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Differences in Survival by Receipt of Lymph Node Dissection in Patients with Invasive Penile cancer: Results from the National Cancer Database.

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Abstract

Background: Inguinal lymphadenectomy (I-LND) remains underutilized in patients with invasive penile cancer. Using a large national cancer registry, we assessed temporal trends in I-LND utilization and evaluated the impact of I-LND on the survival in patients in whom I-LND is an absolute indication per NCCN guidelines (T1b-4 N0/x-1).

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Methods: The National Cancer Database (NCDB) was queried for all non-metastatic penile patients with T1b-4 N0/X-N1 squamous cell carcinoma of the penis from 2004–2014. Adjusting for patient, demographic, and clinicopathologic characteristics, multivariable logistic regression models were used to examine the association between available covariates and receipt of I-LND. Cox-proportional hazards regression analyses were then used to assess the impact of clinical and pathological variables on overall survival. A propensity score weighted analysis was performed to assess the effect of I-LND in overall survival.

Results: A total of 2224 patients met criteria for analysis, of which 606 (27.2%) underwent I-LND. Following adjustment, I-LND utilization was more likely in younger patients, those presenting with palpable adenopathy (cN1), treated in an academic facility, and those with a more contemporary diagnosis. On survival analysis, controlling for all known and measured confounders, I-LND receipt was associated with improved OS (HR 0.79 [CI 0.74–0.84], $p < 0.001$).

Conclusion: In hospitals reporting to NCDB, the overall rate of I-LND for patients with invasive penile cancer was only 27.2%. Receipt if I-LND was associated with an increase in OS, justifying the use I-LND utilization as an important quality metric for performance reporting in patients with invasive penile cancer.

Keywords

Penile Cancer; Inguinal Lymphadenectomy; Utilization; Overall Survival; NCDB

Introduction:

Squamous cell carcinoma (SCC) of the penis is a rare condition diagnosed in approximately 1 in 100,000 men and accounts for less than 1% of cancers diagnosed in men in the US [1]. Although rare, the disease carries significant morbidity and mortality with a 5-year cancer specific survival of approximately 50%. Given its rarity, the management of penile cancer has been based on small retrospective studies and consequently there is significant variation in the treatment of the disease.

Inguinal lymphadenectomy (I-LND) remains the most important staging and therapeutic intervention that can be performed in patients with invasive penile cancer[2,3]. Despite this, a recent population studies showed that in the US only 19% to 37% of patients with high grade or invasive penile disease undergo lymphadenectomy as recommended by the NCCN guidelines[4,5]. A major factor limiting the use of inguinal lymphadenectomy is the high risk of post-operative complications associated with the procedure[6]. Recent retrospective reports have shown the importance I-LND for patients with microscopic or low volume nodal disease; prompting the NCCN[7] recommendation that I-LND be offered to any patient with high grade or invasive penile cancer (pT1b-T4), presenting with no or unilateral/low volume adenopathy (cN0-N1)[7]. For those with bilateral (cN2) or bulky (cN3) adenopathy the recommendation is for neoadjuvant chemotherapy followed by I-LND in select candidates[7].

In this study, we aim to assess the utilization of inguinal lymphadenectomy (I-LND) in patients in whom I-LND is absolutely indicated per the NCCN guidelines (high grade or

invasive penile cancer (T1b-4) with minimal or no nodal involvement (N0/x-N1)), and assess the association between receipt of I-LND and overall survival using the National Base Cancer Database (NCDB).

Methods:

Data Source

The NCDB, a program of the ACS® CoC (Commission on Cancer) and the American Cancer Society, is a national cancer registry established in 1989 that serves as a comprehensive clinical surveillance resource for cancer care in the United States. The NCDB compiles data from more than 1,500 commission accredited cancer programs in the United States and Puerto Rico, and captures approximately 70% of all newly diagnosed cancer cases [8].

Definitions:

Cohort and primary outcome

Patients with penile squamous cell carcinoma were identified in the NCDB based on ICD-O-3 site and histology codes. Cases were selected based on squamous cell histology (8070 and 8071). Our study cohort included patients diagnosed between 2004 and 2014. Patients were selected based on invasive pathology defined as T1b-4, lack or unilateral low volume inguinal adenopathy (N0/x-N1), known surgical excision (partial or radical penectomy) and known lymph node procedure. Patients who died within 30 days of diagnosis, had clinical N2–3 nodal involvement or metastatic disease on presentation, did not receive treatment at the reporting hospital, or had a history of a prior malignancy were excluded from the study (Figure 1). In cases where pathological stage was not available clinical stage was used. To further limit any coding errors, only patients with a reported nodal count were included in the lymphadenectomy group, as well as excluding any patient with a lymph node count from the non-lymphadenectomy group. Our primary outcome measures were receipt of inguinal lymphadenectomy and overall survival.

