Long-Term Followup of Penile Carcinoma With High Risk for Lymph Node Invasion Treated With Inguinal Lymphadenectomy

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Purpose: The current penile cancer problem is defining lymph node invasion types for which inguinal lymphadenectomy is effective in terms of patient survival and the number of inguinal metastases beyond which combination therapy should be proposed. We evaluated survival of patients with penile cancer at high risk for lymph node invasion treated with inguinal lymphadenectomy.

Materials and Methods: A total of 114 patients underwent lymphadenectomy for penile cancer with no palpable inguinal lymph nodes (cN0) but at intermediate or high risk for lymph node invasion, or with 1 or several palpable inguinal lymph nodes (cN1–3). All patients were initially treated for primary penile cancer with clinical and pathological inguinal lymph node staging. Bilateral superficial superomedial, ipsilateral radical plus contralateral modified and bilateral radical procedures were done in 50 cN0, 35 cN1 and 29 cN2–3 cases, respectively. Overall specific and recurrence-free survival was calculated by Kaplan-Meier curves with differences calculated by the log rank test.

Results: Five-year disease-free survival was 93.4%, 83.7%, 32% and 0% for stages cN0 to cN3, and 93.4%, 89.7%, 30.9% and 0% for stages pN0 to pN3, respectively, with a statistically significant difference for cN0–1 vs cN2–3 and pN0–1 vs pN2–3 ($p < 0.001$). The recurrence rate was 10.5%, 10.3%, 32.6% and 30.0% for stages pN0 to pN3, respectively.

Conclusions: After inguinal lymphadenectomy specific and recurrence-free survival in cN1 and pN1 cases was comparable to that in cN0 and pN0 cases. The recurrence rate in the latter was higher than for other occult inguinal metastasis detection techniques. Only superomedial inguinal lymph nodes were studied, missing central and lateral superior zone occult metastasis. Survival was poor in patients with more than 2 lymph nodes invaded. In those cases chemotherapy protocols or chemotherapy combined with lymphadenectomy must be evaluated.

Key Words: penis; carcinoma, squamous cell; mortality; lymph nodes; lymph node excision

Abbreviations and Acronyms

CT = computerized tomography
IL = inguinal lymphadenectomy
MIL = modified IL
RIL = radical IL

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SQUAMOUS cell carcinoma of the penis is a rare tumor in Europe, representing less than 1% of all cancers in men, in which inguinal lymph node invasion is an independent prognostic factor.[1–6] IL has an important role in the treatment strategy for penile carcinoma with clinical lymph node invasion. Tumors with minimal, clinical or subclinical inguinal lymph node involvement without lymph node extracapsular invasion or iliac node involvement can be treated with curative intent with IL alone.[7,8]

In patients with clinically node negative (cN0) disease the occult lymph node metastasis rate is around 20% and routine elective IL repre-

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sents overtreatment in most patients. European Association of Urology guidelines define groups at high risk for subclinical metastasis as a function of tumor pT stage, histological grade, and venous and/or lymphatic emboli, including low—pTis, pTa/grade 1–2 or pT1/grade 1, intermediate—pT1/grade 2 and high—pT2 or greater, or grade 3.[9,10] In the high or intermediate risk group subclinical metastasis can be detected by intraoperative lymph node mapping, as proposed by Kroon et al,[11] or by superficial IL modified from the technique of Catalona.[12] These 2 methods are associated with low morbidity.

The current problem consists of defining forms of lymph node invasion for which IL is effective in terms of patient survival and the cutoff number of inguinal metastases beyond which combination therapy (surgery, radiotherapy and chemotherapy) should be proposed. We evaluated disease specific and recurrence-free survival achieved by IL in 114 patients with infiltrative penile cancer.

