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Opportunities for use of radiation therapy in penile cancer based on patterns of care in the United States from 2007 to 2013

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Abstract

Background: Radiation therapy (RT) is an effective modality for the treatment of squamous cell carcinomas of the penis. The National Comprehensive Cancer Network recommends consideration of primary radiation for penile preservation, in surgically unresectable tumors, and as adjuvant therapy for positive margins, bulky groin nodes or pelvic nodes. We performed a population-based analysis to evaluate the usage of RT in penile cancer from 2007 to 2013.

Methods: We used the *Surveillance, Epidemiology and End Results* (*SEER*) database to identify men diagnosed with squamous cell carcinoma of the penis from 2007 to 2013. Patients were grouped as early stage (T1–T2N0), locally advanced (T3–T4N0), node-positive (T1xN1–3) and metastatic. We used linear regression model to test for factors associated with adjuvant radiation in node-positive patients.

Results: We identified 2200 men diagnosed with penile cancer between 2007 and 2013. Of these, 66.4% had early stage, 10.7% had locally advanced, 15.5% had node-positive, 3.2% had metastatic cancer. Among patient with early stage cancer, RT was used in 14 patients (1.0%) and postoperative radiation in an additional 45 patients (3.1%). Among 340 patients with node-positive cancer, 62.1% received surgery alone, 5.6% radiation alone, 21.8% surgery with adjuvant radiation, and 10.6% neither surgery nor radiation. Of patients who had surgery, 26.0% had adjuvant radiation. On univariate analysis, higher nodal stage (N2–3 *versus* N1) was associated with adjuvant radiation ($p = 0.02$), while there was a trend for higher T-stage (T3/T4 *versus* T1/T2) ($p = 0.08$) and history of prior malignancy ($p = 0.06$). On multivariate analysis, only higher nodal stage (N2–3 *versus* N1) was associated with use of adjuvant radiation [hazard ratio (HR) 1.94, $p = 0.03$].

Conclusions: A small percentage of patient who are eligible for primary or adjuvant RT in the United States receive this treatment. Further work should be done to assess barriers to use of radiation in patients with penile cancer.

Keywords: penile cancer, radiation, adjuvant therapy, SEER, population-based study

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Background

Penile cancer is a relatively uncommon cancer, with 2100 cases and 360 deaths in the United States (US) in 2017.[1] One challenge in the management of uncommon cancers is the lack of prospective data to guide management decisions. Currently, the paradigm in treating penile cancer is surgical treatment of both the primary and the inguinal nodes.[2] Although technical refinement has improved the morbidity of these procedures, the survival of patients with localized penile cancer has remained unchanged over the past several decades.[3,4]

Radiation therapy has been used with success in other squamous malignancies of the anogenital region. For example, in vulvar cancer, adjuvant radiation therapy to the bilateral groins and pelvis

improved survival over lymph node dissections in patients with groin metastases,[5,6] and is considered standard of care. Similarly, definitive chemoradiation has been used with success in cases of unresectable vulvar cancer and is currently utilized in the management of anal and cervical cancers as primary therapy.

The current National Comprehensive Cancer Network (NCCN) guidelines (version 1.2018) recommend radiation therapy as a category 2B option for patients with localized penile cancer. Likewise, the addition of adjuvant chemoradiation is recommended for bulky groin adenopathy or enlarged pelvic nodes, and a category 2B recommendation for patients with pN2–3 disease. These recommendations have been based on institutional reports of efficacy and extrapolation from related disease sites.[7]

Despite these guidelines, prior population-based studies from 1988 to 2006 have demonstrated that very few patients with penile cancer receive radiation therapy as part of their management.[8] We hypothesized that there continues to be under-utilization of radiation therapy in patients with penile cancer. We used the *Surveillance, Epidemiology and End Results* (*SEER*) database to examine opportunities for use of radiation therapy in the US, specifically among patients where current guidelines include radiation as a therapeutic option.

