

Penile cancer and factors associated with metastases in inguinal lymph nodes

Câncer de pênis e fatores associados a metástases em linfonodos inguinais

Cáncer de pene y factores asociados a metástasis en ganglios linfáticos inguinales

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Abstract

Purpose: Penile cancer has a high incidence in some developing countries and metastasis in lymph nodes in the inguinal chain is a major challenge in the treatment of this neoplasia. The aim of this study was to identify the prevalence of metastasis in inguinal lymph nodes and their associated factors in patients with penile cancer. **Methods:** A retrospective analysis was made of all consultations by adult males with regard to penile lesions at our institution. Metastasis in inguinal lymph nodes was the event of interest and was defined based on the presence of squamous cell carcinoma in inguinal lymph nodes which had been confirmed by anatomopathological examination. We performed bivariate logistic regression analysis and the magnitude of the associations was expressed by the Odds Ratio as an estimate of the relative risk with a 90% confidence interval. **Results:** A prevalence of 24% of metastases was found among the 179 analyzed cases of squamous cell carcinoma of the penis. The presence of palpable lymph nodes in the inguinal region at the time of diagnosis ($p = 0.008$) and abuse of alcohol ($p = 0.07$) were independent associated factors for the disease becoming more aggressive. **Conclusions:** Patients diagnosed with penile squamous cell carcinoma, who present palpable lymph nodes in the inguinal region during the clinical examination and those who drink alcohol, should be an early target for interventions in the uro-oncology services.

Keywords: Penile neoplasms; Squamous cell carcinoma; Lymphatic metastasis; Prevalence.

Resumo

Objetivo: O câncer de pênis tem alta incidência em alguns países em desenvolvimento e a metástase em linfonodos da cadeia inguinal é um grande desafio no tratamento dessa neoplasia. O objetivo deste estudo foi identificar a prevalência de metástases em linfonodos inguinais e seus fatores associados em pacientes com câncer de pênis. **Métodos:** Conduzimos uma análise retrospectiva de todas as consultas de lesões penianas realizadas por homens adultos em nossa instituição. Metástase em linfonodos inguinais constituiu o evento de interesse e foi definida a partir da presença de carcinoma escamocelular em linfonodos inguinais, confirmado por exame anatomopatológico. Foi realizada análise de regressão logística bivariada e a magnitude das associações expressa pelo *Odds Ratio* como estimativa do risco relativo com intervalo de confiança de 90%. **Resultados:** A prevalência de metástases observada entre os 179 casos de carcinoma escamocelular de pênis foi de 24%. A presença de linfonodos palpáveis na região inguinal no momento do diagnóstico ($p = 0,008$) e o uso abusivo de álcool ($p = 0,07$) foram fatores associados independentes para que a doença se tornasse mais agressiva. **Conclusões:** Pacientes com diagnóstico de carcinoma epidermóide de pênis, que apresentam linfonodos palpáveis na região inguinal durante o exame clínico e aqueles que fazem uso de bebidas alcoólicas, devem ser alvo precoce de intervenções nos serviços de urooncologia.

Palavras-chave: Câncer de pênis; Carcinoma de células escamosas; Metástase linfática; Prevalência.

Abstracto

Objetivo: El cáncer de pene tiene una alta incidencia en algunos países en desarrollo y la metástasis en los ganglios linfáticos de la cadena inguinal es un desafío importante en el tratamiento de esta neoplasia. El objetivo de este estudio fue identificar la prevalencia de metástasis en los ganglios linfáticos inguinales y sus factores asociados en pacientes con cáncer de pene. **Métodos:** Se realizó un análisis retrospectivo de todas las consultas de varones adultos por lesiones peneanas en nuestra institución. La metástasis en los ganglios linfáticos inguinales fue el evento de

interés y se definió en función de la presencia de carcinoma de células escamosas en los ganglios linfáticos inguinales que se había confirmado mediante examen anatomopatológico. Realizamos análisis de regresión logística bivariante y la magnitud de las asociaciones se expresó mediante el Odds Ratio como una estimación del riesgo relativo con un intervalo de confianza del 90%. Resultados: Se encontró una prevalencia del 24% de metástasis entre los 179 casos analizados de carcinoma epidermoide de pene. La presencia de ganglios linfáticos palpables en la región inguinal en el momento del diagnóstico ($p = 0,008$) y el abuso de alcohol ($p = 0,07$) fueron factores asociados independientes para que la enfermedad se volviera más agresiva. Conclusiones: Los pacientes diagnosticados de carcinoma epidermoide de pene, que presenten ganglios linfáticos palpables en la región inguinal durante el examen clínico y los que consumen alcohol, deben ser un objetivo temprano para las intervenciones en los servicios de urooncología.

