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Original article

Is there a benefit to adjuvant radiation in stage III penile cancer after lymph node dissection? Findings from the National Cancer Database

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Abstract

Objective: The role of adjuvant radiation in advanced penile cancer (PC) is unknown. We used the National Cancer Database (NCDB) to determine factors associated with receiving adjuvant radiation (aXRT) and their influence on prognosis in men who underwent inguinal lymph node dissection (ILND) for stage III disease.

Materials and methods: We queried the NCDB from 1998–2012 for all men with PC who had pathologic nodal status and aXRT data available. Clinical and pathologic variables associated with aXRT were examined using chi-square testing. Logistic regression evaluated the odds of receiving aXRT while multivariate Cox regression analysis evaluated the influence of aXRT on overall survival (OS).

Results: A total of 589 patients underwent ILND for stage III PC with 23% ($N = 136$) receiving aXRT. Mean age was 61.8 ±13.7 years. Factors associated with receiving aXRT included higher pathologic nodal stage (MV OR 1.85, 95% CI: 1.13–3.05), while greater distance of travel (MV OR 0.48, 95% CI: 0.25–0.92), and treatment in an academic setting (MV OR 0.53, 95% CI: 0.35–0.81) were inversely associated with receiving aXRT. On Cox regression analysis, aXRT improved OS (combined HR 0.58, 95% CI: 0.39–0.86), which appeared to have been driven by higher nodal burden (N2: HR 0.53, 95% CI: 0.32–0.88; N1: HR 1.36, 95% CI: 0.60–3.09).

Conclusions: Determinants of aXRT delivery in stage III PC appear to be related to the proximity to community cancer centers and greater nodal burden. We find evidence of a survival benefit with the use of aXRT, particularly in those with higher nodal stage. Multi-institutional studies are needed to confirm these findings and improve treatment algorithms for high-stage PC.

Keywords: NCDB; Penile cancer; Inguinal lymph node dissection; Adjuvant radiation

1. Introduction

Penile cancer (PC) is a relatively rare disease with only 2,120 new cases estimated in 2017, resulting in ~360 deaths (17%) [1]. Survival in PC is dependent upon stage of disease with organ-confined disease (stage I and II) projecting ~85% 5-year survival rates, while those with local spread and lymph node involvement (stage III) have worsened outcomes (~59% 5-year survival rates). [1] As this disease is uncommon, much of the devoted literature comes from single or a limited number of institutions [2–10]. Further, there are no randomized data evaluating different treatment modalities for high-stage disease, and existing guidelines provide limited guidance on the use of adjuvant radiation therapy (aXRT). In other squamous cell carcinoma malignancies, such as vulvar and head and neck cancer, guideline statements outline adjuvant radiation as standard of care for advanced disease [11,12], revealing improved recurrence-free survival or improved overall survival [13,14].

Population databases can play a valuable role in gaining insights about rare diseases such as PC, resulting in hypothesis generating work for future clinical trials. To this end, we queried the National Cancer Database (NCDB) from 1998–2012, to identify men who underwent inguinal lymph node

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dissection (ILND) for stage III PC (T1–3, N1–2), and had groin or pelvis aXRT data available. We then utilized this cohort to evaluate factors associated with receiving aXRT and the influence of aXRT on overall survival.

2. Materials and methods

2.1. Data source

The National Cancer Database (NCDB) is a nationwide oncologic database, founded in 1989, by the American College of Surgeons and the Commission on Cancer in conjunction with the American Cancer Society [15]. Thought to be one of the largest clinical registries in the world, NCDB collects approximately 70% of all new invasive cancer diagnoses in the United States [15]. This database includes patient demographic and socioeconomic variables as well as hospital site-specific factors and referral patterns. Cancer-specific variables include tumor characteristics, grade, stage, treatment, and vital status at the time of last follow up [15,16]. All staging refers to the AJCC Cancer Staging Handbook, Seventh Edition (2010) [17].

