SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 10: 85-92, 2015

Surgical treatment of primary disease for penile squamous cell carcinoma: A Surveillance, Epidemiology, and End Results database analysis

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Received July 30, 2014; Accepted March 27, 2015

DOI: 10.3892/ol.2015.3221

Abstract. Current guidelines recommend penile sparing surgery (PSS) for selected penile cancer cases. The present study described the use of PSS in a population-based cohort, and also examined the role of PSS on penile cancer-specific mortality (PCSM). Data from the Surveillance, Epidemiology, and End Results (SEER) database were used to identify individuals that were diagnosed with penile squamous cell carcinoma between 1998 and 2009 and treated with surgery. Patients were sorted into two groups: Local tumor excision (LTE) and partial/total penectomy (PE). Factors associated with the receipt of LTE and PCSM following LTE were examined. In addition, PCSM was compared between LTE and PE following propensity score matching. Of the 1,292 eligible patients, 24.2% underwent LTE. For stage T1 disease, the rates of LTE increased moderately from 29 to 40% over the last decade. Following multivariate analyses, young age, African descent, a tumor size of <3 cm and stage T1 disease were identified to positively influence the receipt of LTE. With a median follow-up period of 55 months, the four-year PCSM rate was 9.8% in patients treated with LTE. Older age, a tumor size of 3-4 cm and regional/distant disease (SEER stage) were significant predictors of PCSM. Furthermore, in matched cohorts with stage T1 disease, the four-year PCSM rates were 8.9 and 10.0% for patients that received LTE or PE, respectively (P=0.93). In conclusion, underuse of PSS is pronounced in the general community with significant age and ethnicity disparities. The current population-based study provides evidence supporting the oncological safety of PSS compared with PE in early-stage disease.

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Key words: penile neoplasms, SEER program, surgery, survival, multivariate analysis, prognosis

Introduction

Surgery is the mainstay of treatment for penile squamous cell carcinoma (SCC). Partial or total penectomy (PE) has historically been considered the standard treatment for invasive disease (1). Although the local control rate of PE is ~95% (1), it has a significant negative impact on the patient's sexual function, quality of life, social interactions, self-image and self-esteem (2). During the past decade, there has been a change in the management of primary tumors with an emphasis on penile sparing surgery (PSS) (3). This change has been driven by an improved understanding of the biology of the disease (4), quality improvements in pathological evaluation and continuous refinements of surgical techniques (5). PSS has been previously reported to produce excellent cosmetic and functional results without sacrificing oncological outcomes in certain patients with early-stage penile tumors (3,6-9). Accordingly, an organ-sparing approach has been recommended for patients with stage T1 disease, according to the 2009 TNM clinical and pathological classification system (10), in national and international guidelines (11-13). Stage T1 penile tumors are classified as tumors which have invaded the subepithelial connective tissue, without invasion of the corpus spongiosum or corpora cavernosa (10).

Despite the evolution of conservative surgery at academic centers, the national practice pattern of surgical treatment for penile SCC in the United States (US) is largely unknown. Therefore, the aims of the current study were to examine data from the most recent Surveillance, Epidemiology and End Results (SEER) cancer registry (14), and to elucidate whether there are disparities in the use of PSS. Since only a limited number of reports exist regarding the oncological safety of PSS, the current study aimed to examine the penile cancer-specific survival following conservative surgery in a population-based setting, and to compare oncological outcomes between PSS and PE in stage T1 disease.

Materials and methods

Participants and variables. The SEER program was used to identify patients who received surgical treatment for primary invasive penile SCC between 1998 and 2009. The population-based database included 18 cancer registries and covered ~28% of the US population. Since the study used a public set of identified data, it was exempted from institutional review boards.