Covariates

Patients were evaluated using clinical, demographic, and pathologic characteristics available in the NCDB. Variables included patient characteristics such as year of diagnosis, age, race, Charlson-Deyo comorbidity classification [9], insurance status, median household income, and demographic location. Disease characteristics included pathological stage and grade, clinical and pathological nodal stage, and receipt of I-LND. Hospital characteristics included facility type and location.

Statistical Analysis

Temporal trends in the use of I-LND were assessed from 2004–2014 using Cochran-Armitage trend tests. We tested the association between I-LND and patient/tumor characteristics using Chi-squared tests. We then used multivariate logistic regression to simultaneously examine the association between all variables with the receipt of I-LND, accounting for within-hospital correlation with robust standard errors. Cox-proportional

hazards regression analyses were then used to assess the impact of clinical and pathological variables on overall survival. We then conducted a propensity score weighted analysis [10] to assess the effect of I-LND in overall survival (OS). We estimated the propensity score via logistic regression, including all pre-treatment covariates, and using spline terms for age and year of diagnosis. Patients outside of the area of common support were dropped from the analysis, and we assessed balance after applying inverse probability weighting to the final cohort. We then used weighted Kaplan-Meier curves and a weighted Cox regression model to test the association between I-LND and survival. All statistical analyses were done with SAS version 9.4 and R version 3.33, with $p < 0.05$ considered statistically significant.

Results:

We identified 2,224 men that met study inclusion criteria (Table 1). The cohort consistent mostly of older (median age 69), Caucasian (85.3%) men with a low comorbidity index (CCI 0: 65.7%). The majority of patients were treated in a comprehensive community (35.5%) or Academic/Research (45.9%) facility.

606 (27.2%) men underwent lymphadenectomy over the study period (2004–2014). I-LND utilization showed a steady increased over the study period (Figure 2), with 33.6% of eligible patients receiving I-LND in 2014 compared to 23.3% in 2004 ($p<0.001$). When comparing patients who underwent an I-LND and those who did not, significant differences were seen with respect to age (<0.001), Hispanic ethnicity ($p=0.014$), Charlson-Deyo score ($p=0.009$), insurance status ($p<0.001$), Demographic location ($p=0.036$), treatment facility ($p<0.001$), and nodal status ($p<0.001$), as shown in Table 1.

Following adjustment, I-LND was more likely to be performed in patients treated in an Academic/Research facility (OR 4.22 [CI 2.61–6.81], $p < 0.001$), presenting with palpable unilateral inguinal adenopathy (cN1) (OR 5.59 [CI 3.71–8.42], $p < 0.001$), and in those with a more contemporary diagnosis (OR 1.06 [CI 1.02–1.10], $p< 0.001$). In comparison, utilization of I-LND was less likely to occur with increased age ($p <0.001$), especially for those ≥ 71 years old (OR 0.41 [CI 0.27–0.62], $p < 0.001$) and those presenting with T1b pathology (OR 0.41 [CI 0.24–.071], $p = 0.002$). A similar but not statistically significant trend ($p = 0.091$) was seen in regards to worsening comorbidity, with those presenting with severe comorbidity (CCI-2) being less likely to receive I-LND than CCI-0 (OR 0.64 [CI 0.42–.098), $p = 0.040$), shown in Table 2.

On survival analyses, increasing pathological stage (pT3: HR 1.22 [CI 1.06–1.40], $p=0.006$; pT4: HR 2.32 [CI 1.51–3.55], $p<0.001$), pN1 disease (HR 1.49 [CI 1.16–1.92], $p=0.011$) high grade disease (HR 1.46 [CI 1.27–1.69]. $p < 0.001$), increasing age (≥ 71) (HR 1.72 [CI 1.20–2.46], $p = 0.003$) and worsening comorbidity (CCI-1: HR 1.43 [CI 1.22–1.68] CCI-2: HR 1.91 [CI 1.52–2.39], $p < 0.001$ for both) were all associated with decreased survival. Receipt of I-LND (HR 0.59 [CI 0.48–0.72], $p < 0.001$) and Hispanic ethnicity (HR 0.68 [CI 0.51–0.92], $p = 0.039$) were both associated with improved survival, as shown in Table 3. Following propensity score adjustment, receipt of I-LND continued to show a survival benefit in the study cohort (HR 0.79 [CI 0.74–0.84], $p < 0.001$), as shown in Figure 3.

