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PROGNOSTIC FACTORS FOR LYMPH NODE INVOLVEMENT, DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL IN PENILE CANCER

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ABSTRACT **Background** Penile Cancer (PC) is a rare neoplasm. The most important PC prognostic factor is inguinal lymph node (ILN) involvement (pN+). Inguinal lymphadenectomy (ILND) is the most accurate method for ILN staging. Due to high morbidity and quality of life impairment, alternative staging modalities have been researched. This epidemiological study aims to assess risk factors to determine prognosis in PC patients. **Methods** A retrospective review was conducted on 84 PC patients. Mean age was 58.68 (12.98) years. Thirty-Eight (45.3%) patients underwent ILND. The main reasons were primary tumor staging (pT2 and up) and palpable nodes (cN+) in physical examination. **Results** For pN+ risk, cN+, tumor infiltration of penile body, dartos, spongiosum and corpora cavernosa, as well as perineural and lymph vascular invasion (LVI) were significant. For recurrence and metastasis, cN+, penile body invasion, LVI, corpora cavernosa invasion and pN+ showed statistical significance. In overall survival (OS) evaluation, cN+, LVI, penile body, dartos, spongiosum and corpora cavernosa invasion, pT and pN+ presented worst prognosis. In multivariate analysis, cN+ was a risk factor for pN+. Cox regression analysis was also performed. Factors that decreased disease-free survival (DFS), were cN+, penile body, dartos or corpora cavernosa invasion and pN+. When applied to OS, cN+, penile body invasion, LVI, dartos invasion, pT and pN+ were related to worst survival. Most patients (67.5%) stayed disease free. Recurrence was more common on ILN (14.3%). When metastatic (10.7%), mortality was 55.6%.
Conclusion This study confirmed several risk factors for pN+, DFS and OS on PC patients.

KEYWORDS : Penile Cancer, Epidemiology, Overall Survival, Inguinal Lymphadenectomy

1 INTRODUCTION

Penile Cancer (PC) is a rare neoplasm, with the peak incidence in the sixth decade of life. Most cases are diagnosed in developing countries, such as Latin America and Africa. In Brazil, PC represents up to 2% of male tumors[1,2].

There are several known risk factors for PC. Phimosis can increase the risk for PC up to 10 times, due to chronic inflammation and balanoposthitis[3]. Urinary excretion of carcinogenic compounds makes smoking also related to PC. Promiscuous sexual habits and multiple partners can also increase the risk for developing PC[4]. Most recently, HPV infection was established as an important risk factor for PC. This led to a change in pathological staging from the WHO in 2016, which includes HPV related tumors, according to histological subtypes[5,6,7].

Invasive primary lesions are usually exophytic. Histologic subtype and tumor grade are key determinants of prognosis[8]. The UICC classification categorizes the grades from I to III and the sarcomatoid, dedifferentiated type[9]. Cell grading is more difficult with squamous cell carcinomas than adenocarcinomas, leading to high variability among pathologists[10]. Thus, prognosis becomes harder to determine, as highly differentiated tumors can also become invasive and metastatic.

Pathological processing of the primary specimen should be undertaken with great care. It is important to assess lymph vascular and perineural invasions, as both are related to worst prognosis[11]. An accurate final pathological staging (pT) is crucial to a successful disease management[12].

The most important prognostic factor in PC is inguinal lymph node (ILN) involvement[13]. Inguinal lymphadenectomy (ILND) is still the most accurate method for lymph node (LN) staging. However, due to high morbidity and quality of life impairment, alternative staging modalities have been researched[14]. 18F-FDG PET/CT is a promising tool for LN staging. Using fluorodeoxyglucose labelled with fluorine-18, PET/CT provides information on tumor staging and works as a prognostic factor. 18F-FDG PET/CT can become the most important LN staging tool, especially in patients with palpable groin nodes (cN+)[15].

Recent studies in Brazilian population identified a high prevalence of PC, mainly in the low-income country state, Maranhão, with 286 cases between 2004-2014, averaging 13.89 per 100.000 men in this period[16,17]. A study that assessed PC patients in Minas Gerais state between 2012 and 2014 found mean age of 56.6 years and mean time between symptoms and diagnosis of 14.4 months[18]. So far, there are few studies in PC patients with a focus on prognosis. In this scenario, the present study aims to assess prognostic factors for lymph node involvement, disease-free survival, and overall survival in PC patients.

