Survival Following Salvage Surgery after Failed Radiotherapy for Penile Cancer: A SEER-Based Study

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Key Words
Penile cancer • Salvage surgery • Radiotherapy • Survival

Abstract

Objective: Salvage surgery (SS) for penile cancer (PC) is indicated in the management of local failure following radiation therapy (RT). Reports describing survival outcome are rare. This study aims to assess survival outcome of SS following RT failure in PC. Materials and Methods: We used The Surveillance, Epidemiology, and End Results database to identify patients received SS on the penis following RT. Social, demographic and pathological criteria of the patients were gathered. The 1-, 3-, 5-, 10-year survival rates were assessed. Results: Between 1976 and 2013, 17 patients received penile SS following RT. Median age was 65 years (range 47–91 years). The mean follow-up was 51 months (range 3–213 months). Sixteen (94.12%) patients received external beam radiation and 1 (5.88%) received combined external beam radiation with brachytherapy. Tumor histology was squamous cell carcinoma in 16 (94.12%) patients and mucinous adenocarcinoma in 1 (5.88%). The 1-, 3-, 5- and 10-year survival rates were 68.8, 35.7, 35.7 and 10.7%, respectively. The 1-, 3-, 5- and 10-year cancer specific survival rate was 72.7, 48.4, 48.4, and 36.3% respectively. Conclusion: Our results demonstrate, the overall survival of PC patients underwent SS was poor with nearly one third of patients dying within the first year and only one third surviving up to 3 years from the SS.

Introduction

Penile cancer (PC) is a rare type of cancer that accounts for less than 1% of all male cancers in North America and Europe [1]. The mean age at presentation is 60 years with disease risk factors including lack of circumcision, poor genital hygiene, smoking and human papilloma virus infection (types 16 and 18) [2].

Radiation therapy (RT) is a form of organ preservation treatment for PC. It attempts to avoid partial/total amputation of the penis with its resultant devastating psychological and functional outcomes [3]. Radiotherapy has been administered in the form of external beam radiation therapy (EBRT), interstitial brachytherapy or plesiotherapy in which radiation delivered superficially through surface molds and is usually indicated in tumors \leq 5 \text{ mm} in thickness [4]. An essential part of management of patients receiving RT for PC is to obtain a biopsy.
to confirm the diagnosis of PC and possibly identify the depth of invasion. Accurate staging in PC patients receiving RT continues to be difficult. Also, circumcision should be performed prior to RT in those patients who are uncircumcised. This is to expose the lesion and avoid preputial edema [5].

Despite the reported success rates of EBRT or brachytherapy in treating PC, a group of patients will develop local failure and need penile salvage surgery (SS) to achieve local control of PC. The reported rate of SS following RT is 12–61% [6–9]. Reports describing the survival outcome of those patients are rare, usually institutional experiences and are usually reported with the overall survival (OS) outcome of RT [10–12].

This study evaluates the survival outcome of patients who received penile SS following RT using the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods

Data Source and Patient Selection

Data included in this study were collected from SEER Program of the National Cancer Institute. SEER currently collects cancer incidence and survival data from population-based cancer registries covering approximately 28% of US population [13]. The SEER database was queried for PC patients underwent RT as their primary treatment modality for PC then received surgery on the penis. Patients who received surgery as their primary treatment modality for PC control or those who received RT to the penis and did not have SS afterwards were excluded. Patients' demographics, tumor characteristics, recurrence, and type of surgery were analyzed. OS and cancer specific survival (CSS) were calculated from the date of SS to the date of the last follow-up or the date of death.

Statistical Methods

Descriptive statistics were used to summarize the data. Continuous variables were reported with their means and standard deviations. Categorical variables were reported with their frequencies and percentages. Survival probabilities at 1-, 3-, 5- and 10-year were estimated using Kaplan-Meier method.

Results

Between 1976 and 2013, 17 patients were identified in the SEER database who received RT to the penis as their primary treatment modality followed by penile SS. The mean follow-up was 51 months (range 3–213 months), the median age was 65 years (range 47–91 years). Patients’ race was 14 (82.4%) of Caucasian, 2 (11.7%) of African American and 1 (5.9%) of Asian or Pacific Islander. The tumor was squamous cell carcinoma (SCC) in 16 (94.1%) patients. With regards to staging, the SEER data base identifies the tumor stage as localized when the tumor is confined to the penis, regional when it has direct extension to adjacent organs and/or lymph nodes (LN), and distant when it extends beyond organs or tissues or metastases to distant site or distant LN [14].

In our study, tumor stage was found to be localized in 6 (35.2%) patients, with regional metastasis in 6 (35.2%) and distant metastasis in 2 (11.8%), and the staging was unrecorded in 3 (17.6%). Tumor grade was well/moderately differentiated in 9 (52.9%) patients, poorly differentiated/anaplastic in 3 (17.6%) and of unknown grade in 5 (29.4%). Tumor location was as follows: glans penis in 5 (29.4%), penile shaft in 2 (11.8%), prepuce in 1 (5.9%) and unrecorded in 9 (53%).