Palabras clave: Neoplasias del pene; Carcinoma de células escamosas; Metástasis linfática; Prevalencia.

1. Introduction

In recent years, the cure for penile cancer has increased to 80% because of better knowledge of the disease, early diagnosis, technological advances and specialized treatment in referral centers (Brien, et al., 2017; Clark, et al., 2016). In western countries, penile cancer represents an uncommon neoplasm. In the United States of America (USA), this accounts for 0.4% of all malignant tumors, while in regions with a low socioeconomic quality of life index, this type of tumor is found more frequently, e.g., in countries in Africa and South America (Magotha & Ngumi, 2000). In Brazil, its prevalence is greatest in men in their 70s unlike what occurs in men under 30 years old, the age group in which penile cancer is least common (When, et al., 2018; Li, et al., 2020). In the North and Northeast of Brazil, the incidence is about five times higher than in the South and Southeast (Couto, et al., 2014).

Characterized by the insidious onset of loco-regional disease before progressively spreading metastatically, about 95% of these malignancies correspond to squamous cell carcinoma (SCC) and approximately 80% of these develop in the prepuce and glans (Cubilla, et al., 1981; Narayama, et al., 1982). It is of the utmost importance to examine the lymph nodes in the treatment of penile cancer since the lymph nodes of the inguinal chain are the first to be affected and their involvement is the most important prognostic factor for penile cancer (Li, et al., 2019; Teh, et al., 2020).

Currently, early resection of inguinal lymph nodes seems to be controversial due to the possibility of the presence of hidden metastasis, since it is known that physical examination and imaging tests are not adequate to evaluate the inguinal lymph nodes and many patients undergo non-therapeutic lymphadenectomy (Ornellas, et al., 1994; When, et al., 2018). In fact, the high morbidity rates related to inguinal lymphadenectomy associated with a high percentage of non-metastatic lymph nodes cause lymphadenectomy to be postponed in some cases (Clark, et al., 2016) On the other hand, without adequate treatment, patients die within two years after diagnosis due to complications related to local growth or metastasis (Li, et al., 2020). Thus, this paper aimed was to identify the prevalence of metastasis in inguinal lymph nodes and their associated factors in patients with penile cancer.

2. Methods

After approval by the Research Ethics Committee of the Sociedade Pernambucana de Combate ao Câncer (No. 2.284.349), we conducted a retrospective cross-sectional study using all medical records of the penile lesions in adult males, in the last 6 years, treated at the Hospital de Câncer de Pernambuco, Brazil, which offers a specialized service to approximately 80% of males with penile cancer in the State. As for the nature of the research data, it is a quantitative study as described by Pereira et al., (2018).

Hospital records containing an anatomopathological examination confirming penile SCC were included in the study. Records that contained a diagnosis of benign penile lesion did not meet the eligibility criteria and were excluded.

Metastasis in inguinal lymph node constituted the event of interest and was defined based on the presence of SCC in inguinal lymph nodes confirmed through the anatomopathological examination. In addition, we also considered metastasis for

all hospital records reporting use of exclusive adjuvant chemotherapy and/or local radiation doses for penile cancer and death certificates which showed the cause of death as being from an advanced disease (NCCN, 2016; Clark, et al., 2016).

Factors potentially associated with the metastasis in inguinal lymph were analyzed, including age, lifestyle habits such as smoking and alcohol consumption, clinical findings such as inguinal lymph node positivity during palpation performed at the initial physical examination, and pathological factors such as the size of the lesion, angiolymphatic invasion, perineural invasion and grade of tumor, for all of which there was evidence in anatomopathological reports.

The area impaired by the lesion was defined in accordance with the anatomical region of the penis affected and was categorized based on the severity criteria established in the European Association of Urology (EAU) (Bada, et al., 2019) classification system, which shows the areas of lower severity as being the prepuce, glans, prepuce-glans (0) versus areas of greater gravity as being the body, base, base-body, prepuce-glans-body-base (1).