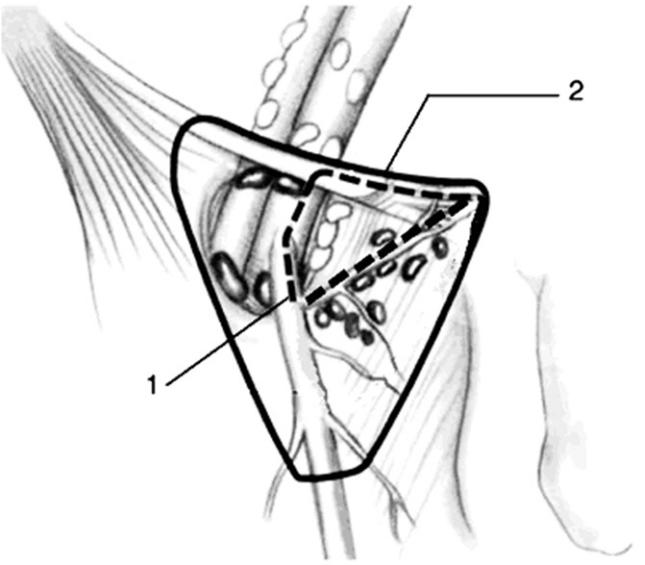

Figure 1. Anatomical limits of MIL (*1*) and RIL (*2*)

MATERIALS AND METHODS

Population

Between 1986 and 2006 IL was done in 114 patients with penile cancer and no palpable inguinal lymph nodes (cN0) but at intermediate or high risk for lymph node invasion, or with 1 or several palpable inguinal lymph nodes (cN1–3) according to the 2002 TNM classification. Cases of fixed inguinal lymph nodes were classified as cN3. Mean ± SD age was 63.3 ± 11.4 years (range 25 to 94). Study exclusion criteria were poor clinical conditions for surgery, distant metastasis, unresectable tumor and low risk of inguinal metastasis, that is clinically node negative and pTis, or pTaG1-2 or pT1G1 disease.

All patients were initially treated for primary penile cancer with clinical and pathological inguinal lymph node staging. The primary tumor with a mean diameter of 30 ± 14 mm (range 7 to 60), which was localized to the glans and coronal sulcus in 92.2% of cases, was treated with conservative surgery in 19.3% and by amputation in 80.7%. According to the European Association of Urology classification 99 and 15 patients were classified as at high or intermediate risk, respectively.[10] Inguinal lymph node status was assessed by bilateral physical examination, ultrasound and abdominopelvic/inguinal CT. Initially 71 patients (62.3%) had palpable inguinal lymph nodes but after antibiotic treatment only 64 (56.1%) had cN+ disease. The change was observed in 7 initially cN2 cases with bilateral multiple but lower inguinal lymph nodes, which were finally staged cN0.

IL Type

Figure 1 shows the anatomical limits of modified and radical lymphadenectomy. Inguinal lymph node pathological staging was done by lymphadenectomy with extent based on cN stage.

Bilateral superficial MIL was done in 50 patients with cN0 at high or intermediate risk for lymph node metastasis with negative CT, according to the Catalona technique.[12] A mean of 3.2 ± 1.1 lymph nodes (range 2 to 5) was removed by each MIL. When subclinical metastasis was discovered on frozen section examination, surgery was completed by ipsilateral RIL. Ipsilateral RIL and contralateral MIL were done in 35 cN1 cases. A mean of 12.0 ± 3.6 lymph nodes (range 7 to 18) was removed by each RIL. Iliac lymphadenectomy was done in 3 cases at the same procedure when there was macroscopic extracapsular extension, or subsequently when several lymph node metastases were identified on frozen section. Bilateral RIL was done in 29 cN2–3 cases. It was associated with bilateral iliac lymphadenectomy in 11 cases, including 7 of cN3 and 4 of cN2 with suspected pelvic lymph nodes on CT. Metastatic lymph node diameter and extracapsular extension were not included in the study since these data were not reported in several cases.

No patient received adjuvant therapy after lymphadenectomy. Second line treatment with surgery and/or chemotherapy was done when there was local recurrence or metastasis. The chemotherapy used during this period was 1,000 mg/m^2 5-fluorouracil intravenously on days 1 to 5 and 100 mg/m^2 cisplatin intravenously on day 1 repeated with a 3-week interval for a maximum of 5 cycles.

Statistical Analysis

Disease specific and recurrence-free survival was calculated from the date of diagnosis to the date of death or last followup, and lymph node and/or systemic recurrence. Statistical analysis was done with StatView®, version 5.0. Overall recurrence-free and disease specific survival was determined by the Kaplan-Meier method. Clinical and histological data were analyzed as factors predictive of survival with statistical comparison using the log rank test and results considered statistically significant at $p < 0.05$.