Methods

Data collection

Data were collected from the *SEER* database. We selected patients diagnosed with squamous cancer of the penis from 2007 to 2014 using ICO-3-disease codes. Demographic data included age, race, insurance status, marital status, and presence of prior malignancy. Tumor characteristics included American Joint Committee on Cancer (AJCC) 6th edition T-, N-, and M-classifications, as well as the derived AJCC 6th edition group stage. We did not use the AJCC 7th edition staging since this was not available on all patients. Additional tumor characteristics included grade, lymphovascular invasion (LVI, available on subset of patients), and tumor size. Treatment characteristics included extent of surgery, number of nodes examined, number of nodes positive, and radiation therapy. Chemotherapy data are not available in the *SEER* database.

Based on AJCC 6th edition, patients were grouped in to four categories: early stage (T1–T2N0M0), locally advanced (T3–T4N0M0), node-positive (T1–4N1–3M0), and metastatic (M1). For the purposes of analysis, penile-preserving therapies including cryotherapy and laser excision were included as surgery.

Analysis

Univariate and multivariable logistic regression models were generated to identify factors associated with radiation therapy use, and are summarized with odds ratios (OR), confidence interval (95% CI), and p values. To fit the multivariable model, variables with a global p value <0.20 in the univariate analysis were included.

For node-positive patients, categorical variables are summarized with frequency and percentages and compared using Chi-squared analysis. Continuous variables are summarized using means and ranges and were compared using Student's t tests. In order to evaluate the hypothesis, patients were categorized based on their receipt of definitive radiation therapy for localized disease and on their receipt of adjuvant radiation therapy for nodally metastatic disease (among patients managed with surgical excision).

All analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC, USA) with two-tailed p values reported and a p value <0.05 considered significant.

Results

Patient demographics

We identified 2200 patients with a diagnosis of squamous cell carcinoma of the penis from 2007 to 2013. The median age of diagnosis was 67.5 (range 22–102) years, and most patients were white or Hispanic (Table 1). The majority of cases were early stage (66%), while 16% presented with lymph node metastasis and 3% presented with distant metastatic disease.

Use of primary RT in early stage (T1–T2N0M0)

Of the 1460 patients with early stage disease, only 14 (<1%) received definitive radiation. Meanwhile, the vast majority (94%) of cases were treated with surgery, of whom only a minority

Table 1. Demographics.

	Number	Percentage
Median age	67.5 (range 22–102)	
Race		
White	1415	65.2%
Black	209	9.6%
Hispanic	433	19.9%
Other	115	5.3%
Married	1181	53.7%
Insurance status		
Insured	1197	54.4%
Insured no specifics	408	18.6%
Medicaid	332	15.1%
Uninsured	132	6.0%
Unknown	131	6.0%
Prior malignancy	448	20.4%
Group stage (AJCC 6th)		
I	1128	51.3%
II	432	19.6%
III	353	16.1%
IV	193	8.8%
Unknown	94	4.3%
Analysis group		
Early stage (T1–T2N0)	1460	66.4%
Locally advanced (T3–T4N0)	235	10.7%
Node-positive (TxN1–N3)	340	15.5%
Metastatic (TxN1M1)	71	3.2%
Unknown	94	4.3%

AJCC, American Joint Committee on Cancer.

(n = 45) received adjuvant radiation therapy. In total, only 59 (4%) of these 1460 patients received any radiation; less than the number of patients who were not managed with any definitive therapy (n = 78). Interestingly, brachytherapy was rarely reported with only four reported cases during this 7-year time frame (Figure 1).