Discussion:

The impact of inguinal lymphadenectomy (I-LND) on the survival of patients with invasive penile cancer has been recognized as early as 1986 [11]. Despite the early evidence and numerous confirming retrospective studies [2,12], I-LND in the US remains underutilized[4,5,13]. The main hesitancy for the use of I-LND is the significant comorbidity associated with the procedure, which has a reported complication rate of 14%–37% [14,15]. Despite strong recommendations in both the NCCN[7] and EUA[16] guidelines, the use of I-LND in patients with high grade or invasive penile cancer and cN0–1 disease remains controversial, mainly due to fear of overtreatment leading to the use of surveillance strategies and fine needle aspiration[17,18] in the hope to improve patient selection. In this observational cohort, consisting of patients with an absolute indication for I-LND per NCCN guidelines (T1b-4 N0/x-1), I-LND was found to have significant impact on survival with a difference in median overall survival of 18.1 months (75.5 months (+) I-LND vs. 57.4 months (−) I-LND).

In our cohort, the rate of lymphadenectomy was calculated at 27.2% over a 10-year period. Although the rate is alarming low, these findings are consistent with those reported by Chippollini et al[5] (NCDB) and Johnson et al[13] (SEER), who using similar patient cohorts calculated comparable lymphadenectomy rates of 19.6% and 26.5%, respectively. Marginal I-LND utilization is not specific to penile cancer with vulvar cancer[19] (20.4%) and lower extremity melanoma[20] (39%) reporting similar sub-standard rates. Encouraging, was the increase use I-LND over the study period (Figure 2), which is likely related to less ambiguous recommendations with the introduction of treatment guidelines[7,16], emphasis in centralization of care[5,21] and the introduction of minimally invasive techniques geared towards improvement of post-operative complications [22]

Utilization of I-LND was more likely to occur in younger patients ($p < 0.001$), those with a more contemporary diagnosis ($p = 0.02$), and those treated in an Academic/Research facility ($p < 0.001$). In contrast, I-LND utilization did not increase with worsening pathological stage, and the likelihood of receiving I-LND was decreased for those presenting with T1b lesions (OR 0.41 [CI 0.24–.071], $p = 0.002$). These findings are worrisome given numerous reports demonstrating the increased incidence of lymphoid metastases associated with lympho-vascular invasion[23] and poorly differentiated cancers[23], which are features that define T1b lesions per AJCC TNM staging system[24]. Furthermore, lymphadenectomy was more common for those presenting with clinically palpable adenopathy (cN1:73.9% vs cN0/x: 23.1%, $p < 0.001$), demonstrating an erroneous risk adapted approach given the far greater benefit seen in those with microscopic nodal disease[25]. Interestingly, comorbidity index ($p = 0.079$), median household income ($p = 0.841$), demographic location ($p = 0.656$), or education level ($p = 0.738$) had no effect in on I-LND utilization, which have been preconceived factors related to access to appropriate care in patients with penile cancer, who often present from rural, and underserved areas.

Similar observations were noted by Bilimoria et al[20], when lymphadenectomy utilization was assessed in melanoma patients. Using the NCDB database, the authors demonstrated that utilization of lymphadenectomy decreased with advancing age, treatment in community

versus academic/research facility and lesion location (lower extremities). As with penile cancer, increasing comorbidity, insurance type, household income, demographic location and race had no effect on lymphadenectomy utilization. Together, the data suggests that the low utilization of I-LND is likely related to physician experience and comfort rather patient factors; emphasizing the need to centralize care for those presenting with rare malignancies[21,26]. This is supported by a recent report in which the adherence to EAU penile guidelines was studied in an Italian population[27]; where the care of penile cancer patients is concentrated at eight tertiary care centers. The study showed that overall adherence to EUA guideline recommendations occurred in 66% of the cases, with an I-LND utilization rate of 70%.

Our survival analyses demonstrated that receipt of lymphadenectomy and Hispanic ethnicity were both associated with improved survival; whereas, increasing age, worsening comorbidity, higher pathological stage, high grade disease, and pathological nodal disease were all associated with decreased survival. Following adjustment for known confounders using propensity score weighting, receipt of I-LND continued to have a beneficial effect on overall survival (HR 0.79 [CI 0.74–0.84], $p < 0.001$). The above findings are of great importance as it validates the findings of several small retrospective reports [2,3,12] on the importance of I-LND in the survival of patients with invasive penile cancer using observational data from a large national cancer registry. Penile cancer remains one of the few disease processes, along with testis cancer [28], in which a modifiable factor such as lymphadenectomy is proven to provide a survival advantage. As such, we must emphasize the use of I-LND as an important quality metric for the management of patients with invasive penile cancer.