Case listing. Case listing was generated using codes specific for primary site and morphology, which included the following: The International Classification of Disease for Oncology 2nd edition (ICD-O-2; codes, C60.0-60.9) and 3rd edition (ICD-O-3; codes, 8070-8076) for histological subtype (SCC type). The sample was limited to patients with adequate information and a preliminary cohort of 1,293 patients diagnosed with invasive penile SCC was identified. A patient who underwent local tumor destruction was excluded. Therefore, this process yielded a sample comprising 1,292 eligible patients.

Surgical procedures. The surgical procedures for primary disease were identified and separated into two groups: Local tumor excision (LTE) and PE. The SEER database was used to retrieve demographic and disease characteristics, including age, ethnicity, marital status, year of diagnosis, tumor stage (T-stage), primary tumor size, SEER stage and grade. T-stages were assigned according to the American Joint Committee on Cancer 6th staging system (15). SEER stage is a simplified version of stage defining the extent of the disease (localized, regional and distant). Survival time was measured as the interval from the date of diagnosis until the date of mortality or until the last follow-up. Mortalities from penile cancer were coded as penile cancer-specific mortality (PCSM) and all other mortalities were considered as other-cause mortality (OCM).

Statistical analysis. Continuous data are presented as the median [interquartile range (IQR)] and categorical data are presented as proportions. The χ^2 test for trend was used to evaluate whether there was a linear trend in the proportions. Multivariate logistic regression analysis was used to evaluate the adjusted associations between covariables and utilization of LTE.

A substantial proportion of patients with penile SCC succumb to the disease as a result of competing causes of mortality, such as ischemic heart disease, stroke and diabetes (16). Competing risk analysis was used to account for the effect of OCM and provide unbiased estimates of PCSM. The cumulative incidence was plotted to graphically depict PCSM and OCM. Gray's test was used to assess the statistical significance of a prognostic factor in a cumulative incidence analysis (17). Multivariable competing risk regression analysis was used to evaluate the adjusted effects of covariates on PCSM, as proposed by Fine and Gray (18).

In order to enable balanced comparisons between LTE and PE, propensity score matching was used to adjust for the inherent selection bias within observational data (19). Using propensity score matching, randomized trials can be statistically reproduced by balancing the characteristics of different treatment groups. The propensity to undergo LTE was calculated using a multivariable logistic regression model that adjusted significant confounders. In addition, the nearest neighbor method matching, with a caliper width of 0.2 of the standard deviation of the logit, was used to match cases. The standardized difference measure was also used to assess how closely the PE patients matched the LTE cases.

Table I. Demographic and disease characteristics of 1,292 patients with penile squamous cell carcinoma (1998-2009).

Characteristics	n (%)
Age, years (median, interquartile range)	67 (57-77)
Ethnicity	
Caucasian	1,107 (85.7)
African descent	119 (9.2)
Other	66 (5.1)
Marital status	
Married	813 (62.9)
Single	479 (37.1)
Year of diagnosis	
1988-2000	250 (15.4)
2001-2003	449 (27.7)
2004-2006	434 (26.7)
2007-2009	490 (30.2)
Tumor stage	
T1	699 (54.1)
T2	381 (29.5)
T3-4	212 (16.4)
Primary tumor size, cm	
<1	106 (8.2)
1-1.9	259 (20.0)
2-2.9	304 (23.5)
3-3.9	261 (20.2)
≥4	362 (28.0)
SEER stage	
Localized	706 (54.6)
Regional	550 (42.6)
Distant	36 (2.8)
Tumor grade	
Grade I	366 (28.3)
Grade II	639 (49.5)
Grade III-IV	287 (22.2)
Treatment of primary disease	
Local tumor excision	313 (24.2)
Partial penectomy	801 (62.0)
Total penectomy	178 (13.8)

SEER, Surveillance, Epidemiology and End Results program.