Use of adjuvant radiation in node-positive cancer

We identified 340 patients from 2007 to 2013 who had node-positive cancer. The majority of these patients were treated with surgery (83.8%), with the remainder either receiving radiation alone (5.6%) or no intervention (10.6%). Of the

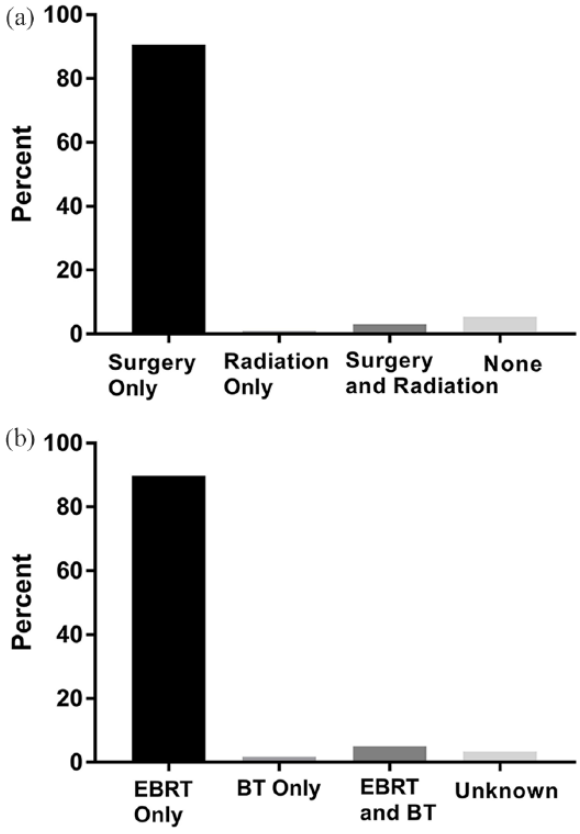

Figure 1. Treatment modality in early stage penile cancer. (a) Frequency of surgery and radiation in patients with early stage penile cancer. (b) Frequency of radiation modality among patients who received radiation therapy for early stage penile cancer.

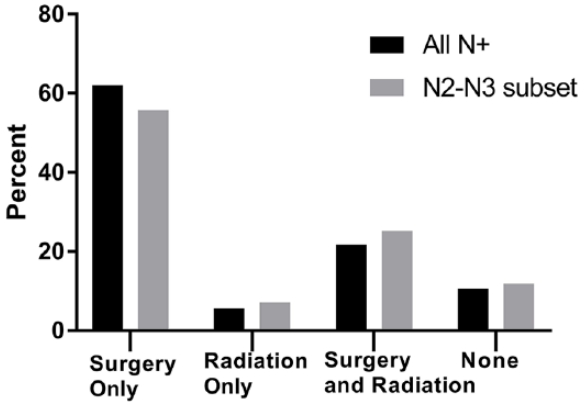

Figure 2. Use of adjuvant radiation in patients with node-positive penile cancer. Use of surgery plus adjuvant radiation was more frequent with higher N-stage.

patients with N1–3 penile cancer, 21.8% were treated with adjuvant radiation therapy (26% of all patients managed surgically). Among patients with N2–N3 disease, the use of adjuvant radiation increased to 31.2% (Figure 2), compared with 18.2% among patients with N1 disease.

Factors associated with the use of adjuvant radiation in node-positive cancers

The demographic characteristics of patients who received adjuvant radiation differed from those who did not (Table 2). In particular, patients who received adjuvant radiation tended to have a higher T-stage and higher N-stage. More importantly, those who received adjuvant radiation had fewer nodes examined, more positive nodes, and higher percent of nodes that were positive.

On univariate analysis of factors associated with the use of adjuvant radiation in patients with node-positive cancer demonstrated that degree of nodal involvement (N2–N3 *versus* N1) was associated with a 2.03-fold increase in the utilization of adjuvant radiation (95% CI: $p = 0.02$). T-stage (T3/T4 *versus* T1/T2) and prior malignancy were borderline significant. Other factors including year of diagnosis, age, race, marital status, insurance status, grade, LVI, extent of surgery, and number of nodes positive or examined were not associated with receipt of adjuvant radiation therapy (Table 3).