Despite its strengths our study is not devoid of limitations. First, large retrospective databases are prone to coding errors, which must be addressed carefully prior to data analysis. We attempted to control for coding errors by excluding patients with a reported lymph node procedure but no documented lymph node count; as well as, any patient with a lymph node count but no documented lymph node procedure. Given the alarming low rate of I-LND utilization calculated from the NCDB database (27.2%), one must wonder if this number represents a true practice representation versus a lack of data capture from the NCDB database. Lymphadenectomy procedures in penile cancer compared to other malignancies may present a coding issue for the NCDB as these procedures are usually performed in staged fashion. The NCDB database only tracks procedures performed in a COC-approved facility and those that pertain to the initial cancer treatment[29] ; therefore, a staged lymphadenectomy performed in a non-COC facility or miss-categorize as a recurrence could potentially be left out by the coders leading to the under reporting of I-LND in the database. Despite, the role that miscoding or under reporting may have played in low I-LND rates reported using the NCDB database, the comparable rates reported using the SEER-Medicare[13] warn of a possible practice phenomenon which we must continue to study if we hope to improve the care of penile cancer patients. Second, the use of the NCDB database may lead to sampling bias as the NCDB only queries records from CoC-approved facilities, which may affect the generalizability of our results. Review of other disease sites by Mettlin et al [30], has shown that patient and disease treatment characteristics between NCDB and SEER (a national representative sample) are comparable which may mitigate this

bias. Third, the overall improvement on overall survival seen in patients receiving lymphadenectomy may be a function of younger and healthier patients undergoing the procedure. To minimize this potential bias in our survival analysis we used propensity adjustment to reduce impact of known confounding variables [10], however, it is possible that residual bias from unmeasured factors may remain. Finally, the NCDB database does not allow for assessment of patient choice on whether to undergo or forgo lymphadenectomy as part of their treatment plan. We attempted to reduce this bias by including only patients in whom a lymphadenectomy is an absolute indication (T1b-4 N0/x-1) in all existing best practice guidelines[7,16].

Conclusion:

In hospitals reporting to NCDB, the overall rate of I-LND utilization for invasive penile cancer was only 27.2%. The use of I-LND saw a statistically significant increase over the study period from 23.3% in 2004 to 33.6% in 2014, which is encouraging. There was a significant increase in median overall survival in patients who received I-LND, justifying use of I-LND utilization an important quality metric for performance reporting in patients with invasive penile cancer.

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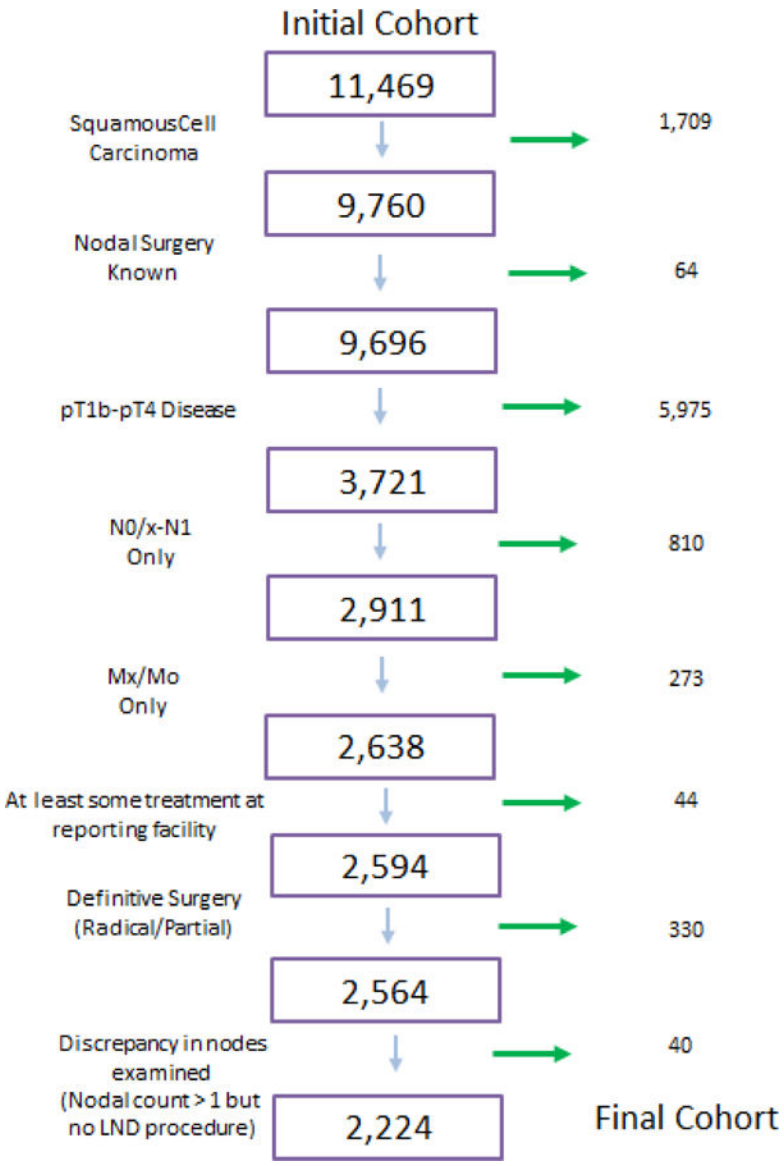