All the analyses were performed using R software (version 3.0.0; http://www.r-project.org.). P-values were two-tailed and P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of patients. The descriptive characteristics of the 1,292 eligible patients with penile SCC are presented

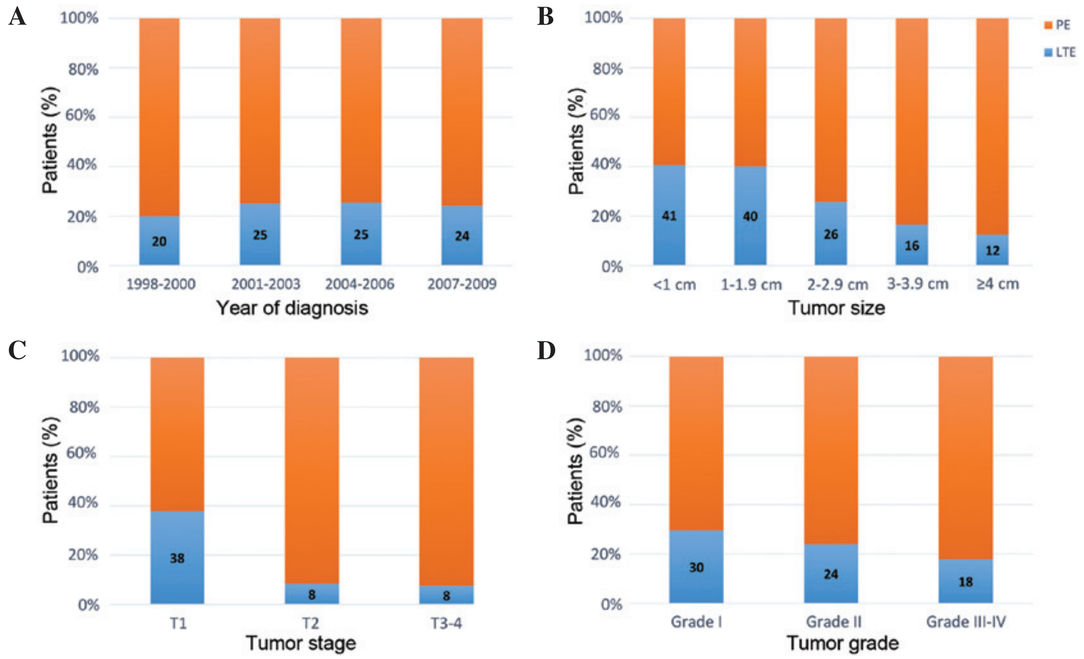

Figure 1. Distribution of LTE vs. PE in the eligible patients (n=1,292), stratified according to (A) year of diagnosis, (B) primary tumor size, (C) tumor stage and (D) tumor grade. LTE, local tumor excision; PE, partial/total penectomy.

in Table I. The median age was 67 years, while the majority of patients were Caucasian (85.7%), married (62.9%) and diagnosed with T1 disease (54.1%). Of these patients, 313 (24.2%) underwent LTE and 979 (75.8%) received partial or total PE.

Distribution of LTE and PE. Fig. 1 illustrates the distribution of LTE and PE stratified according to the year of diagnosis, primary tumor size, T-stage and tumor grade. Increased LTE utilization rates were observed in smaller tumors, lower T-stage and lower tumor grade (all P<0.05). The overall use of LTE in the general population was similar throughout the study period (P=0.53).

Rate of LTE within stage T1 disease patients. The rate of LTE within patients with stage T1 disease was further investigated (Fig. 2). Among the 699 stage T1 patients, 265 (37.9%) were treated with LTE. The rate of LTE increased moderately from 29 to 40% over the study period, however this increase was not statistically significant (P=0.10; Fig. 2A). In addition, patients with smaller tumors were more likely to receive LTE (P<0.01; Fig. 2B). However, lower tumor grade was not associated with a higher rate of LTE (P=0.56; Fig. 2C).

Using multivariate analyses, the adjusted associations between individual characteristics and the use of LTE was assessed. Table II demonstrates that patients treated with LTE were younger, more often of African descent, with tumor size of <3 cm and with stage T1 disease (all P<0.01). Unmarried men were more likely to select PE treatment than LTE, whereas married men were more likely to receive LTE than PE, however, no signficant difference was identified (P=0.08). By contrast, SEER stage and tumor grade were not independent predictors of conservative surgery.

