



## Original article

# Usage and survival implications of surgical staging of inguinal lymph nodes in intermediate- to high-risk, clinical localized penile cancer: A propensity-score matched analysis

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## Abstract

**Objectives:** To evaluate the usage of surgical staging of inguinal lymph nodes (SSILNs) in the United States for intermediate to high-risk, clinically localized penile squamous cell cancer (SCC), to explore patient and hospital factors associated with omission of this staging, and to evaluate the effect on survival.

**Patients and methods:** Retrospective, observational study using the National Cancer Database from 2004 to 2014 of 1,689 men diagnosed with pT1b–T3, cN0 penile SCC, who by current guidelines should receive SSILNs—either by inguinal lymph node (ILN) dissection or sentinel node biopsy. Binomial logistic regression analysis was performed to determine predictors of SSILNs. Multivariate Cox regression analysis was performed to determine the impact of SSILNs on survival in the overall and propensity-score matched patient populations.

**Results:** Only 25.3% of patients underwent SSILNs. Increasing patient age, higher comorbidity status, lower pathologic stage, Medicaid insurance, and treatment at a nonacademic facility were independent factors associated with the omission of SSILNs. Omission of SSILNs was an independent predictor of overall mortality, both in the overall patient population after multivariate adjustment, HR = 1.46 [(95% CI: 1.14–1.88),  $P = 0.003$ ], and in the propensity-score matched adjusted population, HR = 1.59 [(95% CI: 1.20–2.13),  $P = 0.001$ ]. Limitations include an inability to distinguish biopsy from ILN dissection and those inherent in observational study design.

**Conclusion:** Utilization of SSILN for penile SCC is low and has not changed significantly since the publication of guidelines in the United States. In particular, nonacademic institutions were less likely to adhere to recommendations for performance of SSILNs. We found the omission of SSILNs is associated with a significant increase in mortality. © 2017 Elsevier Inc. All rights reserved.

**Keywords:** Penile cancer; Inguinal lymph node dissection; Inguinal lymphadenectomy; Sentinel node biopsy; Survival

## 1. Introduction

Penile squamous cell carcinoma (SCC) spreads predictably to the inguinal lymph nodes (ILNs) [1–3]. Clinical nodal staging is performed by physical examination, yet in patients with nonpalpable ILNs, ILN dissection (ILND) has been shown to reveal micrometastatic disease in approximately 20% to 30% of cases [4,5]. ILND performed

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“prophylactically” is associated with improved cancer specific survival than ILND performed after the patient develops clinically evident ILN involvement [2,6]. Oncologic guidelines recommend surgical staging of ILNs (SSILNs), either with ILND or dynamic sentinel node biopsy (DSNB), in cN0 penile SCC with intermediate to high-risk of harboring ILN metastasis [7,8]. Despite this, there appears to be an underusage of ILND in the United States [7–9]. Reasons for this underusage are speculative, but unfamiliarity with the surgical approaches, perceived lack of clinical benefit, and morbidity associated with inguinal lymphadenectomy may play roles [10–12]. In a recent review of the American Board of Urology, just 1.5% of urologists reported performing ILND in their case logs [13].

Given the rarity of the disease [14], we used the National Cancer Database (NCDB)—a nationwide, hospital-based cancer registry—to study the hospital and patient factors associated with adherence to guidelines for SSILNs in intermediate and high-risk, clinically localized penile cancer. Additionally, we sought to evaluate the impact of pathologic ILN staging on survival outcomes in penile cancer.

## 2. Patients and methods

### 2.1. Data source

The NCDB is a national cancer registry sponsored by the American College of Surgeons (ACS) and the American Cancer Society that collects data on malignancies from ACS-Commission on Cancer (CoC) accredited facilities. It includes approximately 70% of all malignancies diagnosed in the United States from over 1,500 facilities [15–17]. Institutional Review Board approval was waived as NCDB data is deidentified for both patient and facility.

### 2.2. Study population

From 2004 to 2014, there were 11,474 reported cases of cancers involving the penis. The International Classification of Disease for Oncology (third edition) was used to identify men diagnosed with SCC or SCC-variant tumors (codes 8000–8083). Patients with incomplete clinical/pathologic staging or regional lymph node surgery information were excluded. We included only those patients with clinically negative nodes and pathologic pT1b (invasion of subepithelial connective tissue with lymphovascular invasion or high-grade features), pT2 (invasion of corpora), or pT3 disease (invasion of urethra). In 2010, the American Joint Committee on Cancer staging system changed for penile cancer from the sixth to the seventh edition. In the new iteration, pT1 is subdivided into pT1a and pT1b based on the presence of lymphovascular invasion or high-grade features; therefore, no patients with pT1b disease were identified in the period before 2010. The cohort selection

criteria were based on the National Comprehensive Cancer Network (NCCN) guidelines first published in 2013 which recommends ILND or DSNB for intermediate-risk (pT1bG1–2) and high-risk (pT1bG3–4; pT2 or greater) patients with clinically negative ILNs [8]. Similarly, the European Association of Urology (EAU) recommends SSILNs in patients with intermediate-risk (pT1G2) or high-risk disease (pT1G3 or higher) [7].

### 2.3. Definition of surgical SSILNs and covariates

The NCDB records information regarding the performance of “regional lymph node surgery” encompassing both DSNB and ILND as part of the initial treatment plan for patients diagnosed with malignancy. Independent variables recorded in the NCDB registry were analyzed for their association with performance of SSILNs and survival outcomes. Patient level variables included demographics, Charlson-Deyo comorbidity score, insurance status, socioeconomic factors, geographic variables, as well as hospital type [18]. The ACS-CoC categorizes hospitals as academic comprehensive cancer programs, integrated network cancer programs, comprehensive community cancer programs, or community cancer programs based on volume of cancer related treatment, degree of medical services provided, and postgraduate medical training programs [16].

### 2.4. Outcome

The primary outcome of interest was performance of SSILNs. Secondly, we analyzed hospital, patient, and tumor factors to determine predictors of ILN management. The effect of SSILNs on overall survival (OS) was analyzed based on date of initial diagnosis to date of death or censor at last follow-up.

### 2.5. Statistical analysis

Means and standard deviations (SDs) were reported for normally distributed continuous variables. Median and interquartile ranges were reported for nonnormally distributed continuous variables, respectively. Categorical and ordinal variables were presented as proportions. Joinpoint regression was performed to calculate the annual percentage change in SSILNs usage over time. We compared covariates between patients who received SSILNs versus those that did not. Chi-square test was used for categorical values, Mann-Whitney *U* test for ordinal and continuous median comparisons, whereas independent samples *t*-test was used for continuous mean comparisons.

Multivariate binomial logistic regression was performed to ascertain the effect of covariates on the likelihood of SSILNs performance. Kaplan-Meier curves were calculated to compare OS. The effect of covariates on OS was estimated by univariate and multivariate Cox regression analysis to adjust for all observed covariates selected a priori.

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