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Original article

Adjuvant pelvic radiation is associated with improved survival and decreased disease recurrence in pelvic node-positive penile cancer after lymph node dissection: A multi-institutional study

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Abstract

Purpose: Few studies have examined the role of radiation therapy in advanced penile squamous cell carcinoma. We sought to evaluate the association of adjuvant pelvic radiation with survival and recurrence for patients with penile cancer and positive pelvic lymph nodes (PLNs) after lymph node dissection.

Materials and methods: Data were collected retrospectively across 4 international centers of patients with penile squamous cell carcinoma undergoing lymph node dissections from 1980 to 2013. Further, 92 patients with available adjuvant pelvic radiation status and positive PLNs were analyzed. Disease-specific survival (DSS) and recurrence were analyzed using the Kaplan-Meier method and multivariable Cox proportional hazards model.

Results: 43% ($n = 40$) of patients received adjuvant pelvic radiation after a positive PLN dissection. Median follow-up was 9.3 months (interquartile range: 5.2–19.8). Patients receiving adjuvant pelvic radiation had a median DSS of 14.4 months vs. 8 months in the nonradiation group, respectively ($P = 0.023$). Patients without adjuvant pelvic radiation were associated with worse overall survival (hazard ratio [HR] = 1.7; 95% CI: 1.01–2.92; $P = 0.04$) and DSS (HR = 1.9; 95% CI: 1.09–3.36; $P = 0.02$) on multivariable analysis. Median time to recurrence was 7.7 months vs. 5.3 months in the radiation and nonradiation arm, respectively ($P = 0.042$). Patients without adjuvant pelvic radiation was also independently associated with higher overall recurrence on multivariable analysis (HR = 1.8; 95% CI: 1.06–3.12; $P = 0.03$).

Conclusions: Adjuvant pelvic radiation is associated with improved survival and decreased recurrence in this population of patients with penile cancer with positive PLNs.

Keywords: Adjuvant radiation; Lymph node dissection; Penile cancer; Recurrence; Survival

1. Introduction

Squamous cell carcinoma of the penis is a rare urologic malignancy that represents only 0.4% to 0.6% of all malignant neoplasms in the United States and Europe [1]. Prognosis is largely stage dependent with pelvic lymph

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node (PLN) involvement and extranodal extension (ENE) associated with poor overall survival (OS) [2,3]. Various factors have been shown to predict PLN metastasis including inguinal ENE, extent of inguinal lymph node metastasis, and inguinal lymph node diameter [4].

Advanced stages have posed many challenges in penile cancer management owing to a paucity of literature secondary to its rarity. As a result, treatment recommendations have not been uniform in nodal disease. Management options available include a multimodal approach with surgical resection, chemotherapy, and radiation. In high-risk patients, such as the presence of PLN metastasis and ENE, the National Comprehensive Cancer Network (NCCN) recommends considering adjuvant external beam radiation therapy or chemoradiotherapy [5]. The European Association of Urology (EAU), on the contrary, recommends adjuvant chemotherapy for pN2 and pN3 disease.

The role of radiation therapy in penile cancer has also not been well defined owing to sparse published data and mixed results [6–9]. Most of these studies report outcomes related to radiation of inguinal regions in the neoadjuvant and adjuvant settings. Although some reports present a subgroup analysis of pelvic radiation showing no benefit, the cohorts are underpowered with conclusions that are strongly suggestive but not definitive [6,7]. Despite the lack of positive evidence supporting pelvic radiation in penile cancer, it remains a reasonable option to consider owing to the extrapolated efficacy of radiation in other locally advanced or node-positive squamous cell carcinomas such as vulvar and head-and-neck malignancies [10,11]. Therefore, we investigated the treatment results of adjuvant pelvic radiation in patients with known positive PLN. Using a large, multi-institutional, and international cohort, we sought to evaluate the association of adjuvant pelvic radiation with OS, disease-specific survival (DSS), and recurrence.

2. Materials and methods

2.1. Patients and demographics

We performed a retrospective review of 92 patients who underwent inguinal and PLN dissection for locally advanced penile cancer. All patients had adjuvant pelvic radiation status recorded. This cohort was obtained across 4 international tertiary referral centers from 1980 to 2013 following institutional review board approval at all participating institutions. All patients were found to have positive nodes after PLN dissection (pN3) and were not known to be metastatic at the time of dissection. Disease characteristics recorded included primary penile tumor stage (pT), presence of inguinal and pelvic ENE, and number of positive PLNs. Recurrence was defined as clinical evidence of disease on physical examination or imaging after PLN dissection. The location for disease recurrence were recorded as local (penile resection bed), regional (inguinal or pelvic), or distant (lungs, bones, peritoneum, or liver). If disease recurrence occurred in multiple locations, the worse site was recorded. Postoperative chemotherapy was defined as chemotherapy given in the adjuvant setting. Preoperative chemotherapy was defined as chemotherapy given in the neoadjuvant setting. Chemotherapy regimens were either platinum based (cisplatin and 5-FU ± docetaxel; cisplatin, bleomycin, and methotrexate; cisplatin, paclitaxel, and ifosfamide) or with vincristine, bleomycin, and methotrexate. Follow-up for overall and DSS was defined as time of PLN dissection to the date of last contact or date of death. Follow-up for recurrence was defined as time of PLN dissection to date of last contact or date of recurrence. Complete follow-up data for survival was available for all patients. Complete follow-up data for recurrence was available for 91 (99%) patients in the cohort.

2.2. Description of PLN dissection

Before 2008, indications for undergoing PLN dissection were not uniform across centers owing to the lack of available standardized guidelines. However, during the past 5 years of the study, the decision to perform a unilateral or bilateral PLN dissection was based on NCCN and EAU guidelines, which recommend proceeding with a PLN dissection for inguinal ENE or 2 or more positive inguinal lymph nodes [5,12]. Surgical technique was similar across the 4 centers, which included dissection of obturator, internal iliac, and external iliac lymph nodes.

2.3. Histopathological examination

Pathological examination of all PLN was performed at each respective center and classified according to the TNM system of the American Joint Committee on Cancer [13]. Cases before 2010 were reclassified according to the 2010 TNM system. ENE was defined as the extension of tumor through the lymph node capsule into the perinodal fibrous-adipose tissue.

2.4. Indications for adjuvant radiation therapy

Radiation was provided at the discretion of the radiation oncologist at each respective center. All pelvic radiation was given in the adjuvant setting without evidence of recurrence at the time of treatment. In most instances, adjuvant pelvic radiation therapy was offered by the treating physician based on the presence of high-risk features for locoregional recurrence such as positive surgical margins or pelvic ENE. The pelvic radiation field included bilateral iliac, presacral, and obturator regions. However, indications for adjuvant pelvic radiation were not standardized given the absence of evidence-based guidelines and were based largely on the respective institutional policies. Adjuvant therapy was given within 1 to 4 months after PLN