Survival outcomes. The survival outcomes in 313 patients who received LTE were further evaluated. During a

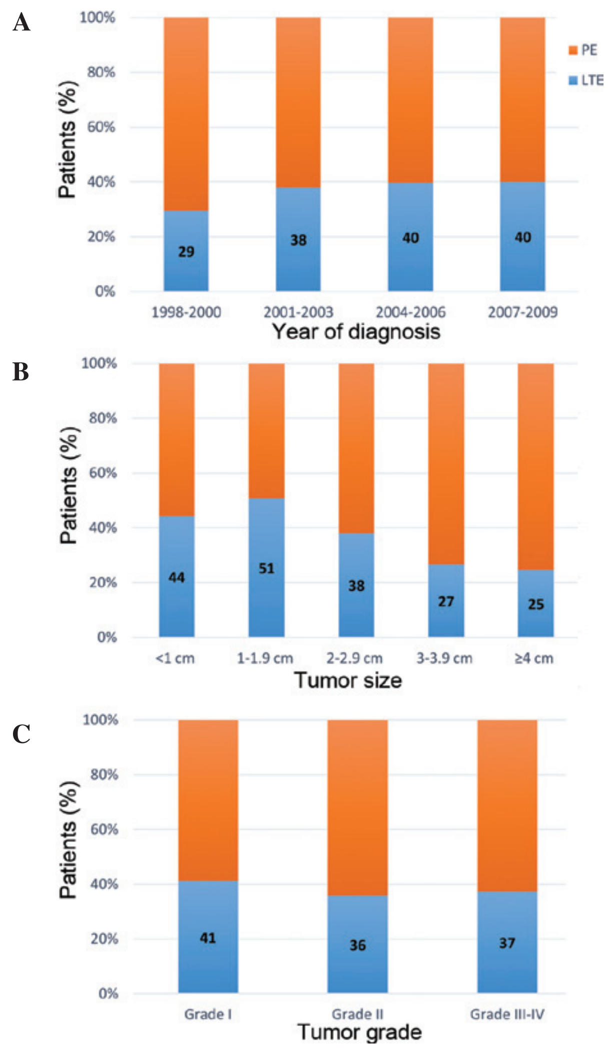

Figure 2. Distribution of LTE vs. PE in patients with stage T1 disease (n=699), stratified according to (A) year of diagnosis, (B) primary tumor size and (C) tumor grade. LTE, local tumor excision; PE, partial/total penectomy.

Table II. Multivariate analyses of predictors for the receipt of local tumor excision in patients with penile SCC (n=1292).

Variables	Odds ratio (95% CI)	P-value
Age	0.99 (0.98-1.00)	<0.01
Ethnicity[a]		
African descent	1.72 (1.07-2.75)	0.02
Other	0.9 (0.46-1.75)	0.75
Marital status[b]		
Unmarried	1.30 (0.97-1.75)	0.08
Primary tumor size[c], cm		
1-1.9	1.20 (0.74-1.96)	0.46
2-2.9	0.70 (0.43-1.14)	0.15
3-3.9	0.44 (0.25-0.75)	<0.01
≥4	0.37 (0.21-0.63)	<0.01
Tumor stage[d]		
T2	0.18 (0.10-0.31)	<0.01
T3-T4	0.16 (0.08-0.31)	<0.01
SEER stage[e]		
Regional	1.09 (0.68-1.74)	0.71
Distant	1.16 (0.40-3.37)	0.78
Tumor grade[f]		
Grade II	0.92 (0.67-1.26)	0.60
Grade III-IV	0.77 (0.50-1.17)	0.21
Year of diagnosis[g]		
2001-2003	1.31 (0.81-2.14)	0.28
2004-2006	1.46 (0.90-2.37)	0.12
2007-2009	1.38 (0.86-2.21)	0.18

