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Disease-specific survival after radical lymphadenectomy for penile cancer: Prediction by lymph node count and density[1]

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Abstract

Objective: To investigate the value of removed lymph node (LN) count and LN density (LND) for predicting disease-specific survival (DSS) rate following radical lymphadenectomy in patients with penile cancer.

Methods: We retrieved data from 146 patients who were surgically treated between 2002 and 2012. receiver-operating characteristic curve analysis was used to calculate the optimal cutoff value of LN count and LND for predicting DSS rate. LND was analyzed as a categorical variable by grouping patients with pN+ tumors into 2 categories. Multivariate Cox regression analysis was used to test the effect of various variables on DSS rate based on collinearity in various models.

Results: Median follow-up was 42 months. Overall, 75 patients (51.4%) had pN0 disease, and 71 patients (48.6%) had pN+ disease. The optimal cutoff value of LN count and LND were 16% and 16%, respectively. Among patients with pN0 tumors, the number of LNs removed ($\geq$16 LNs) was an independent significant predictor of DSS rate in univariate and multivariate analyses (all $P < 0.05$). Stratifying pN+ patients as above versus below the LND threshold demonstrated significant differences in 5-year DSS: 81.2% versus 24.4% ($P < 0.001$). In multivariate models including known prognostic factors, LND was a statistically significant independent predictor of DSS rate (hazard ratio = 4.31 and 3.96 for above vs. below the LND threshold, respectively).

Conclusions: The removal of at least 16 LNs was associated with a significantly longer DSS rate in patients with pN0 penile cancer. Additionally, an LND above 16% is an independent predictor of DSS rate in patients with pN+ tumors. Further independent validation is required to determine the clinical usefulness of LN count and LND in this patient population.

Keywords: Lymph nodes; Lymph node excision; Penile neoplasms; Penis; Prognosis

1. Introduction

The value of properly performed inguinal lymphadenectomy (ILAD) in the treatment of penile cancer is undisputed. Nevertheless, the outcome of the procedure varies widely in patients with pN+ disease [1–4]; prognostication is clearly important in these patients. The lymph node (LN) status is the most important prognostic factor in penile cancer [1,2,5–8]. Therefore, the 7th TNM system stratifies patients with penile cancer with the absolute number and extent of positive nodes for nodal staging [9]. However, there has been little investigation into the optimal number of LNs that should be removed for improving survival in patients with penile cancer [10]. Moreover, LN density (LND) has recently emerged as a prognostic factor for predicting survival after surgery for other solid tumors, including esophageal [11], bladder [12,13], cervical [14], breast [15], and oral cancer [16]. Such a ratio, which has

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been rarely studied in penile cancer, attempts to compensate for surgical and pathological bias due to limited ILAD by recapitulating 2 pieces of information.

However, the updated European Urological Association (EAU) guidelines on penile cancer have not yet addressed the issue of LN count and LND in predicting survival rate [17]. Previous studies on this issue in penile cancer have several drawbacks. First, the number of patients is relatively small [18], the laterality of LNs is not described and patients with only one removed LN are included [10]. Second, the results comprise patients who were treated some time ago: between 1979 and 2007 [18], 1988 and 2005 [10], and 1990 and 2008 [19]. Also, the definition of LND was not accurate in some studies [18]. Finally, some studies incorrectly labeled ILAD of 8 or less nodes as extensive ILAD [10]. Previous studies in patients with other solid tumors hold the view that LND offers a proxy measure to standardize the differences in the number of LNs harvested by accounting for tumor burden in the numerator and extent of dissection in the denominator [11–13]. Less extensive dissection is associated with high rates of non-detected nodal metastases or compromised oncological effectiveness. In addition, how the lymphatic tissue is sent to the pathologists (separate packets vs. en bloc) and how the pathologist handles the tissue also affect the numerator and denominator of LND, thereby making the establishment of LND thresholds more problematic.

In the current study, we optimized LN harvesting by using a standardized lymphadenectomy template [20], submitting LN packets separately and having a dedicated uropathologist evaluate the specimens. The objectives of this analysis were to determine the prognostic values of LN count and LND in a contemporary series of 146 men with penile cancer.

2. Materials and methods

2.1. Patients

The study cohort represents patients with squamous cell carcinoma of the penis treated at our institution between January 2002 and July 2012. Data on 114 patients treated before 2009 were collected retrospectively. Since then, data from another 111 patients had been recorded prospectively. Clinical staging consisted of primary tumor evaluation; inguinal palpation to assess the presence or absence of identifiable LNs; and computerized tomography of the chest, abdomen, and pelvis. Cases with the following criteria were excluded from the study: neoadjuvant chemotherapy, previous surgery or radiotherapy of the inguinal region, clinical evidence of distant metastasis, resection of the primary lesion only, and loss to follow-up. In total, 146 patients treated with bilateral ILAD composed the study population, including 70 with data collected retrospectively and 76 with data collected prospectively. The protocol was approved by the local institutional review board.

2.2. Treatment

The treatment protocols were discussed with each patient. Patients were categorized as 3 risk groups for developing nodal metastases according to EAU guidelines, including low—pTis, pTa/grades 1 to 2, or pT1/grade 1; intermediate—pT1/grade 2; and high—pT2 or greater, or grade 3 [21]. From 2002 to 2011, lymphadenectomy was suggested for intermediate- and high-risk cases, whereas low-risk patients were given the choice of surgery or surveillance. In 2011, this practice was replaced by preoperative ultrasound with fine-needle aspiration cytology and dynamic sentinel LN biopsy. We previously published the details of the anatomically defined radical ILAD [4]. Surgeries were routinely performed bilaterally by 3 experienced urologists. Pelvic lymphadenectomy was not routinely performed before January 2009. Following that time, pelvic lymphadenectomy was performed when histopathology revealed extranodal extension of a metastatic node or the involvement of 2 or more inguinal LNs. The template of pelvic lymphadenectomy included external iliac, obturator, internal iliac, and common iliac LNs. Adjuvant chemotherapy or radiation therapy was advised in case of pN2 and pN3 tumors.

2.3. Histopathology

The LN packets were submitted separately according to anatomical landmarks. A standard method of processing node packages was used, including manually dissecting the LNs from surrounding adipose tissue under bright light. If no nodes could be palpated, the tissue was submitted for microscopic examination in its entirety. All tissue sections were stained with hematoxylin and eosin, and evaluated by 2 uropathologists. The total number of histopathologically confirmed LNs and metastatic nodes was recorded for each lymphadenectomy specimen. All histopathology reports were based on the 2009 American Joint Committee on Cancer TNM system [9].

2.4. Statistical analysis

The receiver-operating characteristic (ROC) curve analyses were performed to examine and graphically explore the probability of finding LN metastasis relative to the number of histopathologically confirmed LNs. All eligible cases were first categorized into 2 cohorts based on pathological LN status. Further, these 2 cohort of patients were stratified by the number of histopathologically confirmed LNs (≥ 16 LNs vs. <16 LNs) (data shown below). Patients with pN+ disease were divided into 2 risk groups according to LND. In cases where the denominator was large (e.g., among patients without pelvic LN metastasis undergoing a pelvic lymphadenectomy), LND might be "diluted" or rendered less relevant. Therefore, LND was defined as the number of positive nodes divided by the number of removed LNs, which may or may not include the number of pelvic LNs