Figure 1.
Consort Diagram Depicting Inclusion Criteria for the analyzed cohort

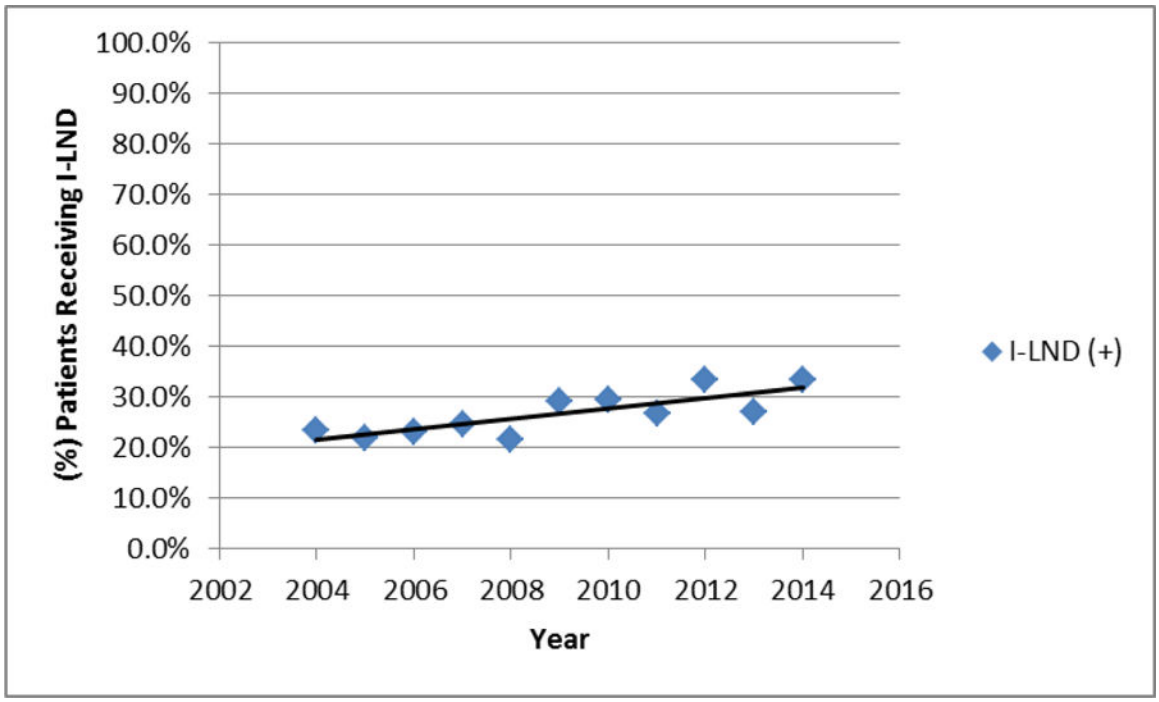

Figure 2.
Graph depicting the percentage of patient with pTlb-4 cNO/x recieving Inguinal Lymaphenectomy (l-LND)