Compared with: [a]Caucasian ethnicity; [b]married status; [c]tumor size of <1; [d]T1 stage; [e]localized tumor; [f]Grade I tumor; [g]diagnosis in 1988-2000. SCC, squamous cell carcinoma; CI, confidence interval; SEER, Surveillance, Epidemiology and End Results program.

median follow-up of 55 months (IQR, 45-65 months), 29 patients (9.3%) succumbed to penile cancer and 79 patients (25.2%) succumbed to another cause. Estimates of PCSM and OCM are presented in Fig. 3. Mortality in patients treated with LTE was not usually a result of the penile cancer. The risk factors associated with PCSM were investigated in this cohort (Table III). Patients who were older, with a tumor size of 3-4 cm and with regional or distant disease (SEER stage) had a significantly increased likelihood of mortality associated with penile cancer (all P<0.05). Multivariate analyses were also performed to identify risk factors in males that underwent PE (n=979). By contrast, only tumor grade and SEER stage were independent predictors of PCSM (data not shown).

Risk of PCSM in T1 disease patients. Whether LTE was associated with a higher risk of PCSM was investigated in the T1 disease subgroup. Of these patients, 265 (37.9%) and 434 (62.1%) were treated with LTE or PE, respectively. During a median follow-up period of 59 months (IQR, 54-66 months), penile cancer was identified as the cause

Table III. Multivariate analyses of predictors of penile cancer-specific mortality in patients treated with local tumor excision (n=313).

Variables	Hazard ratio (95% CI)	P-value
Age	1.03 (1.00-1.05)	0.03
Ethnicity[a]		
African descent/Other	0.15 (0.02-1.21)	0.08
Marital status[b]		
Single	0.75 (0.31-1.80)	0.52
Primary tumor size[c], cm		
1-1.9	1.00 (0.19-5.17)	1.00
2-2.9	2.41 (0.50-11.52)	0.27
3-3.9	6.79 (1.32-35.07)	0.02
≥4	1.99 (0.35-11.32)	0.44
Tumor stage[d]		
T2-T4	0.49 (0.15-1.55)	0.22
SEER stage[e]		
Regional/Distant	4.83 (1.74-13.38)	<0.01
Tumor grade[f]		
Grade II	0.76 (0.29-2.00)	0.58
Grade III-IV	0.94 (0.27-3.23)	0.92

Compared with: [a]Caucasian ethnicity; [b]married status; [c]tumor size of <1; [d]T1 stage; [e]localized tumor; [f]Grade I tumor. CI, confidence interval; SEER, Surveillance, Epidemiology and End Results program.

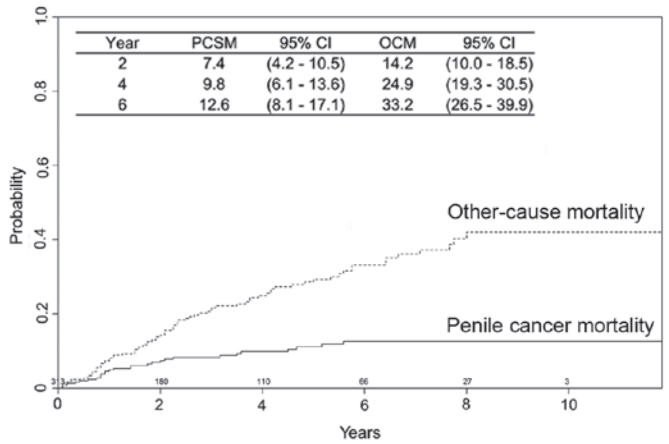

Figure 3. Cumulative incidence plot depicting PCSM and OCM rates in patients treated with local tumor excision (n=313). PCSM, penile cancer-specific mortality; CI, confidence interval; OCM, other cause mortality.

of mortality in 22 patients (8.3%) treated with LTE and 41 patients (9.4%) treated with PE. As shown in Fig. 4, no statistically significant difference in PCSM was observed between the treatment groups (P=0.66). In addition, OCM was comparable for patients treated with LTE or PE (P=0.21). In order to reduce selection bias in the assignment of treatments, matched groups were generated using the propensity score matching method. Table IV demonstrates that significant variations of covariates were diminished following statistical

Table IV. Propensity score matching of surgical procedures in patients with stage T1 disease.