Sixteen (94.1%) patients received EBRT and only 1 (5.9%) received combined EBRT with brachytherapy. SS was performed in the form local excision/partial penectomy in 5 (29.4%) patients, total penectomy in 5 (29.4%) and was unrecorded in 7 (41.2%). LN dissection was performed in only 3/17 (17.6%) patients, and of these patients 2 had positive metastatic LN disease.

Survival data showed 3 (17.7%) patients remained alive. Fourteen (82.3%) patients were dead. Of these dead patients, the cause of 6/14 (42.9%) deaths was attributable to PC and 8/14 (57.1%) to other causes. The 1-, 3-, 5- and 10-year OS rate were 68.7, 35.7, 35.7 and 10.7%, respectively. The CSS rate at 1-, 3-, 5- and 10-years was 72.7, 48.4, 48.4, and 36.3%, respectively. Details of individual patients are illustrated in table 1.

Discussion

RT emerged as an alternative to surgical therapy for PC with the potential of organ preservation and the availability of SS if RT fails. However, the survival outcome of these patients who underwent SS remains unknown.

EBRT was advocated for early stage localized T1 to T2 SCC, with the challenge of positioning the organ with proper separation from the adjacent normal structures [3]. RT can be offered for T1 grade I and II with other options like surgery and laser, and in grade III as well. Other modalities for grade III include surgery and chemoradiotherapy [15]. EBRT is usually administered in a dose of 66 to 70 Gray (Gy) over 6.5 to 7 weeks [9]. The reported 5-year CSS following EBRT varied from 78 to 88% [10]. Prognostic factors associated with poor response to EBRT included dose less than 60 Gy, longer
Similarly, only 1 of 6 patients with moderately differentiated tumors received inguinal LN dissection. Also based on clinical staging in current group of patients, 6 were described as having enlarged inguinal LN, yet only 2 patients (patients 5 and 17) received inguinal LN dissection. Regardless of tumor stage, poorly differentiated SCC of the penis is an indication for prophylactic inguinal LN dissection. On the other hand, RT can be offered in the surgically unresectable LN disease. LN metastasis is the most important prognostic indicator for patient survival in PC [15]. However, in the initial radiation studies, inguinal LN dissection was not routinely performed and even in more contemporary radiation series, the LN dissection was offered only in patients with positive needle biopsy of the inguinal LN [6, 22]. Clearly, LN management in PC should be the same whether the patient received surgery or RT as their local treatment modality.

In our study, 1 patient (5.9%) had mucinous adenocarcinoma, however it is a rare tumor and only reported in the literature as case reports [23]. All our patients received EBRT and 1 received combined EBRT and brachytherapy. Reported SS in PC patients treated by EBRT ranges 29–61% [7, 11, 24]. In Azrif et al. [7] study, 12/41 (29.26%) patients who received RT developed a biopsy confirmed local recurrence. The median time to local recurrence was 7 months (range 3–84 months). Recurrences were salvaged by partial/total penectomy according to the urologist preference. In Ozsahin et al. [11] study, 19/33 (57.5%) patients developed local failure after pri-
mary RT. SS varied between total, partial penectomy and local excision. It rates high as 61% (14/23) were reported following EBRT in the study of Zouhair et al. [9].

The reported SS in PC patients who initially received brachytherapy ranges 12–15.9% [6, 8, 25]. In Crook et al. [6] study, 8/67 (11.9%) patients received SS after local failure of brachytherapy with a mean follow-up of 48 months (range 4–194 months). The authors reported healing was not impaired after surgery. Five patients received partial penectomy, 2 received total penectomy and 1 received local excision. In a larger study, De Crevoisier et al. [25] reported 19/144 (13.19%) received SS following local failure after brachytherapy. SS was described as partial penectomy in 12 patients, total penectomy in 6 and local excision in 1. In this study, at a mean follow-up of 5 years (range 0.5–24 years), 18 patients continued to be in complete remission. Escande et al. [8] reported 32/201 (15.9%) patients received SS rate following brachytherapy with all relapses confirmed by biopsy. Of these patients 11 received partial glansectomy, 14 received total glansectomy and 7 had total penectomy.

Our results and previous reports demonstrate that patients who failed RT may still undergo an organ sparing surgery. At least, one third of the patients received an organ sparing SS. Also SS rate after brachytherapy was reported to be less than EBRT. This may have to be related to patient selection for brachytherapy or better dose frequency in brachytherapy than EBRT [26].

Our study suffers from inherent limitations of being retrospective and uncontrolled study. Also, the SEER database does not have information on patient comorbidities, functional or performance status which might affect the treatment modalities offered by the urologist rather than patient preference in terms of sexual and psychological limitations resulted after surgery [27]. This information will help us better understand the role of RT in node positive and metastatic PC disease. Additionally, it may have affected the OS rates reported in our study. However, our report describes the survival outcome of SS in PC, at a national level and with long-term follow-ups. We also acknowledge that some of the tumor data in some patients were missing in addition to data related to chemotherapy received by the patients. However, the main aim of our study is to report the survival in PC patients who received SS and this particular information with the cause of death was available in the SEER.

Conclusion

Our results demonstrate most patients who underwent SS for PC following RT did not enjoy a long-term survival. Nearly 2/3 of the patients died before 3 years of the SS either from PC or other causes. Also, patients selected for RT, do not often receive inguinal LN dissection as per defined indications which may affect patient survival.

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