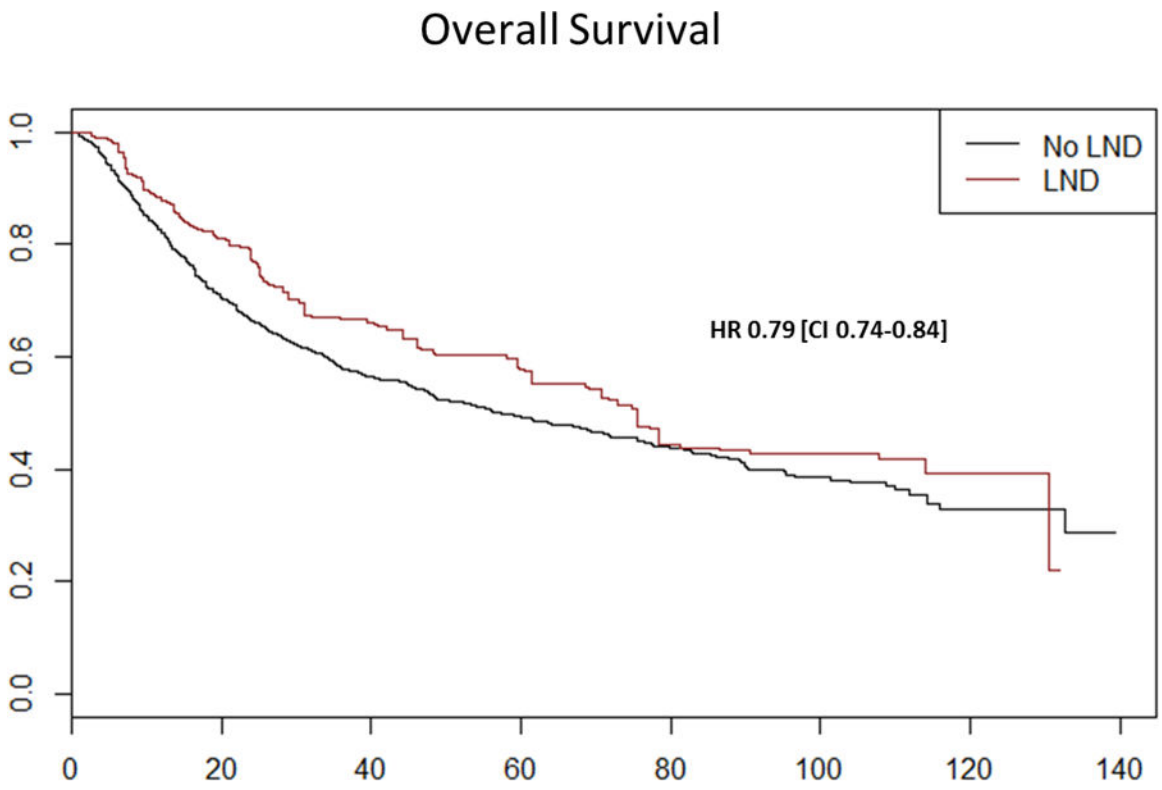

Figure 3.

Kaplan-Meier survival curves of overall survival of penile cancer patients as function of receipt of lymphadenectomy after propensity score weighting

Table 1.

Sociodemographic and Clinical Characteristics of 2224 patients with pT1b-4 cN0/x-N1 Penile Squamous Cell Carcinoma

Patient Characteristic	All Patients	(%)	I-LND Performed	(%)	I-LND Not Performed	(%)	p-value
Age							<0.001
<50	233	10.5	99	42.5	134	57.5	
51–60	369	16.6	152	41.2	217	58.8	
61–70	539	24.2	171	31.7	368	68.3	
71+	1083	48.7	184	17.0	899	83.0	
Race							0.986
White	1898	85.3	516	27.2	1382	72.8	
Black	231	10.4	64	27.7	167	72.3	
Other/Unknown	95	4.3	26	27.4	69	72.6	
Hispanic							0.014
No	1846	83.0	487	26.4	1359	73.6	
Yes	259	11.6	90	34.7	169	65.3	
Unknown	119	5.4	29	24.4	90	75.6	
Charlson-Denyo Score							0.009
0	1461	65.7	416	28.5	1045	71.5	
1	564	25.4	154	27.3	410	72.7	
2	199	8.9	36	18.1	163	81.9	
Insurance Status							<0.001
Not Insured	162	7.3	60	37.0	102	63.0	
Private Insurance	553	24.9	193	34.9	360	65.1	
Medicaid	156	7.0	51	32.7	105	67.3	
Medicare	1268	57.0	268	21.1	1000	78.9	
Other Government	27	1.2	10	37.0	17	63.0	
Unknown	58	2.6	24	41.4	34	58.6	
Median Income							0.489

Patient Characteristic	All Patients	(%)	I-LND Performed	(%)	I-LND Not Performed	(%)	p-value
< 30,000	497	22.3	133	26.8	364	73.2	
30,000 – 34,999	625	28.1	173	27.7	452	72.3	
35,000 – 45,999	563	25.3	156	27.7	407	72.3	
46,000 +	513	23.1	141	27.5	372	72.5	
Unknown	26	1.2	3	11.5	23	88.5	
High School Graduate							0.166
29% or more	526	23.7	159	30.2	367	69.8	
20% - 28.9%	664	29.9	171	25.8	493	74.2	
14% – 19.9%	626	28.1	175	28.0	451	72.0	
< 14%	384	17.3	98	25.5	286	74.5	
Unknown	24	1.1	3	12.5	21	87.5	
Demographic Location							0.036
Large Metropolitan	955	42.9	286	29.9	669	70.1	
Small Metropolitan	690	31.0	166	24.1	524	75.9	
Suburban	307	13.8	87	28.3	220	71.7	
Rural	200	9.0	54	27.0	146	73.0	
Unknown	72	3.2	13	18.1	59	81.9	
Facility Type *							<0.001
Community Cancer	194	8.7	24	12.4	170	87.6	
Comprehensive Community	762	34.3	113	14.8	649	85.2	
Academic/Research	984	44.2	389	39.5	595	60.5	
Integrated Cancer Network	206	9.3	42	20.4	164	79.6	
Facility Location by Region *							0.269
New England	149	6.7	26	17.4	123	82.6	
Mid Atlantic	307	13.8	82	26.7	225	73.3	
South Atlantic	486	21.9	127	26.1	359	73.9	
East North Central	380	17.1	103	27.1	277	72.9	
East South Central	199	8.9	61	30.7	138	69.3	

