sample size. Second, our data represents a retrospective analysis with high potential for selection biases. To maximally reduce these biases, we relied on IPTW-based adjustment [20]. However, it is possible that important difference persisted according to variables that are unavailable, including surgical selection bias, in retrospective databases, such as the SEER, or the NIS or the NCDB databases [10,11]. Particularly, within the SEER and NCDB databases lack of central pathology, as well as nonstandardized and nonassessable rate of imaging represent weaknesses. Moreover, the nature of the SEER database that relies on consensus stage assignment does not allow to discriminate between clinical and pathological nodal stage. For example, it is not possible to identify patients who did not undergo ILND because of inoperable nodal mass. Lastly, the SEER database does not provide insurance status, hospital information, such as hospital volume or hospital teaching status, as well as it does not provide any surgeon information.

Regarding LOS, complications and in-hospital mortality data analyzed within the NIS database, the results may be limited by the retrospective nature of the data repository

and by the relative low sample size. Moreover, the complication rates observed in the current study may reflect the nature of the reporting, which was limited to in-hospital events. In consequence, delayed complications such as delayed flap necrosis, delayed flap infections, and others that are recorded after hospital discharge, as well as the readmission rate, could not be examined within the current analyses. Moreover, it could be possible that ILND complication rates reflect additional complications that originate from chemotherapy administration that may have been given to a proportion of patients prior to ILND. Additionally, some patients may have received additional radiotherapy. However, adjuvant radiotherapy is usually administered after ILND and its effects should not be captured within our results. Unfortunately, NIS database does not allow us to directly access this information. Lastly, the NIS database does not allow to discriminate if ILND was performed with prophylactic or curative intent, whether a full or modified template was used, what was the number of removed lymph nodes or what was the procedure duration.

5. Conclusions

The adherence to guidelines for ILND was low (24.7%), and did not change over time. Nonetheless, a CSM benefit related to ILND was observed in N1, N2, and N3 patients. Complication rates and in-hospital mortality did not differ according to LNI. These observations warrant efforts aimed at sensitizing the urologic community about the importance of ILND in SCCP patients especially when LNI is clinically or radiologically suspected. Finally, it should be noted that lack of distinction between clinical and pathological N-stage represents an important limitation.

Conflict of interests

Authors declare no conflicts of interest, including specific financial interests or relationships or affiliations relevant to the subject matter or materials discussed in the manuscript.

Informed consent

For this type of study formal consent is not required.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.05.024.

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