ORIGINAL ARTICLE

Factors associated with locoregional recurrence in penile cancer: a case-control study

Factores asociados a recurrencia locoregional en cáncer de pene: un estudio de casos y control

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Abstract

Purpose: *Surgical excision of the primary tumor in penile cancer (PC) has shown good local control with a risk of locoregional recurrence (LR) of 4-8%. The magnitude of such risk and the characteristics that distinguish patients who develop LR from those who do not is controversial. Our goal was to estimate, clinical and oncological characteristics, and outcome of LR in a cohort of patients with PC.* **Materials and methods:** *A retrospective, case–control study of ten patients with LR of PC and ten controls. Using a multivariate analysis for clinical and oncological characteristics was evaluated to determine their association with LR.* **Results:** *Cases and controls were similar in regards to the prevalence of diabetes, age, grade of differentiation, presence of lymphovascular invasion (LVI), and positive margins. In our multiple logistic regression analysis clinical stage (CS), LVI and positive margins were associated with LR. Time to LR had a median of 15 months.* **Conclusions:** *Our study confirms that patients with advanced CS, LVI and positive margins after surgical excision of the primary tumor could have higher risk of LR. We believe that a close oncological follow-up should be done in patients with adverse oncological characteristics.*

Key words: *Penile. Cancer. Locoregional. Recurrence.*

Resúmen

Objetivo*: La escisión quirúrgica del tumor primario en cáncer de pene (PC) ha demostrado un buen control local con un riesgo de recurrencia locorregional (LR) del 4-8%. La magnitud del riesgo y las características que distinguen a los pacientes con recurrencia locorregional de los que no la presentan son motivo de controversia. Nuestro objetivo fue analizar características clínicas y oncológicas para establecer su relación LR en una cohorte de pacientes con PC.* **Material y métodos:** *Estudio retrospectivo de casos y controles de 10 pacientes con LR de PC y 10 controles. Mediante un análisis multivariado se analizaron características clínicas y oncológicas y se determinó su asociación con LR.* **Resultados:** *Los casos y controles fueron similares en cuanto a prevalencia de diabetes, edad, grado de diferenciación, invasión linfovascular y márgenes positivos. En nuestro análisis de regresión logística múltiple, el estadio clínico (CS), la invasión linfovascular y los márgenes positivos se asociaron con LR. El tiempo a la LR tuvo una mediana de 15 meses.* **Conclusiones:** *Nuestro estudio confirma que los pacientes con CS avanzado, invasión linfovascular y márgenes positivos podrían tener mayor riesgo de LR. Creemos que debe realizarse un seguimiento oncológico estrecho en pacientes con características oncológicas adversas.*

Palabras clave: *Cáncer. Pene. Recurrencia. Locoregional.*

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Introduction

Penile cancer (PC) is a rare neoplasm most common in men aged 50-70 years old[1]. In 2018, the prevalence in all age males worldwide was 24,974 cases/100,000, accounting for 0.4-0.6% of malignant diagnoses in Europe and the USA with a higher incidence in developing countries[2].

Several risk factors for PC have been identified, including poor hygiene, circumcision status (circumcision in infants or up to adolescence is protective), human papillomavirus infection, phimosis, human immunodeficiency virus infection, smoking, and low socioeconomic status[3,4].

Pathologically, the vast majority of tumors are classified as squamous cell carcinoma (SCC) of which several subtypes have been recognized, including warty, basaloid, verrucous, papillary, adenosquamous, mixed, and sarcomatoid. Subtypes of PC comprising nonsquamous cell types include basal cell carcinoma, Kaposi sarcoma, leiomyosarcoma, extramammary Paget disease, and melanoma[5].

The primary site of SCC is the glans penis in 48% of diagnosed cases; followed by 21% affecting the prepuce, 9% involving both glans penis and prepuce, 6% emerging from the coronal sulcus, and 2% the shaft[6]. Surgical excision of the primary tumor remains the oncologic gold standard for definitive treatment of the penile primary tumor[7]. This treatment has both shown to result in good local control with a risk of locoregional recurrence (LR) of 4-8%[8].

The most important prognostic factor of survival in patients with SCC of the penis is the extent of lymph node metastasis[9]. Approximately 80% of men with low-stage PC achieve prolonged survival but, as the extent of lymph node metastasis increases, survival decreases precipitously (5-year cancer-specific survival pN0 = 85-100%, pN1 = 79-89%, pN2 = 17-60%, and pN3 = 0-17%)[10,11].