On multivariable analysis using a logistic regression model, the extent of nodal involvement remained significant (OR 1.94, $p = 0.03$), but this was the only significant predictive factor (Table 3).

Discussion

Opportunity exists for the improvement in the management of penile cancer. The use of organ-sparing surgery has increased over time.[9] While organ-sparing approaches may be associated with increased recurrence rate, local recurrence may be successfully treated with salvage surgery and does not affect 5-year survival. Despite these advances, survival from penile cancer has not changed from 1998 to 2009, suggesting the need for additional studies in the management of this rare cancer.[3,4]

In early stage cancer, radiation therapy may offer an alternative organ-preserving option for patients. Retrospective data have suggested that brachytherapy may achieve local control rate up to 85%

Table 2. Characteristics of pN+ patients by receipt of adjuvant radiation therapy.

Characteristic	No adjuvant radiation	Adjuvant radiation	*p* value
n	211	74	
Mean age	63.3	63.4	0.9208
Race			0.2809
White	56.4%	64.9%	
Black	11.8%	6.8%	
Hispanic	24.6%	25.7%	
Other	7.1%	2.7%	
Prior malignancy	19.0%	9.5%	0.0582
Group stage			0.0136
II	34.6%	18.9%	
III	45.0%	47.3%	
IV	20.4%	33.8%	
T-Stage			0.2031
I	25.1%	37.0%	
II	41.2%	28.4%	
III	30.3%	37.8%	
IV	2.8%	6.8%	
Unknown	0.5%	0%	
N-Stage			0.0318
N1	44.5%	28.4%	
N2	36.5%	41.9%	
N3	19.0%	29.7%	
LVI			0.8955
Yes	21.8%	20.3%	
No	27.0%	29.7%	
Unknown	51.2%	50.0%	
Grade			0.2720
Well differentiated	8.1%	14.9%	
Moderately differentiated	55.0%	44.6%	
Poorly differentiated	32.2%	35.1%	
Unknown	4.7%	5.4%	
Mean nodes examined	19.8 (1–73)	16.5 (15–69)	0.1688
Mean nodes positive	2.4 (0–15)	3.4 (1–19)	0.0569
Percent nodes positive	25.3%	41.6%	0.0021

LVI, lymphovascular invasion.

Table 3. Multivariate and univariate predictors of use of adjuvant radiation in node-positive cases.

Univariate predictor	**OR**	***p value***
Year of diagnosis	1.062	0.35
Age at diagnosis	1.001	0.38
Race		
Black *versus* white	0.496	0.59
Hispanic *versus* white	0.906	0.21
Other *versus* white	0.331	0.28
Marital status	1.18	0.54
Insurance	0.541	0.19
Poorly differentiated grade	1.156	0.61
LVI	0.845	0.75
T-stage (T3/T4 *versus* T1/T2)	**1.61**	**0.08**
N2–N3 *versus* N1	**2.028**	**0.02**
Prior malignancy	**0.447**	**0.06**
Extent of surgery		
Partial penectomy *versus* local excision	0.812	0.25
Total penectomy *versus* local excision	1.217	0.28
Nodes positive	1.002	0.46
Nodes examined	0.998	0.42
Multivariate predictor	**OR**	***p value***
T-stage (T3/T4 *versus* T1/T2)	1.317	0.43
N2–N3 *versus* N1	**1.941**	**0.03**
Prior malignancy	**0.446**	**0.07**
Extent of surgery		
Partial penectomy *versus* local excision	0.774	0.31
Total penectomy *versus* local excision	1.089	0.55
Insurance status	0.69	0.44

LVI, lymphovascular invasion; OR, odds ratio.

with brachytherapy and 60% with external beam radiation.[7,10] These numbers compare well with other organ-preserving surgical approaches.[11] Furthermore, if recurrence is detected, both penile-preserving approaches may be salvaged with secondary penectomy.