		Prior to matching		Subsequent to matching	
Variables	Tumor excision	Penectomy	P-value	Penectomy	P-value
Total number, n	265	434		265	
Mean age, years	64.7	67.7	<0.01	65.0	0.84
Ethnicity			0.48		0.21
Caucasian	222	375		229	
African descent	30	37		19	
Other	13	22		17	
Marital status			0.53		0.23
Married	167	285		181	
Single	98	149		84	
Tumor grade			0.42		0.33
Grade I	100	143		85	
Grade II	122	219		138	
Grade III-IV	43	72		42	
Primary tumor size, cm			<0.01		0.92
<1	38	48		44	
1-1.9	97	94		88	
2-2.9	67	109		68	
3-3.9	33	91		33	
≥4	30	92		32	
SEER stage			0.29		0.66
Localized	242	384		238	
Regional/Distant	23	50		27	
Mean propensity score	0.59	0.64	<0.01	0.59	0.55

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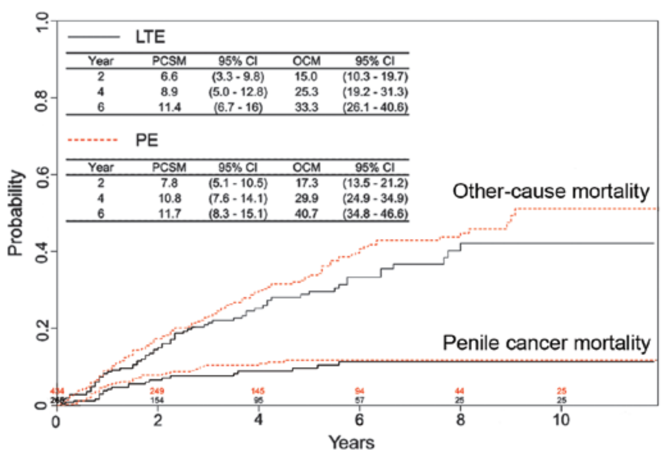

Figure 4. Cumulative incidence plot depicting PCSM and OCM rates stratified according to the surgical procedures in stage T1 patients (n=699). PCSM, penile cancer-specific mortality; OCM, other-cause mortality; CI, confidence interval; LTE, local tumor excision; PE, partial/total penectomy.

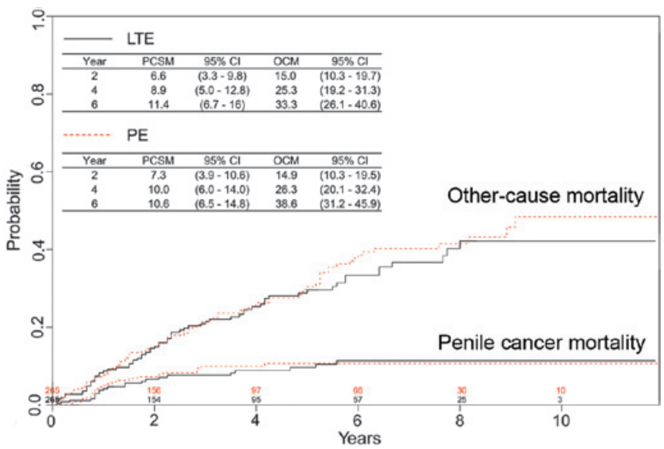

Figure 5. Cumulative incidence plot depicting PCSM and OCM rates stratified according to the surgical procedures in matched stage T1 patients (n=530). PCSM, penile cancer-specific mortality; OCM, other-cause mortality; CI, confidence interval; LTE, local tumor excision; PE, partial/total penectomy.

processing. In the matched series, the rate of PCSM did not differ significantly between patients treated with LTE or PE, with four-year PCSM rates of 8.9 and 10.0%, respectively (P=0.93; Fig. 5).