2 METHODS

Study population

A retrospective review was conducted on adult males diagnosed with penile squamous cell carcinoma, between March 2014 and March 2019. All patients were treated at Instituto Mário Penna, a tertiary referral center for oncology. Demographic information including age, smoking history, phimosis, and symptom onset time were recorded. Patients without vital information on medical record or follow up loss under minimum time were excluded. The Ethical Committee of Instituto Mario Penna approved this study (CAAE 39670720.6.0000.5121).

Initial research retrieved 131 patients from database. Of this total, 29 were excluded due to insufficient data and 11 were duplicated entries. Other 7 subjects were excluded, 4 for presenting other oncological cell types (e.g., melanoma) and 3 with negative histopathological analysis. Thus, the final number consisted of 84 patients.

Surgical procedure and pathology

Patients underwent primary tumor resection after preliminary biopsy. Depending on local conditions, surgery ranged from local excision to total penile amputation. Lymphadenectomy was performed following clinical and histological features, as follow: palpable inguinal nodes (cN+), primary lesion pT2 or above (regardless of groin clinical status) and pT1 primary lesion with poorly differentiated cells. Inguinal surgery was not performed in fixed nodal masses (cN3) and in patients

with prohibitive preoperative evaluation.

Histopathological specimens were appraised by experienced pathologists. The TNM classification (according to the AJCC Cancer Staging Manual)[20] and the current WHO criteria for tumor grading were used[7].

Follow up and Survival Analysis

Minimum follow up was six months after primary tumor surgery, except for those who died sooner from PC. Disease progression was established as local recurrence, lymph node or distant metastasis, confirmed by histopathology or imaging methods. Patients without local recurrence or metastasis up to last clinical appointment were defined as disease free. For evolutive analysis, primary endpoint was overall survival (OS). Recurrence time was considered to calculate disease free survival (DFS).

Statistical analysis

Descriptive statistical analysis was performed for all variables. Chi-square test was applied to all potential qualitative prognostic factors for pN+, recurrence/metastasis, and OS. Linear regression was applied for collinearity test. Logistic regression analyses were performed for potential prognostic variables. Cox survival regression analysis was then applied on significant prognostic factors. Null hypothesis was tested using a significance level $\alpha<0,05$. Statistical analyzes were performed in IBM SPSS (version 20.0).

3 RESULTS

Epidemiological data

Mean age was 58.68 years (SD=13.0), and symptoms started an average of 11.2 months (SD=13.4) prior to initial surgery. Only 31 subjects had records on smoking, with 18 (58%) active or ex-smokers. Regarding phimosis, 26 patients had data recorded, with a prevalence of 92%. Surgical treatment for primary lesion had a low complication rate. Most patients (75%) had no post operative intercurrences. From those who intercurred, only 1 was readmitted.

Mean tumor size was 33,5 mm (SD=20.1). Almost all (95.2%) patients had free surgical margins. The glans was the most common site of tumor invasion (96.4%). Interestingly, corpora cavernosa invasion (pT3) was more prevalent (28.6%) than spongiosum (pT2) invasion (10.8%) in this series. Cell differentiation evaluation showed the majority (54.2%) of patients with well differentiated tumors, while 29 (40.3%) had moderately differentiation and 4 (5.5) were poorly differentiated. In this series, 12 subjects had no grading due to extensive tumor necrosis and inflammatory reaction. Concerning histological prognostic factors, 51.3% had perineural invasion and 38.8% had lymph vascular invasion (LVI). Four patients had no information on pathological report.

Thirty-eight subjects underwent ILND. The main reasons were primary tumor staging (pT2 and up and/or poor cell differentiation) and cN+, at the initial analysis or during follow-up. The majority (76.3%) of procedures were bilateral. Mean hospital stay was 8.78 days (SD=5.9). In all surgeries, an active drain was positioned and removed when drainage was small (usually <100ml/24h). Mean drain stay was 11.7 (SD=10.0) days. Sixteen patients (42.1%) needed reintervention due to postoperative complications (Clavien-Dindo 3 and 4). No deaths from these procedures were recorded on this series.

