Association Between Lymph Node Density and Disease Specific Survival in Patients With Penile Cancer

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Purpose: We assessed the value of lymph node density for predicting disease specific survival after lymphadenectomy for penile cancer.

Materials and Methods: Data were collected retrospectively in 75 and prospectively in 88 consecutive patients with squamous cell carcinoma of the penis treated at M. D. Anderson Cancer Center between 1979 and 2007. We identified 45 patients with penile cancer and nodal metastasis who underwent lymphadenectomy with curative intent. Lymph node density was analyzed as a categorical variable by grouping patients into 2 or 3 categories based on equal percents. We explored the prognostic value of lymph node density for predicting disease specific survival in this cohort.

Results: Median followup was 23.7 months in all patients. By the time of analysis 22 patients had died, including 18 (82%) of penile cancer and 4 (18%) of other causes. Median lymph node density in patients alive or dead of other causes was 3.4% (IQR 2.9–5.9) compared to 43.3% (IQR 15.6–80) in those dead of disease ($p < 0.001$). Median lymph node density in all patients was 6.7%. Estimated 5-year disease specific survival in patients with lymph node density 6.7% or less was significantly better than that in patients with lymph node density greater than 6.7% (91.2%, 95% CI 53.9–98.8 vs 23.3%, 95% CI 7.0–45.1, $p < 0.001$). In models comparing lymph node density to known prognostic features lymph node density remained statistically significant, while the other factors were no longer statistically associated with disease specific survival.

Conclusions: Lymph node density proved to be a significantly better prognosticator of disease specific survival than the current TNM nodal staging system in patients with penile cancer and nodal involvement. Further independent validation is required to determine the clinical usefulness of lymph node density in this patient population.

Key Words: penis, penile neoplasms, lymph nodes, lymph node excision, prognosis

Abbreviations and Acronyms

DSS = disease specific survival
ENE = extranodal extension
KM = Kaplan-Meier
LN = lymph node
LND = lymph node density

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Study received local institutional review board approval.

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LYMPH node involvement is the single most important prognostic indicator of survival in patients with penile squamous cell carcinoma.[1–3] The finding of nodal metastasis influences the patient outcome more than any clinical or pathological feature of the penile tumor.[1–3] Nevertheless, the outcome varies in patients with pathologically proven nodal disease. The 5-year survival rate in these patients is 0% to greater than 85% depending on the extent of nodal

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involvement.[1–3] Unlike for other genitourinary cancers, the ability of properly performed lymphadenectomy to cure some patients with nodal metastasis is clearly recognized.

In patients with penile squamous cell carcinoma and nodal metastasis the total number of lymph nodes involved with tumor significantly impacts the probability of survival.[4–7] However, neither the total number of involved lymph nodes nor pathological nodal stage captures the completeness of lymphadenectomy or the degree of pathological processing.

LND has been used as a prognostic factor for other solid tumors, including esophageal[8] and bladder[9–11] cancer. LND is defined as the total number of lymph nodes involved with tumor divided by the total number of lymph nodes removed. Thus, this variable simultaneously incorporates the extent of nodal dissection and the nodal disease burden. We explored the prognostic value of LND for predicting DSS in patients with penile cancer and nodal metastasis after lymphadenectomy.

METHODS

All studies were performed after receiving approval from and under the oversight of the local institutional review board. The study cohort represents patients with squamous cell carcinoma of the penis treated at M. D. Anderson Cancer Center between 1979 and 2007. Retrospective data were collected on 75 patients with information available from January 1979 to December 2002. Beginning January 2003 all data on 88 patients were recorded prospectively. For this analysis 49 of these patients who underwent lymphadenectomy were identified with lymph node metastasis. Four of these 49 patients presenting with distant metastatic disease underwent nodal dissection for palliative reasons and were excluded from analysis. Therefore, 45 patients comprised the study population, including 11 with data collected retrospectively and 34 with data collected prospectively.

Pathological nodal status was determined based on 2002 TNM staging criteria (see Appendix).[12] This classification system has not been changed since its introduction in 1987[13] but its prognostic usefulness has been challenged.[2,14] Therefore, we performed additional analysis using a recently proposed pathological nodal staging system (see Appendix).[14] A total of 16 patients received perioperative chemotherapy, including 3 in the neoadjuvant setting, 6 in the adjuvant setting and 6 in the neoadjuvant and adjvuant settings. Chemotherapy was administered based on adverse clinical features and treating physician discretion.

In 41 of 45 patients (91%) the extent of lymphadenectomy was determined using our standard protocol. Patients without clinical evidence of nodal involvement underwent bilateral superficial inguinal lymph node dissection in the presence of high risk primary tumor features, ie lymphovascular invasion, poorly differentiated tumors or tumor stage T2 or greater. Subsequent deep inguinal node dissection and pelvic node dissection were done when 1 or more positive lymph nodes were identified on frozen section analysis. Patients with clinically evident inguinal or pelvic nodal involvement underwent ipsilateral ilioinguinal lymphadenectomy with contralateral superficial inguinal or ilioinguinal dissection based on clinical circumstances. Four patients did not undergo this standard approach, including 3 who underwent unilateral node dissection alone and 1 who underwent unilateral nodal dissection and contralateral needle aspiration biopsy. Our surgical approach to inguinal and pelvic nodal dissection was published previously.[15]

All lymph node packets were dissected out by the pathologists using standard pathology dissection techniques. All lymph nodes were completely submitted for pathological examination except lymph nodes in which metastatic carcinoma was grossly evident. Only representative sections of these grossly positive lymph nodes were submitted for pathological evaluation. Lymph node density was defined as the number of positive nodes divided by the number of nodes harvested from all sites in each patient.

The KM method[16] was used to estimate median DSS. The Mann-Whitney U test was used to compare median LND in different patient groups. The Cox proportional hazards regression model[17] was used to determine the prognostic significance of each variable studied, including LND and TNM nodal status, in univariate fashion. We report the HR for potential prognostic factors with the 95% CI. Because only 18 patients died of disease, no multivariate model was fit to the data.[18] However, we fit models with 2 factors at a time to assess the relative importance of the 2 factors. The total number of lymph nodes excised and the number of positive lymph nodes were not included in these analyses to avoid collinearity. However, they were used to determine LND, which was included as a single variable. In all statistical analyses $p < 0.05$ was considered statistically significant and all p values are 2 sided. All statistical analyses were done using SAS® 9.1 for Windows®.

RESULTS

Table 1 lists clinical and pathological characteristics in the study population. By the last followup 22 patients had died, including 18 (82%) of penile cancer and 4 (18%) of other causes. Another 2 patients had disease. Overall median survival from lymphadenectomy to death from disease or the last evaluation was 85.6 months. Estimated 5-year DSS in the entire study population was 56% (95% CI 38–71).

Median LND in patients alive or dead of other causes was 3.4% (IQR 2.9–5.9) compared to 43.3% (IQR 15.6–80) in patients dead of disease ($p < 0.001$). The relationship between LND and death from disease was analyzed using the KM method after patient categorization by LND into 2 and 3 equal percentiles (fig. 1). Estimated 5-year DSS in patients with LND 6.7% or less was significantly better than that in patients with LND greater than 6.7% (91.7%, 95% CI 53.9–98.8 vs 23.3%, 95% CI 7.0–45.1, $p < 0.001$). Similarly estimated 5-year DSS was sig-