

The Relationship between Characteristics of Inguinal Lymph Nodes and Pelvic Lymph Node Involvement in Penile Squamous Cell Carcinoma: A Single Institution Experience

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Purpose: We determined predictors of pelvic lymph node metastases in patients with penile cancer.

Materials and Methods: We retrieved a total of 188 node positive inguinal groins from 142 patients treated for penile cancer. Logistic regression models were fitted to test for predictors of pelvic lymph node metastases. The minimum p value method was used to determine the most significant cutoff values of each predictor.

Results: Pelvic lymph node metastases were observed in 45 cases (31.7%). The 5-year cancer specific survival rate was 71.0% vs 33.2% in patients with inguinal vs pelvic lymph node metastases. The most significant cutoff values were 3 inguinal lymph node metastases and a metastasis diameter of 30 mm. According to univariable logistic regression models the number of inguinal metastases (OR 1.92, $p < 0.001$), the diameter of the metastases (OR 1.03, $p = 0.001$) and extranodal extension (OR 8.01, $p < 0.001$) were significant predictors of pelvic lymph node metastases. These variables were also independent predictors of metastases in multivariable logistic regression models ($p \leq 0.012$). Patients with 3 or more inguinal lymph node metastases and those with a metastasis diameter of 30 mm or greater were at 4.77 and 2.53-fold higher risk, respectively, of harboring pelvic lymph node metastases ($p \leq 0.006$). The proportion of metastases increased significantly from 0% in cases with no risk factors to 57.1% when all 3 risk factors were observed ($p < 0.001$).

Conclusions: The number and diameter of inguinal lymph node metastases as well as extranodal extension are significantly associated with pelvic lymph node metastases. These variables should be considered to determine the need for pelvic lymph node dissection. Patients with no risk factors may be spared this dissection.

Key Words: penis; carcinoma, squamous cell; lymph node excision; neoplasm metastasis; prognosis

PELVIC LNM have a tremendously detrimental effect on the survival of patients with penile SCC.¹⁻³ Those with pathologically determined

inguinal LNM are at increased risk for further lymphatic spread to the pelvic lymph nodes.^{3,4} However, the proportion of patients with pelvic

Abbreviations and Acronyms

CSS = cancer specific survival
DSNB = dynamic sentinel lymph node biopsy
EAU = European Association of Urology
ENE = extracapsular extension
LND = lymph node dissection
LNM = lymph node metastases
RSS = risk stratification score
SCC = squamous cell carcinoma

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LNM among those with inguinal LNM is extremely variable. It is difficult to assess pelvic lymph nodes with conventional imaging.^{5,6} Pelvic LND is frequently performed as an adjunct to inguinal LND but it may represent overtreatment in a non-negligible proportion of patients, resulting in additional morbidities and hospitalization costs.^{7,8}

According to the 2010 EAU penile cancer guidelines pelvic LND should be done when 2 or more metastatic inguinal lymph nodes are found at inguinal LND or ENE is observed in at least 1 inguinal lymph node metastasis.⁹ We evaluated predictive factors associated with pelvic LNM in a contemporary population of patients with pathologically determined inguinal LNM.

MATERIALS AND METHODS

Study Population

At our institution 142 consecutive patients with penile SCC and pathologically ascertained inguinal LNM were treated between 1985 and 2012. A total of 188 node positive inguinal groins were evaluated and ipsilateral pelvic lymph node involvement was determined. A total of 28 patients with no clinical evidence of pelvic LNM underwent inguinal LND only. Since they did not experience recurrent disease at a minimum 2-year followup post-operatively, they were included in study and grouped together with individuals without evidence of pelvic LNM at pathological evaluation.