Pathological analysis showed ILN involvement in 17 (44.7%) specimens. Mean number of lymph nodes dissected was similar on right and left sides (12.3 ± 4.4 and 13.9 ± 6.8 respectively). Extracapsular extension was identified more often on left side lymph nodes (84.6%) than on right side ones (30%).

Mean follow-up time was 28.4 months (SD=17.9). Most patients (61.9%) stayed disease free during clinical accompaniment. Lymph node recurrence was more common than local recurrence (14.3% vs 3.6% respectively), requiring surgical approach, chemotherapy or radiotherapy. Mean time for recurrence was 15.8 months (SD=11.2). From the 9 patients (10.7%) that developed metastatic disease, 55.6% died with a mean time between diagnosis and death of 13.2 months (SD=5.5).

Survival analysis

Chi-square test was applied to identify possible prognostic factors regarding ILN invasion (pN+), recurrence or metastasis (Rec/Met+), and OS. Statistically significant factors were then tested with univariate logistic regression, for each dependent variable separately. For pN+, clinically palpable groin nodes, tumor invasion/infiltration of penile body, dartos, spongiosum and corpora cavernosa, as well as perineural and vascular invasions were found to be significant. For recurrence and metastasis, cN+, penile body invasion, LVI, corpora cavernosa invasion and pN+ showed statistical significance. In OS evaluation, cN+, LVI, penile body, dartos, spongiosum and corpora cavernosa invasions, pathological T staging and pN were related to worst prognosis (Table 1). In a multivariate analysis, only cN+ was an independent prognostic factor for lymph node involvement on PC patients.

Table 1 - Univariate Logistic Regression Analyses Of Penile Cancer Prognostic Factors

Prognostic Factors	OR	CI95%		p Value
		Inferior	Superior	
Lymph Node Involvment (pN+)				
cN	10.5	2.77	39.806	0.001
Body Inv.	3.85	1.358	10.916	0.011
Perineural Inv.	3.173	1.081	9.318	0.036
Lymph Vasc. Inv.	3.701	1.308	10.478	0.014
Dartos Inf.	11.769	1.13	122.628	0.039
Spongiosum Inf.	4.531	1.088	18.869	0.038
Cavernosa Inf.	3.182	1.122	9.022	0.030
pT	2.885	1.001	8.309	0.050
Recurrence or Metastasis (Rec/Met+)				
cN	5.222	1.179	23.139	0.030
Glans Inv.	-	-	-	0.999
Body Inv.	3	1.034	8.702	0.043
Lymph Vasc. Inv.	3.6	1.272	10.186	0.016
Dartos Inf.	-	-	-	0.999
Cavernosa Inf.	3.413	1.154	10.088	0.026
pN	50	9.616	259.981	0.001
Overall Survival (Death)				
cN	10.095	1.859	54.808	0.007
Body Inv.	4.6	1.197	17.676	0.026
Lymph Vasc. Inv.	4.156	1.066	16.198	0.040
Dartos Inf.	16.875	1.554	183.219	0.020
Spongiosum Inf.	6.75	1.156	39.398	0.034
Cavernosa Inf.	5.127	1.321	19.903	0.018
pT	4	1.018	15.717	0.047
pN	47.7	7.999	284.44	0.001

Note: OR: Odds Ratio; CI95%: 95% Confidence Interval; cN: palpable groin nodes; Inv.: Invasion; Vasc.: Vascular; Inf.: Infiltration; pT: pathological T staging; pN: pathological N staging.

Univariate Cox Proportional regression analysis was also performed. Factors that decreased time to recurrence or metastasis, thus impacting in disease-free survival (DFS), were cN+, penile body, dartos or corpora cavernosa invasions and pN+. When applied to OS, significant prognostic factors were cN+, penile body invasion, LVI, dartos infiltration, pT staging and pN+ (Table 2). On multivariate analysis, significant prognostic factors that shortened DFS were dartos infiltration and pN+. Regarding OS, cN+ and pN+ were related to poorer survival.