The size of the lesion size was defined according to the extent to which the penile area had been affected and categorized as $< 2.5\text{cm}$ and $\geq 2.5\text{cm}$ (Bada, et al., 2019).

The EAU classification system (2016) was used to classify the grade of the tumor. This correlates the pathological stage of the primary tumor and the histological grade and is categorized as high and low.

To classify the patterns of alcohol consumption, information was gathered regarding the volume and frequency of taking alcoholic drinks. The frequency of alcohol use was coded into categories ranging from “never” (for tee-totallers) to “every day” and this also includes the number of units. Individuals were classified as “teetotal” (if they never drink alcohol or drink less than eight units per year); a “light drinker” (if they drink not exceeding 10 units, on a monthly basis or on not more than one or two days a week); a “heavy drinker” (if they drink in excess of five units daily or on 3–4 days a week), and “alcohol dependent” (in treatment). For the purpose of the regression analysis, the variable of “alcohol consumption” was categorized into two levels: “Yes” (light drinker, heavy drinker and alcohol dependent) and “No” (tee-totallers).

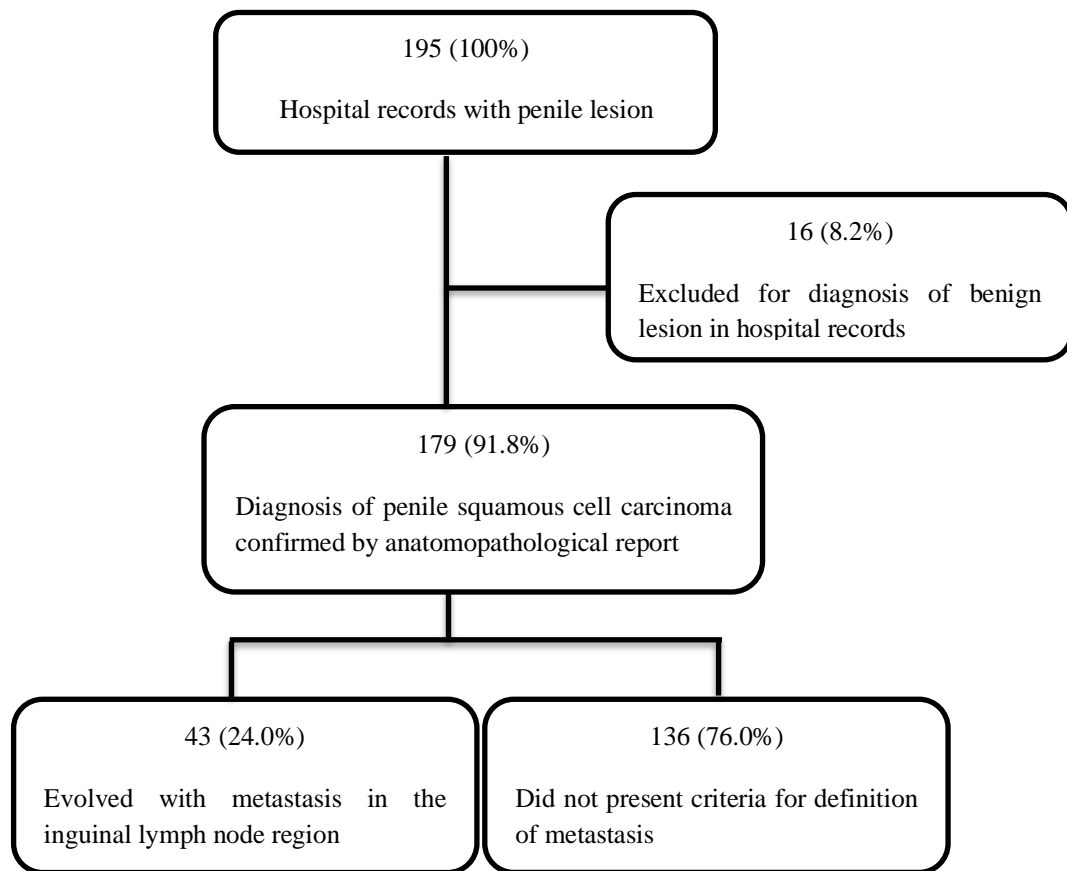
Data were stored in a database created for this research. All data were double entered (validated in EPI-INFO 6.04) and were subsequently compared to identify possible typing errors.