Patient Characteristic	All Patients	(%)	I-LND Performed	(%)	I-LND Not Performed	(%)	p-value
West North Central	167	7.5	44	26.3	123	73.7	
West South Central	188	8.5	54	28.7	134	71.3	
Mountain	87	3.9	19	21.8	68	78.2	
Pacific	183	8.2	52	28.4	131	71.6	
Pathological T-Stage							0.070
T1b	122	5.5	21	17.2	101	82.8	
T2	1354	60.9	371	27.4	983	72.6	
T3	703	31.6	200	28.4	503	71.6	
T4	45	2.0	14	31.1	31	68.9	
Tumor Grade							0.364
1 & 2	1520	68.3	428	28.2	1092	71.8	
3 & 4	619	27.8	156	25.2	463	74.8	
Unknown	85	3.8	22	25.9	63	74.1	
Clinical Nodal Stage							<0.001
N0/x	2094	94.2	518	24.7	1576	75.3	
N1	130	5.8	88	67.7	42	32.3	
Year of Diagnosis							0.001
2004	129	5.8	30	23.3	99	76.7	
2005	151	6.8	33	21.9	118	78.1	
2006	165	7.4	38	23.0	127	77.0	
2007	188	8.5	46	24.5	142	75.5	
2008	196	8.8	42	21.4	154	78.6	
2009	196	8.8	57	29.1	139	70.9	
2010	215	9.7	63	29.3	152	70.7	
2011	226	10.2	60	26.5	166	73.5	
2012	228	10.3	76	33.3	152	66.7	
2013	248	11.2	67	27.0	181	73.0	
2014	282	12.7	94	33.3	188	66.7	

* Missing information in 78 patients

Table 2.

Multivariate Regression Analysis for Receipt of Lymphadenectomy

Patient Characteristics	OR	95% CI		p-value
Age				**<0.001**
<50	Ref	Ref	Ref	Ref
51–60	1.15	0.78	1.71	0.470
61–70	0.99	0.65	1.51	0.972
71+	0.43	0.29	0.65	<0.001
Race				**0.076**
White	Ref	Ref	Ref	Ref
Black	0.93	0.65	1.32	0.687
Unknown/Other	0.59	0.37	0.94	0.025
Hispanic				**0.962**
No	Ref	Ref	Ref	Ref
Yes	1.05	0.74	1.50	0.788
Unknown	1.02	0.63	1.64	0.940
Charlson-Denyo Score				**0.091**
0	Ref	Ref	Ref	Ref
1	0.97	0.79	1.19	0.765
2	0.64	0.42	0.98	0.040
Insurance Status				**0.818**
Private Insurance	Ref	Ref	Ref	Ref
Not Insured	0.91	0.61	1.36	0.657
Medicaid	0.78	0.51	1.19	0.246
Medicare	0.93	0.69	1.25	0.645
Other Government	0.94	0.43	2.05	0.876
Unknown	1.26	0.64	2.48	0.512
Median Income				**0.655**
< 30,000	Ref	Ref	Ref	Ref

Patient Characteristics	OR	95% CI		p-value
30,000 – 34,999	1.15	0.83	1.59	0.414
35,000 – 45,999	1.19	0.85	1.66	0.318
46,000 +	1.31	0.85	2.03	0.218
High School Graduate				**0.474**
29% or more	Ref	Ref	Ref	Ref
20% – 28.9%	0.87	0.63	1.21	0.411
14% – 19.9%	1.05	0.74	1.49	0.795
<14%	0.84	0.52	1.36	0.483
Demographic Location				**0.489**
Rural	Ref	Ref	Ref	Ref
Large Metropolitan	1.10	0.68	1.78	0.689
Small Metropolitan	0.98	0.64	1.51	0.939
Suburban	1.07	0.64	1.79	0.784
Unknown	0.56	0.21	1.49	0.249
Facility Type				**<0.001**
Community Cancer	Ref	Ref	Ref	Ref
Comprehensive Community	1.23	0.75	2.02	0.403
Academic/Research	4.04	2.53	6.45	<0.001
Integrated Cancer Network	1.75	0.93	3.27	0.082
Facility Location				**0.384**
New England	Ref	Ref	Ref	Ref
Mid Atlantic	1.19	0.68	2.10	0.538
South Atlantic	1.58	0.90	2.77	0.110
East North Central	1.14	0.63	2.08	0.671
East South Central	2.21	1.10	4.43	0.025
West North Central	1.16	0.57	2.35	0.684
West South Central	1.38	0.72	2.65	0.329
Mountain	1.23	0.54	2.79	0.623
Pacific	1.63	0.90	2.97	0.107