Table 2 - Univariate cox proportional analysis of penile cancer prognostic factors

Prognostic Factors	HR	CI 95%		p Value
		Inferior	Superior	
Recurrence or Metastasis (Rec/Met+)				
cN	3.526	1.386	8.97	0.003
Body Inv.	2.289	1.016	5.159	0.046
Dartos Inv.	11.468	3.146	41.801	0.000
Cavernosa Inv.	2.538	1.125	5.725	0.025
pN	10.826	4.571	25.642	0.000
Overall Survival (Death)				
cN	6.551	1.91	22.472	0.003
Body Inv.	3.665	1.118	12.017	0.032
Lymph Vasc. Inv.	3.453	1.01	11.8	0.048
Dartos Inf.	7.702	2.027	29.27	0.003
Spongiosum Inf.	4.555	1.207	17.185	0.025

Cavernosa Inf.	4.074	1.242	13.363	0.02
pT	3.461	1.055	11.357	0.041
pN	21.167	4.557	98.318	0.000
Note: HR: Harzard Ratio; CI95%: 95% Confidence Interval; cN - palpable groin nodes; Inv.: Invasion; pN - pathological N staging; Vasc.: Vascular; Inf.: Infiltration; pT: pathological tumor.				

Cox Proportional survival analyses showed significant differences in DFS between cN+ and cN0 patients (Figure 1a), and between LN invasion (pN+ vs. pN-) (Figure 1b). As OS concerns, there were significant survival differences between cN+ and cN0 patients (Figure 1c), and between pN+ patients (Figure 1d).

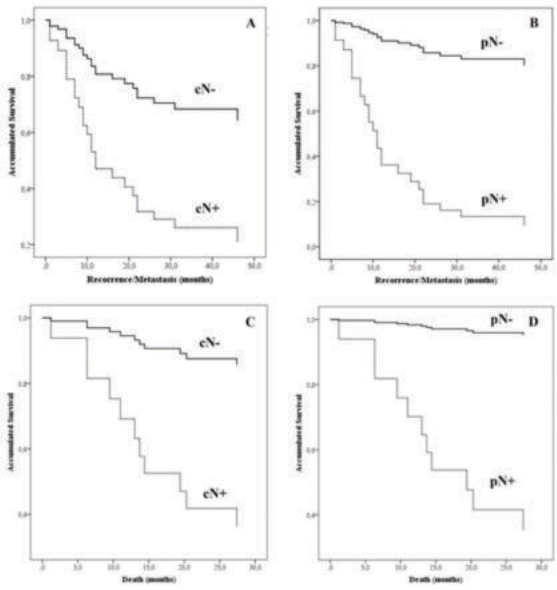

FIGURE 1 – DISEASE FREE SURVIVAL AND OVERALL SURVIVAL CURVES
Note: cN-: clinical negative lymph node; cN+: clinical positive lymph node; pN-: pathological negative lymph node; pN+: pathological positive lymph node.

4 DISCUSSION

Penile Cancer is still a very challenging disease due to multiple factors altering prognosis and lack of clinical studies. ILND is still the gold standard for lymph node staging. However, high morbidity demands careful patient selection. For this reason, prognostic factors are essential to elaborate management templates. Moreover, risk for recurrence and/or metastasis is still underassessed in PC. Understanding elements that interfere with DFS is crucial to improve OS.

In this series, the mean age was 58.68 ± 12.98 years. Previous published Brazilian studies found similar data. In the state of Maranhao, mean age was 56.8 years and in Minas Gerais 56.6 years. This confirms PC as a sixth decade of life disease[16,17,18].

Fear of treatment, embarrassment or low educational level may be causes for delay in seeking medical care. This can lead to late diagnosis, with large and advanced primary lesions. In this study most penile tumors were invasive (pT1 and above), with a small rate of pTa and pTis, leading to more aggressive organ amputations and fewer minimally invasive treatments. Despite having worst functional outcome, penile amputation is proven to be safe, with a minimal local recurrence rate (3.6%) and low surgical complications, very similar to medical literature[19].