To check the statistical significance of differences in the frequency distribution of variables in accordance with metastasis in the inguinal lymph node, we used the chi-square test and, when necessary, the Fisher exact test. We carried out bivariate logistic regression analysis and the magnitude of the associations was expressed by the odds ratio (OR) with a confidence interval of 90% regression. To adjust the associations regarding possible confounding factors, we conducted a multivariate logistic regression analysis and used the statistical significance level of 20% ($p < 0.20$) in the bivariate analysis as the criterion for entering variables into the model. The criterion for the variables that remained in the final model was their association with metastasis with a statistical significance of 10% ($p < 0.1$). Analysis was performed using STATA 12.0 (Statistical Software for Professionals, StataCorp LP, UK).

3. Results

Of the 195 hospital records of penile lesion which were analyzed, 16 (8.2%) did not present eligibility criteria and were excluded. Among the 179 (91.8%) assessed data, 43 (24.0%) presented one of the criteria for metastasis in the region of the inguinal lymph node and were the event of interest for this study (Figure 1).

Figure 1 – Flowchart of the study.



Source: Authors.

Table 1 shows the frequency distribution and demonstrates the crude association between all the variables studied and metastases in inguinal lymph nodes in penile squamous cell carcinoma.

The population was predominantly elderly (60%), non-smoker (61.8%) and tee-total (72.5%). Clinically, the area of the penis most affected by the SCC was the glans and prepuce (50.6%). The presence of palpable lymph nodes at the initial examination of the patients was recorded in 21.9% of the cases reviewed, while lesions larger than 2.5 cm were present in 74.2% of them. From the anatomopathological point of view, it was observed that 11.8% had perineural invasion, 10.1% had angiolymphatic invasion and 49.4% of cases were classified as having a high grade of tumor (Table 1).

Table 1 - Association between risk factors and metastases in inguinal lymph nodes in penile squamous cell carcinoma.

	Total		Metastasis				OR	CI 90%	p-value
			Yes		No				
	N	%	N	%	N	%			
Age (years)									
< 60	71	39.9	18	25.4	53	74.6	1.17	(0.5-2.4)	0.653
≥ 60	107	60.1	24	22.4	83	77.6	1		
Smoker									
Yes	49	27.5	12	24.5	37	75.5	1.16	(0.5-2.6)	0.710
No	110	61.8	24	21.8	86	78.2	1		
Alcohol consumption									
Yes	27	15.2	10	37.0	17	62.9	2.44	(1.0-5.9)	0.05*
No	129	72.5	25	19.4	104	80.6	1		
Lymph nodes palpable									
Yes	39	21.9	16	41.0	23	58.9	4.36	(1.7-10.7)	0.001*
No	80	44.9	11	13.7	69	86.3	1		
Size of lesion									
≥ 2.5 cm	132	74.2	34	25.7	98	74.2	1.79	(0.6-4.6)	0.232
< 2.5 cm	37	20.8	06	16.2	31	83.8	1		
Area affected**									
1	90	50.6	25	27.8	65	72.2	1.64	(0.7-3.3)	0.182*
0	79	44.4	15	18.9	64	81.0	1		
Perineural invasion									
Yes	21	11.8	08	38.1	13	61.9	2.14	(0.8-5.6)	0.120*
No	148	83.2	33	22.3	115	77.7	1		
Angiolymphatic invasion									
Yes	18	10.1	08	44.4	10	55.6	2.86	(1.1-7.8)	0.04*
No	151	84.8	33	21.8	118	78.1	1		
Grade of tumor									
High	88	49.4	26	29.5	62	70.4	1.91	(0.9-4.0)	0.084*
Low	78	43.8	14	17.9	64	82.0	1		

OR = odds ratio; CI = confidence interval. * Statistically significant (p < 0.20). ** Area affected: prepuce, glans, prepuce-glans (0) versus body, base, body-base, prepuce-glans-body-base (1).

Source: Authors.

The final multivariate logistic regression model for the risk factors associated with inguinal lymph node metastasis in penile SCC is presented in Table 2. The variables that remained in the model, thus significantly increasing the risk for metastasis, were the presence of palpable lymph nodes in the inguinal region and being an alcohol drinker.

Table 2 - Multivariate model of the association between the risk factors studied and metastasis in inguinal lymph nodes in penile squamous cell carcinoma.

