Establishing Criteria for Bilateral Pelvic Lymph Node Dissection in the Management of Penile Cancer: Lessons Learned from an International Multicenter Collaboration

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Abbreviations and Acronyms

EAU = European Association of Urology

ENE = extranodal extension

LAD = lymphadenectomy

LNM = lymph node metastasis

NCCN® = National Comprehensive Cancer Network®

OS = overall survival

PLND = pelvic lymph node dissection

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Study received internal review board approval at each center.

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Purpose: Penile carcinoma with bilateral pelvic lymph node metastasis is a relatively rare condition with poor outcomes. There are little data available on optimal strategies for staging and treating this group of patients. We assessed factors predicting bilateral pelvic lymph node metastasis in patients with penile cancer and confirmed inguinal lymph node metastasis.

Materials and Methods: Multi-institutional data from a total of 4 centers in Europe, the People's Republic of China and the United States were retrospectively analyzed. Patients with penile carcinoma and inguinal lymph node metastasis who underwent bilateral pelvic lymphadenectomy were included in analysis. The Kaplan-Meier and log rank tests were used to express overall survival. Logistic regression was used for multivariate analysis of factors predicting bilateral pelvic lymph node metastasis. Cox regression was done in the multivariable analysis of overall survival.

Results: We identified 140 patients with penile carcinoma who had confirmed pelvic lymph node metastasis. Of the patients 83 had bilateral inguinal lymph node metastasis and 64 underwent bilateral pelvic lymphadenectomy. Bilateral pelvic lymph node metastasis was observed in 16 patients (25%). The ROC of the total number of inguinal lymph node metastases and the detection of bilateral pelvic lymph node metastasis had an AUC of 0.76 ($p = 0.002$) with 95% sensitivity for the cutoff point of 4 inguinal nodes. On logistic regression analysis the detection of 4 or more positive inguinal nodes was the only independent predictor of bilateral pelvic lymph node metastasis (OR 14.0, CI 1.71–115). On Cox regression analysis 4 or more inguinal lymph node metastases, adjuvant chemotherapy, inguinal extraprostatic extension and bilateral procedures were associated with overall survival.

Conclusions: Patients with bilateral inguinal lymph node metastasis who are treated with unilateral pelvic lymphadenectomy should be considered for bilateral pelvic lymphadenectomy in the presence of 4 or more metastatic inguinal nodes.

Key Words: penile neoplasms, lymph node excision, algorithms, neoplasm metastasis, mortality

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PENILE cancer is a relatively uncommon urological malignancy. Additionally, inguinal and subsequent pelvic LNMs are seen only in a fraction of penile cancer cases.[1] Therefore, there is a relative lack of data on the natural history and treatment strategies for these men, in particular those with pathological involvement of pelvic lymph nodes.

Secondary to relative unreliability of pelvic imaging,[2] several groups have identified risk factors for predicting pelvic LNM in the presence of inguinal LNM.[3–5] Based on these studies the EAU and NCCN® have clinical guidelines pertaining to this topic.[6–8] However, these data and recommendations do not distinguish between patients with unilateral or bilateral inguinal disease. It is known that patients with bilateral LNM have a different clinical course with worse survival.[8,9] Therefore, alternative criteria may need to be considered when defining indications for pelvic LAD in patients with bilateral inguinal LNM.

The objectives of this study were to report clinical outcomes using multi-institutional data on patients with pelvic LNM, assess factors predicting bilateral pelvic LNM in patients with pathologically confirmed inguinal nodes who meet criteria for unilateral pelvic LAD and propose specific criteria for bilateral LAD in patients treated for penile cancer.

METHOD

Study Population

Four international institutions in The Netherlands, Italy, the People's Republic of China and the United States (70, 53, 11 and 6 patients, respectively) contributed to this study. Relevant internal review board approval was obtained at each center. Data were collected on patients with stage pT1-4 N3 M0 squamous cell carcinoma of the penis. All patients had inguinal and pelvic LNM on at least 1 side. The decision to perform pelvic LAD has varied with time in each institution but currently it is based on 2 or more inguinal LNMs, ENE or suspicious pelvic imaging.[3–5] The PLND technique was similar at all 4 locations with at the minimum removal of all lymphatic tissue in the obturator, internal iliac and external iliac regions. All procedures were performed as open surgery. Histopathology results are reported according to the 2009 TNM classification, 7th edition, for penile cancer.

Indications for Additional Therapies

Systemic therapy was given in neoadjuvant, adjuvant or salvage fashion. When used in the neoadjuvant setting, indications for chemotherapy included locally advanced unresectable primary tumor and cN2-N3 disease. Chemotherapy regimens were platinum based (cisplatin, 5-fluoroacil and docetaxel, cisplatin, bleomycin and methotrexate or cisplatin, paclitaxel and ifosfamide) or vincristine, bleomycin and methotrexate. The indications for adjuvant external beam radiotherapy and the extent of treatment varied across centers, following single institutional policies secondary to the absence of evidence-based guidelines.

Statistics

Categorical and continuous variables were compared with the chi-square test and Mann-Whitney U-test, respectively. Survival analysis was performed using the Kaplan-Meier method. Group comparisons were done with the log rank test. Logistic regression analysis was used to form a model to assess factors predicting bilateral pelvic LNM. Only the 2 most clinically relevant factors (ENE and the number of inguinal LNMs) were included on multivariate analysis, given the small number of events for the dependent variable. The ROC curve of the total number of positive inguinal nodes and the presence of bilateral pelvic LNM was plotted. A cutoff point for the number of inguinal LNMs predicting pelvic LNM was chosen based on ROC curve values as well as on the minimum p value method.[10] The lowest number of positive inguinal nodes with the smallest p value predicting bilateral pelvic LNM was chosen as the cutoff point to stratify the data. Cox proportional HR was used in multivariable analysis for OS.

RESULTS

From 1978 to 2014, 83 patients with bilateral inguinal LNM and pelvic LNM were included in study. Median age of this cohort was 64 years (range 51 to 71). Of the patients 34 (41%) received pelvic radiotherapy postoperatively. An additional 27 and 14 patients received chemotherapy preoperatively and postoperatively, respectively, and a further 11 received palliative chemotherapy.

Of the patients 64 (77%) underwent bilateral pelvic LAD and 15 were treated with unilateral pelvic LAD. This information was not available on 4 patients. A total of 16 patients had bilateral pelvic LNM (table 1).

The median number of total metastatic inguinal nodes was 4 (range 2 to 5) in unilateral and 6 (range 5 to 7) in bilateral pelvic LNM cases ($p < 0.001$). The proportion of inguinal nodes with ENE was similar in the unilateral and bilateral pelvic LNM groups (85% vs 81%, $p = 0.69$, table 1).

Predictors of Bilateral Pelvic LNM

The subgroup of 64 patients with bilateral inguinal LNM treated with bilateral pelvic LAD was assessed for predictors of bilateral pelvic disease. A ROC curve was plotted of the total number of positive inguinal nodes and the presence of bilateral pelvic disease. The AUC was 0.76 ($p = 0.002$, fig. 1). Based on p values the lowest number of total metastatic inguinal nodes that significantly predicted bilateral pelvic LNM was 4. This point had 95% sensitivity for detecting bilateral pelvic LNM on the ROC curve. Bilateral pelvic LNM was seen in only