Indications and Surgical Technique

At our institution the indications for and extension of LND for penile cancer slightly changed with time. Until the 2000s only patients with clinically evident nodal disease and those with clinical T2 or greater disease were selected for bilateral inguinopelvic LND. Patients with T1 and grade 1 or 2 SCC of the penis were initially spared from surgery.¹⁰ Since 2001, only patients with a T1 G1 tumor have been spared LND (fig. 1). Inguinal LND was performed in patients with 1) clinical N0 disease in whom DSNB revealed metastases in biopsied node(s) or who had no tracer accumulation in the groin, 2) clinical N0 disease who were at intermediate or high risk for lymph node involvement according to institutional guidelines (all G2 or greater and all pT2 or greater) and who did not undergo DSNB and 3) clinically resectable cN+ disease. Synchronous pelvic LND was performed in patients with cN2 or greater inguinal metastases or pelvic lymph nodes suspicious on preoperative cross-sectional imaging. According to EAU guidelines, delayed pelvic LND was planned when 2 or more positive inguinal lymph nodes were found at pathological examination or ENE was observed in the ipsilateral groin. Inguinal LND consisted of the removal of superficial and deep inguinal lymph nodes.¹¹ Pelvic LND consisted of the removal of external iliac and obturator lymph nodes.

Node Count and Staging

Any lymph node containing viable cancer was counted as positive as well as lymph nodes showing complete

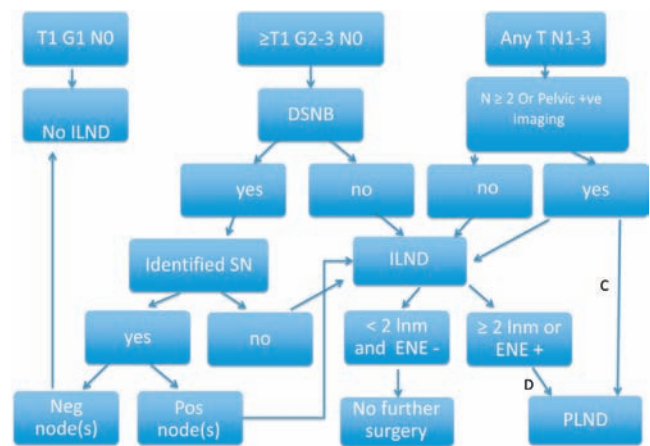


Figure 1. Decisional algorithm for inguinal and pelvic LND in patients with penile cancer treated at our institution since 2001. *ILND*, inguinal LND. +ve, positive. *SN*, sentinel node. *Inm*, LNM. *PLND*, pelvic LND.

pathological remission, considered fibrosis after chemotherapy.^{12–14} A fixed or gross nodal mass was counted as 1 lymph node regardless of size, and as ENE.¹² We used the UICC TNM, 7th edition to determine clinical and pathological nodal category. Pathology reports included the number of lymph nodes removed from each groin, number of positive lymph nodes, ENE and lymph node diameter (maximum diameter determined by the pathologist).

Statistical Analysis

We used the chi-square and Mann-Whitney tests to compare categorical and continuous variables, respectively. The Kaplan-Meier method was used to explore CSS rates and the log rank test was used to compare survival curves. The minimum p value approach according to Mazumdar and Glassman¹⁵ was applied to determine the most significant cutoff value for each variable. Univariable and multivariable logistic regression models were fitted to test the predictors of the primary outcome (pelvic LNM), defined as LNM on pathological evaluation on the same side where positive inguinal lymph nodes were detected. Univariable and multivariable predictive accuracy values were quantified according to the ROC AUC. The method of DeLong et al¹⁶ was used to test the statistical significance of different accuracy values. All statistical tests were performed using S-PLUS Professional, version 1 (MathSoft®) or SPSS®, version 17.0. All tests were 2-sided with statistical significance considered at 0.05.

RESULTS

Descriptive Analysis

Median patient age was 63 years (IQR 53–72). The median number of inguinal lymph nodes removed was 9 (IQR 6–12) and the median number of positive inguinal nodes was 2 (IQR 1–3). The median diameter of positive inguinal lymph nodes was

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