	OR	CI	OR	CI	p value
	Non-adjusted	(90%)	Adjusted	(90%)	
Lymph node enlargement	4.3	(1.7 - 10.7)	3.6	(1.4 - 9.6)	0.008*
Alcohol consumption	2.4	(1.0 - 5.9)	2.3	(0.9 - 6.1)	0.07*
Angiolymphatic invasion	2.8	(1.1 - 7.8)	1.9	(0.6 - 5.9)	0.23
Perineural invasion	2.1	(0.8 - 5.6)	1.3	(0.5 - 4.0)	0.54
Grade of tumor	1.9	(0.9 - 4.0)	1.2	(0.6 - 2.9)	0.53

OR = odds ratio; CI = confidence interval. * Statistically significant (p < 0.10).

Source: authors.

4. Discussion

The prevalence of metastasis in inguinal lymph node among cases of penile SCC was 24%. This result is similar to that observed in other studies conducted in Brazil and India (Shah, et al, 2017). On the other hand, a study conducted in the Netherlands (Brien, et al., 2017), but over a longer period and that had a larger population than ours, revealed a prevalence of metastasis of 16% among cases of penile SCC. Indeed, the geographical variation of penile cancer in the world is already well established in the literature, and factors such as the low socioeconomic and hygiene levels of the population, especially in underdeveloped countries like Brazil and India, contribute to SCC cases being of a greater severity (Shah, et al., 2017), which corroborates with what was observed in our population.

Studies have shown a higher incidence of the disease between the sixth and seventh decade of life (Ornellas, et al., 1994; Wen, et al., 2018). However, we found a percentage of 39.9% of men aged less than 60 years were affected by this cancer. In addition, we observed a higher percentage of metastasis (25.4%) in this population when compared to that observed in the elderly population (22.4%). These data disagree with other studies developed in Brazil that show the incidence of the tumor spreading through the lymphatic route has increased from the fourth decade of life. This fact can be explained due to the immunological condition of this population who have come in contact with the risk factors for the early development of penile cancer, such as HPV (Clark, et al., 2016; Aita, et al., 2016). Although, in this study, age was not considered a factor associated with metastasis, data in this regard are considered important because it is a segment of the population that is sexually and economically active and that, inevitably, suffered psychological damage as a result of mutilation caused by treatment.

This study reveals that the positivity of lymph nodes in the inguinal region during the initial physical examination of patients with penile lesion presents 3.6 times more chances of lymphatic tumor dissemination when compared to those patients who do not have lymph nodes on palpation and is an independent factor for lymph node metastasis ($p = 0.008$). In fact, penile SCC is a disease that presents a pattern of dissemination through the lymphatic pathway, initially affecting the inguinal lymph nodes and, later on, the pelvic ones. This metastatic spread determines the evolution of the disease and the survival of the patients, and is, therefore, the most important risk factor (Li, et al., 2019).

Thorough physical examination at the initial consultation of patients with penile cancer is essential for the early detection of lymph node enlargement (Brien, et al., 2017). In our case-by-case analysis, we can analyze only 119 (66.5%) of the data referring to the initial examination of these patients. Among them, we observed a percentage of 41% metastasis in the inguinal region in those with a positive examination in the clinical evaluation of the lymph nodes, which not matches the result observed in a retrospective study carried out in Italy in which the lymph node having been affected was evidenced in 70% of the cases that presented palpable lymph nodes during initial physical examination (Hakenberg (Chair), et al., 2016). Of course, the high percentage (27.9%) of medical records which do not mention an examination of the inguinal region may have contributed to this difference, and this constitutes one of the main limitations of this paper.

The standard treatment of lymph node metastasis in penile cancer is regional lymphadenectomy. Given the rarity of penile cancer in the world, it is difficult to conduct randomized controlled prospective studies, even in multicenter settings, in order to test hypotheses such as the benefits between prophylactic and therapeutic lymphadenectomy, as well as the associated risk of morbidity associated with the procedure, especially with regard to prophylactic treatment (Li, et al., 2019; Li, et al., 2020)

It is known that 20% of the negative patients in the clinical evaluation of the lymph nodes, when submitted to regional lymphadenectomy, present micro metastases to the histopathological examination (Wen, et al., 2020). We observed a lower percentage (13%) of metastasis among patients whose inguinal lymph nodes were not palpable at the initial diagnosis, which reinforces the need to identify associated factors to improve the prediction of lymph node involvement and to reduce the number of unnecessary lymphadenectomies (Teh, et al., 2020).