Patient Characteristics	OR	95% CI		p-value
Pathological T-Stage				**0.005**
T2	Ref	Ref	Ref	Ref
T1b	0.41	0.24	0.71	0.002
T3	0.93	0.75	1.15	0.500
T4	0.65	0.33	1.28	0.211
Tumor Grade				**0.421**
1 & 2	Ref	Ref	Ref	Ref
3 & 4	1.11	0.87	1.40	0.399
Unknown	0.79	0.48	1.31	0.363
Clinical N-Stage				**<0.001**
N0	Ref	Ref	Ref	Ref
N1	5.59	3.71	8.42	<0.001
Year of Diagnosis				**0.002**
Trend from 2004–2014	1.06	1.02	1.11	0.001

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Table 3.

Cox Multivariate Regression Analysis for Overall Survival

Patient Characteristics	HR	95% CI		p-value
Age				**<0.001**
<50	Ref	Ref	Ref	Ref
51–60	0.97	0.68	1.38	0.843
61–70	1.06	0.74	1.51	0.755
71+	1.72	1.20	2.46	0.003
Race				**0.337**
White	Ref	Ref	Ref	Ref
Black	1.19	0.93	1.51	0.165
Unknown/Other	1.13	0.77	1.66	0.539
Hispanic				**0.039**
No	Ref	Ref	Ref	Ref
Yes	0.68	0.51	0.92	0.012
Unknown	1.03	0.79	1.34	0.835
Charlson-Denyo Score				**<0.001**
0	Ref	Ref	Ref	Ref
1	1.43	1.22	1.68	< 0.001
2	1.91	1.52	2.39	< 0.001
Insurance Status				**0.964**
Private Insurance	Ref	Ref	Ref	Ref
Not Insured	0.97	0.68	1.38	0.860
Medicaid	1.05	0.74	1.48	0.794
Medicare	1.06	0.87	1.29	0.558
Other Government	1.19	0.62	2.26	0.604
Unknown	0.88	0.54	1.42	0.599
Median Income				**0.746**
< 30,000	Ref	Ref	Ref	Ref

Patient Characteristics	HR	95% CI		p-value
30,000 – 34,999	0.89	0.71	1.11	0.311
35,000 – 45,999	0.92	0.70	1.20	0.531
46,000 +	0.95	0.70	1.30	0.767
High School Graduate				**0.738**
29% or more	Ref	Ref	Ref	Ref
20% – 28.9%	0.89	0.71	1.10	0.274
14% – 19.9%	0.90	0.70	1.16	0.415
<14%	0.93	0.69	1.25	0.627
Demographic Location				**0.712**
Rural	Ref	Ref	Ref	Ref
Large Metropolitan	0.92	0.70	1.21	0.551
Small Metropolitan	0.85	0.66	1.09	0.206
Suburban	0.89	0.66	1.19	0.415
Unknown	0.90	0.59	1.37	0.627
Facility Type				**0.572**
Community Cancer	Ref	Ref	Ref	Ref
Comprehensive Community	1.15	0.90	1.48	0.266
Academic/Research	0.89	0.69	1.15	0.365
Integrated Cancer Network	1.06	0.76	1.48	0.745
Facility Location				**0.272**
New England	Ref	Ref	Ref	Ref
Mid Atlantic	1.19	0.86	1.64	0.306
South Atlantic	1.35	0.98	1.84	0.063
East North Central	1.46	1.06	2.00	0.019
East South Central	1.39	0.96	2.00	0.081
West North Central	1.26	0.87	1.80	0.220
West South Central	1.13	0.77	1.67	0.533
Mountain	1.56	1.06	2.30	0.024
Pacific	1.28	0.88	1.85	0.193

Patient Characteristics	HR	95% CI		p-value
Pathological T-Stage				**<0.001**
T2	Ref	Ref	Ref	Ref
T1b	0.89	0.58	1.34	0.5649
T3	1.22	1.06	1.40	0.0063
T4	2.32	1.51	3.55	< 0.001
Tumor Grade				**<0.001**
1 & 2	Ref	Ref	Ref	Ref
3 & 4	1.46	1.27	1.69	< 0.001
Unknown	1.08	0.77	1.52	0.6482
Pathological N-Stage				**0.002**
N0	Ref	Ref	Ref	Ref
N1	1.49	1.16	1.92	0.0018
Inguinal Lymphadenectomy				**<0.001**
No	Ref	Ref	Ref	Ref
Yes	0.59	0.48	0.72	< 0.001
Year of Diagnosis				**0.605**
Trend from 2004–2014	1.01	0.98	1.04	0.6054