The aim of the present study was to examine our institutional experience for factors associated with LR after the multimodal primary treatment of PC according to the National Comprehensive Cancer Network (NCCN) guidelines.

Materials and methods

All cases presenting with LR of PC after the initial treatment and their respective matched controls were selected from a database of 30 patients with histopathology confirmed disease and treated at our third level medical facility from 2012 to 2017.

Surgical management of the primary tumor and regional lymph nodes, as well as treatment with chemotherapy/radiotherapy was performed according to the NCCN guidelines.

Patients were follow-up for at least 2 years after the initial treatment. LR was defined as locoregional disease confirmed by histopathology after the initial treatment.

Statistical methods

Quantitative variables are presented either as means ± standard deviation (SD) or as medians with interquartile ranges (IQR), according to their distribution. Data distribution was determined by means of the Shapiro-Wilk's test. Quantitative variables were analyzed using Student's t, Mann–Whitney U, or Wilcoxon tests, whereas for qualitative variables, we used either c2 or exact Fisher tests. A multivariate, stepwise logistic regression analysis was carried out to explore which clinical and oncological characteristics were associated with LR. Time to LR was calculated from date of primary treatment and was plotted using Kaplan–Meier curve.

Ethics statement

The present study was reviewed and approved by the institutional review board of Hospital de Especialidades de Puebla, Instituto Mexicano del Seguro Social. Informed consent was not need.

Results

The analyzed cohort consisted of 20 patients with PC diagnosed, treated, and followed between 2012 and 2017 (mean follow-up was 40 ± 20 months). During follow-up, ten patients have LR confirmed by histopathology. The control group consisted of ten patients without evidence of LR.

Table 1 describes the baseline clinical and oncological characteristics of both groups (Table 1). The mean age of the population at diagnosis was 59 ± 14 and 69 ± 11 years for cases and controls, respectively. The prevalence of diabetes mellitus (cases 57% vs. controls 42%; p = 0.63) was similar among cases and controls.

Table 1. Baseline characteristics of patients with penile cancer

Variable	Controls (No recurrence)[a]	Cases (Recurrence)[b]	p
n	10	10	
Age (years) ± SD	69 ± 11	59 ± 14	0.12
% with diabetes mellitus	42	57	0.639
Differentiation % Grade 1	20	10	0.373
% Grade 2	80	90	
% Lamina propia invasion	90	100	0.305
% Lymphovascular invasion	40	40	1
% Positive margin	20	40	0.329
% Clinical stage I	20	10	0.531
II	50	10	0.05
III	20	40	0.329
IV	10	40	0.121

[a]Control group, patients without locoregional recurrence of penile cancer. [b]Cases group, patients with locoregional recurrence of penile cancer. SD: standard deviation.

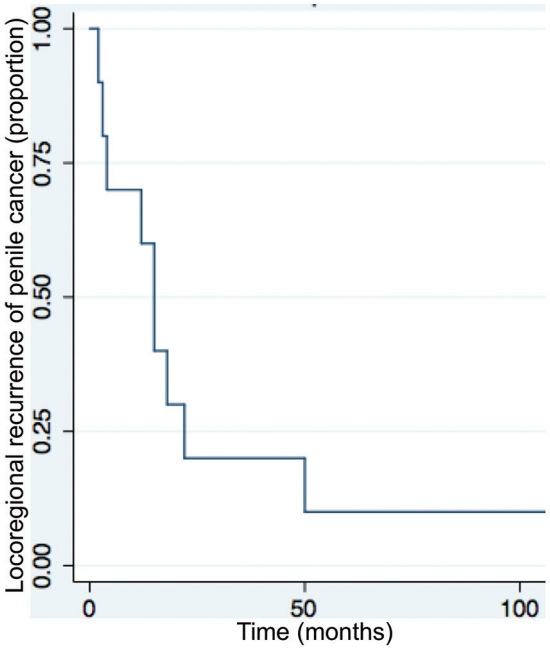

Figure 1. *Kaplan–Meier estimates of time to locoregional recurrence in the patients included with penile cancer.*

The proportion of patients showed CS I was (cases 10% vs. controls 20%; p = 0.531), for CS II was (cases 10% vs. controls 50%; p = 0.05), for CS III was (cases 40 % vs. controls 20%; p = 0.329), and for CS IV was (cases 40 % vs. controls 10%; p = 0.121). We find statistically significant difference only for CS II.

All cases of the analyzed cohort presented SCC. The differentiation grade of the primary tumor was Grade 1 in 20% and Grade 2 in 80% of the patients in the control group; while in the case group it was 10% and 90%, respectively (p = 0.373).

