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Original article

Contemporary survival trends in penile cancer: Results from the National Cancer Database

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Abstract

Objective: To investigate contemporary survival trends in penile cancer.

Methods: The National Cancer Database was queried for men with penile cancer diagnosed between 1998 and 2009. Patient, tumor, treatment, and facility characteristics were obtained. Overall survival (OS) was analyzed using the Kaplan-Meier method and multivariable Cox proportional hazards regression model for all cases and stratified by stage.

Results: A total of 8,122 cases of penile cancer were reported from 1998 to 2009 in the National Cancer Database. Complete staging, survival, and covariate data were available for 5,043 cases. The estimated crude 5-year OS for the entire cohort was 61.0%. For all patients, no significant differences in crude 5-year OS were detected between 2006 to 2009 and 2002 to 2005 compared to 1998 to 2001. On multivariable analysis, OS did not significantly differ across all eras. Regional lymph node dissection was associated with improved OS (hazard ratio [HR] $= 0.777$, $P \leq 0.0001$). In patients who underwent lymph node dissection, dissection of ≥8 nodes significantly improved survival (HR $= 0.672$; $P = 0.0011$). Additional modeling stratified by stage revealed that OS for stage II cancers increased significantly in 2006 to 2009 compared to 1998 to 2001 (HR $= 0.714$; $P = 0.0034$).

Conclusions: Survival in penile cancer has remained unchanged as a whole and for each stage, except for stage II disease. An improved survival trend was detected in stage II penile cancer. Performing a lymph node dissection, especially extensive dissections, may benefit long-term survival.

Keywords: Penile cancer; Survival trends; United States; National Cancer Database

1. Introduction

Penile cancer is a rare malignancy in the developed world. The American Cancer Society estimates that penile cancer will account for 2,030 new cases and 340 deaths in the United States in 2016 [1]. The prognosis is excellent when diagnosed early but dramatically worsens with nodal metastasis [2]. One report recently estimated the U.S. 5-year overall survival (OS) as 66% [3]. Recently, evidence has emerged supporting that survival and quality of life can be improved through organ-sparing techniques [4,5], earlier detection of inguinal adenopathy [6–9], and postchemotherapy surgical consolidation of metastases [10–12]. The distribution of care has also changed at a facility-level. Community hospitals and academic hospitals are comparably likely to diagnose the disease, yet the responsibility of treatment is centralizing toward academic centers [13].

Despite these changes, little data exists examining mortality trends in the past 2 decades. One report of 1,800 patients

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found that U.S. 5-year survival declined from 72% in cases from 1990 to 1995 compared to 63% in 2002 to 2007 [14]. Using a larger sample, we further evaluated OS trends in penile cancer cases diagnosed between 1998 and 2009 through the National Cancer Database (NCDB).

2. Materials and methods

The NCDB is a national cancer registry jointly supported by the American College of Surgeons Commission on Cancer and the American Cancer Society. Over 1,500 accredited hospital-based cancer programs contribute to the NCDB, capturing >70% of newly diagnosed cancers in the United States and Puerto Rico. All data are entered by participating institutions and standardized according to coding guidelines published in the Facility Oncology Registry Data Standards (https://www.facs.org/quality-programs/cancer/ncdb/registrymanuals/cocmanuals/fordsmanual). Data include the following: patient and hospital characteristics, staging, histology, anatomic location, first-line treatment, and outcomes. All patient data were deidentified before the date of query. This study was approved by the University of North Carolina's Institutional Review Board.

The NCDB was queried for cases of penile cancer. Cases with the histologic International Classification of Diseases for Oncology (ICD)-O-3 codes pertaining to the following histologies were included: squamous cell carcinoma (8070, 8071, 8072, 8073, 8074, 8075, 8076), erythroplasia of Queyrat (8080), and Bowen disease (8081). From 1998 to 2009, the American Joint Committee on Cancer staging definitions for penile cancer remained unchanged [15,16]. Data were available for patients diagnosed in 1998 through 2012, but only cases between 1998 and 2009 were included to maintain consistent staging definitions and owing to the absence of 5-year OS data available from 2010 and later. Cases diagnosed at autopsy were excluded. The analysis was limited to NCDB sequence numbers 00, corresponding to cases with only 1 lifetime cancer diagnosis, and 01, representing tumors that were the first of multiple cancer diagnoses. Cases with the NCDB class code 00, which were those diagnosed but not treated by the reporting facility and did not require follow-up per Commission on Cancer guidelines, were excluded. We used NCDB analytic stage groups, which corresponded to pathologic stage group when available, and clinical stage group when pathologic data was unavailable. Cases without complete analytic staging and survival data were excluded. Our final sample was limited to patients with complete covariate data within the multivariable analysis with the exception of unknown grade for stage IV.

Demographic variables included age, race/ethnicity, insurance status, median household income of the patient's area of residence, and travel distance to facility. The NCDB began recording Charlson/Deyo scores in 2003, and owing to the large volume of missing scores within our sample, Charlson/Deyo scores were described but excluded from the primary multivariable model. A sensitivity analysis including comorbidity in the multivariable model was then performed with patients diagnosed during 2003 to 2009. Facility-level characteristics included academic vs. community centers and facility region. Tumor characteristics included analytic stage group, grade, and the presence of invasive or in-situ disease. Primary site was described but excluded from the multivariable analysis owing to a substantial proportion of cases with missing data. Cases recorded as erythroplasia of Queyrat (ICD-O-3 8080), Bowen disease (ICD-O-3 8081), and analytic stage group 0 with pathologic stage Tis were analyzed as having well-differentiated grade. Treatment characteristics analyzed included regional lymph node dissection (LND), chemotherapy, and radiation therapy. When a case met 3 criteria of having an unclear history of LND owing to missing data, was described to be pN0, and was reported to have "no lymph nodes examined" within the data, the case was regarded in the model as not having undergone LND. The survival impact of lymph node yield on survival was evaluated through a separate multivariable model limited to patients that underwent LND.

Descriptive statistics are reported overall and by era, with comparisons between era made by chi-squared tests. The Kaplan-Meier method was used to estimate crude median survival and 5-year OS rates. The log-rank test was used for comparisons of survival curves. Multivariable Cox proportional hazards regression models were used to evaluate the combined effect of patient and clinical characteristics on survival, for the entire cohort, and stratified by stage. Chemotherapy and radiation therapy were included in the model as time-varying covariates [17]. For the stratified analysis for stage IV patients, grade was excluded from the model owing to the large amount of missing data and its relatively low clinical importance in systemic disease. Estimates from the adjusted Cox model were used to create the adjusted Kaplan-Meier curves [18]. Analyses were performed using SAS statistical software v.9.4 (Cary, NC).

3. Results

Between 1998 and 2009, a total of 8,122 cases, in whom penile cancer was the only cancer diagnosis or the first of multiple cancer diagnoses, were reported to the NCDB. Of these, 5,043 had complete analytic staging, survival, and covariate information (Fig. 1). Pathologic staging was not reported for 1,743 (34.6%) cases, requiring the usage of clinical staging. Patient, tumor, treatment, and facility characteristics are summarized in Table 1. The median age of diagnosis was 65 years. Non-Hispanic White, non-Hispanic African-American, and Hispanic patients accounted for 79.0%, 9.2%, and 9.4% of cases, respectively, 93.6% were insured. Stages were distributed, in