Discussion

Over the past decade, growing evidence has indicated the safety, efficacy and benefit of PSS over PE for certain patients

Table V. Literature review of oncological outcomes following penile-sparing surgery.

First author, year (ref)	Number of patients, n	Tumor stage ≥T1, %	Follow-up, months	Local recurrence rate, %
Smith, 2007 (3)	72	100.0	27 (mean)	4.2
Leijte, 2008 (1)	415	69.4	60.6 (median)	27.7
Morelli, 2009 (20)	17	88.2	36 (mean)	0.0
Feldman, 2011 (21)	56	50.0	60 (median)[a]	21.4
Li, 2011 (8)	32	78.1	26.5 (median)	9.3
O'Kane, 2011 (22)	25	76.0	28 (mean)	4.0
Li, 2012 (23)	12	25.0	62.5 (mean)	8.3
Philippou, 2012 (6)	179	100.0	39 (median)	8.9
Veeratterapillay, 2012 (7)	65	76.9	40 (median)	6.2
Total	873	77.8		17.8

[a]For patients without recurrence.

with early-stage penile tumors. A total of 10 studies reported in the literature were identified, which investigated the role of conservative surgery in invasive penile cancer (Table V; 1, 3,6-8,20-23). Local disease control was achieved in 82.2% of the cases following PSS. Although PSS was associated with an increased risk of local failure, it did not appear to compromise long-term cancer-specific survival. The five-year cancer-specific survival rate following local recurrence was 92% in two large studies (1,6). In addition, sexual function, micturition and cosmetic results were generally well maintained following conservative surgery (3, 6-8,20-23). Accordingly, the use of PSS has risen dramatically at tertiary care centers and has been recommended by certain guidelines, including the European Association of Urology (EAU) Guidelines Group on Penile Cancer, as a standard surgical approach (11-13).

The surgical treatment paradigm for primary disease emphasizes the underuse of PSS in the USA. In the present study, ≥50% of patients with a T1 tumor of <2 cm were identified to have undergone traditional radical surgery. Although the results identified that the utilization rate of LTE has increased from 29 to 40% in stage T1 disease over the last decade, PE remains the most commonly performed type of surgery for early-stage penile tumors. The reasons for this are multifactorial and may include the lack of substantial evidence for oncological safety and the technical challenges associated with PSS. The long-term outcomes of PSS have not previously been available to prove that conservative surgery provided comparable cancer-specific survival as conventional procedures (1,6). Furthermore, there may be a requirement for additional training of surgical skills to safely and effectively perform PSS. Since there is no centralized management of this rare disease in North America, treatment standardization and gain of experience are slow in the community setting.

The disparities in the use of LTE in the general practice pattern were also investigated in the present study. As expected, tumor size and T-stage were strongly associated with the use of LTE. Furthermore, LTE was more frequently performed in younger patients or those of African descent. The reason for the disparities in the use of LTE in different ages and ethnicities remains unclear. However, the same phenomenon was observed in patients choosing to receive a penile implant following treatment of prostate cancer (24). In multivariate analysis, predictors of penile implant surgery were younger and of African-American descent. Therefore, the authors speculated that physicians may have a better appreciation of the impact of PSS in young male patients and those of African-American descent (24). Further investigation of these biases is warranted, and increased education of physicians and patients may alleviate the discrepancy of care.