The consumption of alcohol was also an independent factor for lymph node metastasis. Our results show that males who drink alcohol are 2.3 times more likely to develop inguinal lymph node metastases when compared to tee-totals. This is a ratio not yet described in cases of penile SCC, but it is already well established in cases of SCC of the head and neck (Li, et al., 2019) A study conducted in Kenya, one of the countries with the highest incidence of penile cancer in the world (Magotha, et al., 2000; Menach, et al., 2014), demonstrated that alcohol consumption was positively associated with the poorly differentiated forms of laryngeal SCC, implying a more unfavorable outcome than the more differentiated tumor (Teh, et al., 2020). By a mechanism still unknown, it is probable that the action of alcohol on the other systems makes a considerable contribution to the appearance of some types of mutations in cancer (Jiun-Hung, et al., 2015; Wen, et al., 2020).

In addition to biological influences, coupled with the consumption of alcohol, there is the behavioral influence associated with lifestyle. Men's health researchers have shown that male alcoholics have a deficit in self-care, culminating in their delaying seeking health care. Therefore, there is a delay in early diagnosis and, consequently, the clinical and pathological state of the disease progress (Menach, et al., 2014). In Brazil, excessive alcohol consumption is an important public health problem, and the prevalence of excessive alcohol consumption is similar to that shown in different countries (Munhoz, et al., 2017). One study, conducted in the United States, found that the effects of economic problems, such as a reduction in salary and loss of job, are associated with the higher consumption of alcohol and that individuals aged 50 years or older have higher rates of negative health outcomes, including morbidity, mortality, and functional disability (Wen, et al., 2020). These factors may be closely related to the higher prevalence of penile cancer in alcoholics.

Information on the biological behavior of the tumor, such as histological grade, angiolymphatic invasion, perineural invasion and the invasion pattern of the tumor are important aspects in predicting lymph node metastases (Li, et al., 2019; Li, et al., 2020) and were evaluated in this study. In the univariate analysis, angiolymphatic invasion had a strong statistically significant association ($p < 0.05$) for lymph node metastasis. This was corroborated by the study by Lopes et al., in which the lymphatic and venous invasions were described as the only independent predictors of lymph node metastases in 145 patients with penile cancer. However, we believe that due to the sample size, this important risk factor has lost strength and was not maintained in the final model of the multivariate analysis. Angiolymphatic invasion is strongly associated with more aggressive subtypes of penile carcinoma, as shown in the review of the literature study developed by Cubilla, et al., They found a broad correlation of special subtypes of penile squamous cell carcinomas that resulted in the regional lymph node being the first site that was affected when the tumor spread according to its histological characteristics (Shah, et al., 2017).

Our study has the limitations of a retrospective observational study with patients attending a routine medical care setting. Certainly, the information made available in the medical records, which are created by different professionals, contributed to the absence of some of the data that we analyzed. However, this did not make it impossible for us to demonstrate, for example, that the consumption of alcohol is associated with the risk of inguinal metastasis in this population. Naturally, if we had obtained data on alcohol consumption from the 179 hospital records analyzed, instead of only 156, we would have a more robust statistical analysis with smaller confidence intervals, thereby reinforcing the association of alcohol consumption and the development of inguinal lymph nodes metastasis in this population. Therefore, the volume of information we obtained for this variable was sufficient to demonstrate the strength of this association. The present study was rigorously planned. We constructed a data collection instrument with questions that require precise answers. In addition, the data were collected by previously trained professionals.

5. Final Considerations

Given the infrequency of this disease and the consequent absence of follow-up studies involving this type of cancer, it became necessary to make a retrospective study of all cases of penile cancer attended at our service in the last 6 years. We

know of the valuable contribution that the present study brings to the scientific community, since our sample is representative of the population studied in addition to which sectional studies, necessarily, constitute the beginning of cohort studies. Despite the difficulty of conducting prospective studies on a rare disease, multicenter studies should be performed in order to provide greater reliability in the evaluation and follow-up of patients diagnosed with penile cancer.

These results are relevant for improving support to males with penile cancer in the specialized services for uro-oncology. Identifying associated factors for metastasis in inguinal lymph node among this population contribute to the exercise of greater disease control.

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