The presence of invasion of the lamina propria in the primary tumor was present in 90% of patients in the control group and in all of patients in the case group (p = 0.305). While the presence of lymphovascular invasion (LVI) was 40% in both groups (p = 1).

After surgical excision of the primary tumor, positive margins were found in 40% of cases and 20% of controls (*p*=0.329). The time to LR in our study had a median of 15 months (IQR 12-18) (Fig. 1).

In a multiple logistic regression analysis that included age and oncologic characteristics, CS, LVI, and positive margins were associated with LR; however, CS was the only variable that showed a statistically significant difference (Table 2).

Discussion

Although cancer of the penis is a rare genitourinary malignancy, it frequently poses a clinical management dilemma for the urologist. Such dilemmas can arise due to delays in clinical presentation, diagnostic error, and ambiguous strategies for treatment, in terms of efficacy versus morbidity[10]. Notwithstanding therapeutic intent, prognosis is largely dictated by the pathological stage of the disease, including the extent of lymph node metastasis, coupled with the histological features of the primary tumour[11].

Surgery is central to the management of PC, having pivotal roles in diagnosis and staging of the primary tumor. Intervention has evolved from conventional surgical amputation (that is, partial or total penectomy) to organ preserving surgery. Today, a range of minimally invasive therapeutic options, including topical treatments, laser ablation, and modified local excision have been developed. Emerging opinion suggests that organ preserving treatment offer the opportunity for disease control and should be sought when oncologically feasible to retain quality of life and maximize sexual function[10,12].

Largest series of patients with PC have shown that while after a partial penectomy, the risk of LR is 4-5%, organ preservation strategies have local recurrence rate of 13.7%. However, long-term survival does not appear to be compromised by local recurrence since most cases are still surgically salvageable[8,12,13]. Previously, it has been illustrated in other series that LVI, presence of high grade and Stage T2 or greater predicted the occurrence of LR in a series on penile-preserving treatment[14]. Our data support this

Table 2. Multiple logistic regression analysis for risk factors associated with locoregional recurrence in penile cancer

Variable	OR	CI 95%	p
Age	0.832	(0.689 1.005)	0.056
Differentiation grade[a]	0.239	(0.001 34.741)	0.574
Lymphovascular invasion	3.238	(0.115 90.902)	0.490
Positive margin	2.559	(0.015 434.665)	0.720
Clinical stage	4.244	(1.069 16.842)	0.04

[a]Tumor differentiation grade.

conclusion. In addition, we identified the presence of a positive margin as risk factor for LR, without reaching statistical significance. This shows that perioperative frozen section assessment can be of significant value, especially in cases suspicious for tumor involvement at the excision margins[15].

In a retrospective study, Albersen et al. identified four risk factors for LR in a univariate model: perineural invasion, carcinoma *in situ*, positive margins on definitive pathology, and the presence of high-grade SCC. None of these risk factors was a significant predictor of LR in multivariate cox regression[16]. These findings contrast with our results.

We have identified three risk factors for LR in a multiple logistic regression model: CS, LVI and positive margins. However, CS was the only variable that showed a statistically significant difference, which may likely be attributed to a low number of events in this cohort. Other series have identified 1 single risk factor to be significant for LR. However, we believe additional emerging predictive factors which now do not reach statistical significance may be of equal importance[13,16].

In the previous series, 66% of all LR occur within 2 years[16], this finding is consistent with our results. The time to LR in the present study had a median of 15 months (IQR 12-18) so we believe that a close oncological follow-up should be done in the 1st months after the treatment in patients with adverse oncological characteristics.

In this cohort, the age at diagnosis of PC coincides with previous studies with a peak during the sixth decade. In relation to this, it is interesting to note that patients in our cases group were younger that patients in the control group, but without reaching statistical significance. During the review of clinical records, no data were found about the time elapsed between the appearance of the first symptom and clinical diagnosis. Perhaps other important factors also have a role and were overlooked.

We consider that studies with a longer follow-up and with a larger number of patients are needed to determine the association of clinical and oncological characteristics, with LR.

Conclusions

Our study confirms that patients with advanced CS, LVI and positive margins after surgical excision of the primary tumor could have higher risk for LR.

Our findings should to be considered with caution in view of the inherent limitations of the study, namely, its retrospective nature and the low number of evaluated subjects. Undoubtedly, larger scale, prospective studies are needed to determine the magnitude of risk.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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