In the population-based cohort, the six-year PCSM rate following LTE was 12.6%, which is consistent with other large studies (1,6). On the contrary, mortality in long-term survivors were more likely from a cause other than penile cancer. Accounting for the influence of competing risk, the factors that predict mortality from penile cancer following conservative surgery were examined in the present study. Notably, old age and large tumor size were independent predictors of PCSM in patients treated with LTE. Therefore, these two factors may indicate an increased risk of failure to the specific treatment. Mohs *et al* (25) previously reported the five-year follow-up of penile cancer patients treated with micrographic surgery. Initial tumor size appeared to be an important factor in local control with 0% recurrence in males with lesions <2 cm and 50% recurrence in those with lesions >3 cm. As the average length of the glans is ~4 cm (26), local excision of tumors with a size >3 cm may result in a tumor-free margin of <1 cm. Agrawal *et al* (4) observed an absence of grade 1-2 penile SCC that extended 1 cm beyond the gross tumor margin; however, 25% of grade 3 lesions were histologically positive at 1 cm (4). In these patients with larger tumors, glansectomy with reconstruction is a better alternative to achieve satisfactory oncological and functional outcomes (27). The reason why age was a negative predictor in LTE patients is not clear. One explanation is that elderly patients may be subject to suboptimal follow-up, which is critically important following PSS. In addition, other causes of mortality may be misattributed as mortality due to penile cancer in older patients. Furthermore, the natural disease course of penile SCC may be more aggressive in the elderly. Epidemiology studies of vulval cancer have demonstrated a bimodal age distribution; human papillomavirus (HPV)-associated cancer manifests at an earlier age compared with HPV-unrelated cancer (28). Bezerra *et al* (29) reported a significantly lower HPV infection rate in elderly patients. It is possible that penile cancer in elderly patients may arise from a carcinogenesis pathway with a high degree of genetic alterations not driven by HPV (30). Since detailed follow-up data regarding tumor recurrences were not available and the SEER database does not contain further information on tumor characteristics beyond stage and grade, the explanations proposed in the present study remain speculative.

Although stage T1 disease is recommended as an appropriate indication for PSS (11-13), no direct comparison exists between LTE and PE in these patients. In the SEER database, 37.9 and 62.1% of stage T1 disease patients underwent conservative surgery or PE, respectively. Although no randomized assignment of treatment existed in the observational study, statistical processing may aid in the adjustment for differences of baseline characteristics and reduce the inherited selection bias. Therefore, the propensity score matching method was employed in the current study to mimic random allocation of treatment in stage T1 penile SCC. The comparisons of PCSM between matched cohorts concluded that penile cancer-specific survival following PSS was not reduced. Corroborating the findings from tertiary care centers, the results of the present study provide considerable evidence to support the generalization of conservative surgery on a large scale. In stage T1 disease, the utilization rate of LTE has improved from 29 to 40% over the last decade. Although encouraging, the changing trend remains slow compared with the similar situation in breast-sparing surgery (31). The accumulating evidence may accelerate the dissemination of PSS in early-stage penile tumors.

However, the current study is not devoid of limitations. Although the SEER program provides the largest and most comprehensive cancer registry in the USA, there are other variables not routinely collected, including anatomical features, comorbid conditions and patient preferences. These factors may account for some of the observed disparities in the use of PSS. Since the SEER program only records the first course of treatment received, adjuvant therapy for primary disease and its effect on PCSM may not be evaluated from this data. The conclusions of the present study may be biased due to excluding a proportion of patients from analyses as a result of missing information. Furthermore, there are inherent difficulties in accurately determining the types of LTE based on ambiguity in coding. Despite these limitations, the current study represents a comprehensive and contemporary analysis of the surgical treatments for primary lesions of penile cancer in the USA. The results may add value to existing knowledge since the majority of previous case studies were single-center based and thus more likely to have a selection bias. Furthermore, accumulating large cohorts from contemporary practice is challenging for rare cancer types.

In conclusion, the underuse of PSS is pronounced in the general community with significant disparities in age and ethnicity. The present population-based study provides evidence supporting the oncological safety of PSS as compared with PE in early-stage disease. Awareness of these issues may improve the quality of health care in penile cancer patients.

Acknowledgements

The authors would like to thank all the study participants, urologists and study coordinators for participating in the study.

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