In oncological follow up, most patients stayed disease free. Mean recurrence/metastasis time was 15.8 months and was more common in ILN. This corroborates with the safety and effectiveness of local PC excision and reaffirms PC as a disease with a high micro-invasion capacity, even in localized tumors.[10] As ILN invasion is the main sign of disease progression, pN+ patients required more invasive treatment, such as rescue surgery, neoadjuvant or adjuvant chemotherapy or local radiotherapy. Another study found similar data on LN invasion, with 92% of recurrence occurring in the first 5 years of follow-up[20].

ILN remains the most important prognostic factor for PC. Even in clinically negative patients, there is still up to 25% risk of micrometastasis[21]. However, ILND is a high morbidity procedure, with long hospital stay and an elevated rate of surgical complications. In the present series, significant complications (Clavien-Dindo 3 and up) ratio was comparable with other studies with similar population[22]. Advanced primary lesions stay as the most important predictor for pN+, but also lymph vascular and perineural invasion are important prognostic factors. In a recent metanalysis, perineural invasion was related to pN+, results compatible with the present data. However, worst cancer specific survival and a higher cancer specific mortality were also found in the metanalysis, differently this study[23].

Recently, LVI has been gaining strength as a factor for poor prognosis in PC, even causing a stratification in pT1 tumors rating. Winters et al. also found LVI as a prognostic factor for pN+, placing these patients as high-risk[24]. A study in Brazil related LVI with worst survival rates[22]. In the present study, not only was LVI related to pN+ risk, but also to higher recurrence and/or metastasis rates and worst OS.

DFS is very important and still underrated in PC. As recurrence was shown to be more often in ILN and ILN invasion being determinant for OS, factors that change recurrence must be assessed. More infiltrative primary lesions, Dartos infiltration and cN+ presented worst DFS. Also, pN+ patients showed more local recurrence and distant metastasis, even in multivariate analysis. In a recent study, pN+ patients had higher recurrence and worst DFS, mainly if ILND was delayed[25]. Curiously, data on Dartos infiltration is scarce in medical literature. No recent studies in the main databases have useful information on this prognostic factor.

In PC patients, OS is affected by several factors. Advanced tumors, especially with cavernosa and/or spongiosum infiltration, as well as low cell differentiation had a negative impact on OS. This data is coherent with medical literature, including a recent study in Brazil, showing worst survival in pathological stages 3 and 4[16,17]. Some of these factors were already included in the TNM classification[7]. Surprisingly, a higher rate of cavernosa infiltration was detected than spongiosum invasion, leading to more pT3 primary lesions than pT2. This goes against recent data with a similar population, with most tumors clinically and pathologically staged as T2[22]. A low instruction level and the difficult access to health care probably led to worst lesions at diagnosis. Also, penile body and dartos infiltration had a negative impact on OS, as found in a similar study[17,18]. In a multivariate analysis, both clinical and pathological ILN involvement maintained significance as prognostic factors. This data confirms ILN invasion as the main prognostic factor for PC.

Patients with clinically palpable nodes should be considered high-risk for ILN involvement and staged invasively[25]. In these subjects, FDG PET/CT can be helpful to differentiate neoplastic from inflammatory nodes[15]. As staging tools are still inaccurate for cN0 patients, the best solution is to use prognostic models and always choose surgical staging in case of doubt[8,26]. Shao and collaborators recently proposed a nomogram considering age, pT, cell differentiation, LVI and cN status. A calculator was then elaborated to assess pN+ risk. Although promising, this model still needs clinical validation before adoption in clinical practice[27].

When metastatic, PC becomes a deadly and rapid evolving disease. More than half patients with metastasis died in this series, with mean time of 13.2 months. Most of these subjects had to receive a multimodal treatment, including chemotherapy and/or adjuvant radiotherapy. However, none of these therapies seem to cease disease progression. The main prognostic factor for metastatic disease is also pN+, and patients with more advanced ILN staging have a higher recurrence rate after ILND[28].

As a retrospective evaluation, the present study has some limitations. A small sample size and lack of standardization in medical files can lead to relevant information loss. Abandonment is also an issue, making follow-up and treatment effectiveness verification harder.

5 CONCLUSIONS

In the present study, we were able to reaffirm several prognostic factors for OS and DFS in PC patients. As this is a rare neoplasm, this data will be beneficial to guide future clinical studies for disease management.

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