2.2. Study population

We queried the NCDB from 1998–2012 to identify men with penile cancer who underwent ILND and had information regarding pelvic or groin aXRT. Patients were limited to final pathologic, AJCC stage III penile cancer (pT1–3, N1–2) with squamous cell carcinoma (SCC) histology. Demographic variables included age, race (White, Black, Asian, or Other), Charlson-Deyo score, year of diagnosis, median household income (by zip code), insurance type, facility type, and distance of travel (<50 vs. ≥ 50 miles from home zip code to treating hospital). In the NCDB, the Charlson-Deyo variable is a truncated score given the majority of patients have a baseline Charlson Comorbidity index of <2, with a score of zero indicating no comorbid conditions were recorded [18]. The principle facilities examined within NCDB include Comprehensive Community Cancer Programs (CCCP, Accessions of more than 500 or more newly diagnosed cancer cases each year), Community Cancer Programs (CCP, Accessions more than 100 but fewer than 500 newly diagnosed cancer cases each year), and Academic Comprehensive Cancer Programs (ACAD, Provides postgraduate medical education in at least 4 program areas, including internal medicine and general surgery with accessions of more than 500 newly diagnosed cancer cases each year) (www.facs.org). Additional clinical and pathological variables included size of primary tumor, primary treatment (ablation, partial/total penectomy, no surgery) stage, grade, presence of nodal involvement, lymph node density, extra-nodal extension, presence of lymphovascular invasion, chemotherapy status, and radiation treatment data. Some variables (ENE, LVI) were only recorded for the years 2010–2012.

2.3. Statistical analysis

Chi-square analysis and univariate and multivariate logistic regression were performed to evaluate demographic factors associated with receiving adjuvant radiation therapy. Univariate logistic regression analysis was performed for each variable of interest with subsequent multivariate analysis performed on those variables with significance ($P < 0.05$). Multivariate Cox regression, adjusting for year of diagnosis, age, race, Charlson-Deyo score, pathologic T stage, grade, nodal stage, and primary surgery was performed to evaluate aXRT effects on overall survival (OS). Stratified analyses were then performed on N1 and N2 patients separately. All analyses were performed on Stata 14 (Stata, Inc., College Station, TX).

3. Results

3.1. Demographic variables associated with aXRT

A total of 589 patients with stage III PC underwent ILND with 23% ($N = 136$) receiving aXRT. Age, comorbidities, income, and insurance type were not associated with receiving aXRT on chi-square analysis. Patients treated in an academic setting and those with further distances to travel (≥ 50 miles) were less likely to receive aXRT ($P < 0.001$; $P = 0.003$, respectively) (Table 1). These latter 2 findings were confirmed on both univariate and multivariate logistic regression analysis with patients treated at academic centers being ~50% less likely to receive aXRT compared with community cancer programs (adjusted Odds Ratio [OR] 0.53, 95% CI: 0.35–0.81) with a similar decrease found in those traveling greater distances (adjusted OR 0.48, 95% CI: 0.25–0.92).

3.2. Pathologic variables associated with receiving aXRT

For those whom radiation dosing is available, 75% ($N = 442$) received at least 4,500 cGy and 45% ($N = 265$) of men received a radiation boost. Size of the primary tumor, primary treatment type, pathologic stage, and histologic differentiation were not associated with receiving aXRT. A larger proportion of cN2 patients received aXRT, compared with all others at diagnosis ($P < 0.001$) (Table 2). Increasing pathologic nodal stage and lymph node density were also significantly associated with receiving aXRT ($P = 0.03$; $P = 0.003$, respectively). A small percentage of the patient population received chemotherapy ($N = 169$) with 49% of these patients receiving aXRT ($N = 82$). The timing of the relationship between radiation and chemotherapy is unavailable in the NCDB, and there is no information on specific chemotherapy regimens, though 76% ($N = 448$) of patients received "multi-agent" chemotherapy. On univariate and multivariate analysis, patients with N2 disease were