Our purpose here is not to advocate radiation therapy as a replacement for surgery. Rather, in evaluating the utilization of management options for penile cancer, we observed that fewer patients are being treated with radiation than those patients not managed with any definitive therapy.

While some of these patients may not have been fit for surgical intervention, we feel that this disparity in utilization of effective, noninvasive treatment suggests an area for care improvement. Additionally, between the radiation modalities, brachytherapy has been associated with improved local control,[7,12] and is the preferred modality for tumors <4 cm as per the NCCN guidelines (version 2.2018). Brachytherapy should be considered more frequently as an option in patients treated with radiation therapy, though the availability of this specialized skill limits applicability

In more advanced disease, only about 26% of patients who nodal spread of penile cancer received postoperative radiation. The use of postoperative radiation in penile cancer is controversial. We note from our data that more advanced nodal disease (N2–3 *versus* N1) was associated with higher likelihood of use of adjuvant radiation. Given the lack of progress in improving survival, this may be a group with opportunity to improve outcome with greater use of adjuvant therapy. The current NCCN (version 2.2018) guidelines do recommend the use of postoperative radiation in bulky groin nodes or enlarged pelvic nodes, and to consider it in pN2–3 disease. This recommendation has generally been based on extrapolation from other anogenital region squamous malignancies. In particular, the randomized GOG 37 clinical trial compared adjuvant pelvic and groin radiation with pelvic nodal dissection in patients with node-positive vulvar cancer. There was improved survival with the addition of radiation therapy.[5]

Certainly, there is controversy in the role of adjuvant radiation. For instance, the 2014 European Association of Urology (EAU) guidelines do not recommend neoadjuvant or adjuvant radiation, on the basis that there are no data to suggest an improvement in penile cancer.[10] The ongoing InPACT clinical trial will assess the role of neoadjuvant and adjuvant therapy in patients with high-risk penile cancer.

We intentionally did not report survival analysis to compare overall or cause-specific survival by receipt of adjuvant radiation in node-positive cases. Based on the characteristics of patients by receipt of radiation (Table 2), these appear to be very different groups, with more aggressive features for poor outcome such as higher group stage, fewer nodes examined, and greater percentage of positive nodes in those who received radiation. In this situation, the effect of radiation is difficult to accurately model as covariates which predict for receipt of radiation also predict for poorer survival. We used propensity score analysis to generate a 1:1 matched control group from patients who did not receive radiation, but this still did not yield groups which were balanced for known predictors of poor outcome. The inability to perform a survival analysis on the effect of radiation therapy represents a large limitation to our data. Greater number of patients may allow for improved matching and ability to model the effect of radiation therapy on survival.

Of note, a recent hospital-based National Cancer Database (NCDB) study evaluated the impact of adjuvant radiation therapy on survival in patients with adverse pathologic features. This study did show improvement in survival for patients with N2 but not N1 disease.[13]

There are some limitations to using the *SEER* database to study patterns of care, particularly as it pertains to radiation therapy. Specifically, there is concern for the under-reporting of radiation therapy usage. Comparison of the *SEER* database with *SEER*-Medicare claims have reported that while the specificity of radiation treatment reporting was near 100%, the sensitivity of capturing radiation usage in *SEER* was about 80%.[14] In the current patterns of care analysis, there is some risk in under-reporting radiation usage. However, even increasing the rates we have noted by 20% would not alter our core findings. Additional limitations include lack of information on patient comorbidity, intent of radiation (palliative *versus* curative), radiation dose and field extent, surgical margin status, and incomplete reporting of relevant data such as extranodal extension.

Conclusion

Opportunities exist for the increased use of radiation therapy in penile cancer. In particular, fewer patients receive radiation therapy, a potentially curative treatment, than those who receive no treatment at all. The InPACT study will look at the incorporation of chemotherapy and radiation therapy for high-risk penile cancers. In the meantime, greater multidisciplinary discussion on the optimal management of these cancers is warranted.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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