

# Squamous cell carcinoma of the penis: clinicopathologic study of 34 cases \*

## Carcinoma epidermoide do pênis: estudo clínico-patológico de 34 casos

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**Abstract:** BACKGROUND: In Brazil, the incidence of penile cancer is 8.3 cases per 100,000 population, in contrast to 0.7 in Europe and the United States. 95% of these cases correspond to squamous cell carcinoma (SCC). It is usually diagnosed late.

OBJECTIVES: To describe the clinicopathologic features of squamous cell carcinoma of the penis registered at the Hospital between 1978 and 2004.

METHODS: A cross-sectional observational study. We included cases of squamous cell carcinoma of the penis that were histologically confirmed. Those patients who responded to the study call were evaluated in person, while others had their data researched in medical records.

RESULTS: 34 patients with squamous cell carcinoma of the penis were registered: 8 *in situ* and 26 invasive, with a mean age of 54.7 ± 22.4 and 64.7 ± 12.5 years, respectively. Glans cancer was involved in 91.1% of the cases and the foreskin in 41.1%. SCC *in situ* exhibited papules or erythema and erosion, usually smaller than 2 cm. Invasive SCC was characterized by ulcers and/or vegetation, usually single and bigger than 2 cm. Of the invasive cases, 80.8% were well differentiated; half was in the TNM stage I and the remaining in stages II to IV. 16 patients had their penis amputated, and 3 died.

CONCLUSIONS: Cancer of the penis is rare and affects adults of all ages and treatment can be aggressive. The nonspecific clinical appearance of early lesions, insufficient medical training in skin lesions and lack of routine diagnostic investigation, treatment and follow up of these cases contribute to the poor prognosis of this neoplasm.

Keywords: Carcinoma, squamous cell; Penile diseases; Penile neoplasms; Penis

**Resumo:** FUNDAMENTOS: No Brasil, a incidência do câncer do pênis é de 8,3 casos/100.000 habitantes, contrastando com 0,7 na Europa e nos Estados Unidos. Em 95% dos casos, trata-se do carcinoma epidermoide. Em geral, é diagnosticado tardiamente.

OBJETIVOS: Descrever as características clínico-patológicas do carcinoma epidermoide do pênis, registradas no Hospital entre 1978 e 2004.

MÉTODOS: Estudo observacional transversal. Incluíram-se os casos de carcinoma epidermoide do pênis, confirmados histologicamente. Avaliaram-se, pessoalmente, os pacientes que atenderam à convocação para o estudo, enquanto os demais tiveram seus dados pesquisados nos prontuários médicos.

RESULTADOS: Registraram-se 34 pacientes com carcinoma epidermoide do pênis: 8 *in situ* e 26 invasivos, com idade média de 54,7 12,5 anos, respectivamente. A ± 22,4 e 64,7 ±, A glândula foi acometida em 91,1% dos casos e o prepúcio, em 41,1%. Os carcinomas epidermoides *in situ* exibiam pápulas ou eritema e erosão, geralmente menores do que 2 cm. Os invasivos mostravam úlceras e/ou vegetações, geralmente únicas, e maiores do que 2 cm. Dos CE invasivos, 80,8% eram bem diferenciados; metade encontrava-se no estágio I TNM e o restante, do II ao IV; 16 pacientes tiveram o pênis amputado e 3 faleceram.

CONCLUSÕES: O câncer do pênis é raro, acomete adultos de todas as faixas etárias e o tratamento pode ser agressivo. O aspecto clínico inespecífico das lesões iniciais, o insuficiente treinamento médico em lesões dermatológicas e a carência de rotinas de investigação diagnóstica, tratamento e acompanhamento destes casos contribuem para o mau prognóstico desta neoplasia.

Palavras-chave: Carcinoma de células escamosas; Doenças do pênis; Neoplasias penianas; Pênis

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## INTRODUCTION

Penile cancer is rare and 95% of the cases histologically correspond to squamous cell carcinoma (SCC).<sup>1,2</sup> In Brazil, SCC represents 2% of all types of cancer in males, being significantly more frequent in the North and Northeast regions of the country, where the cases of SCC outnumber those of bladder and prostate cancer.<sup>3</sup> In the United States and Europe, SCC of the penis accounts for 0.4 to 0.7% of all malignancies found in men.<sup>4,5</sup> The incidence of penile SCC is 8.3 cases per 100,000 population in Brazil, reaching 20% in African countries.<sup>4,5</sup> In contrast, it varies from 0.1 to 0.7 per 100,000 population in Europe and in the United States.<sup>4</sup>

Infection with oncogenic types of *Human Papilloma Virus* (HPV) and lichen sclerosus seem to be the main risk factors for this neoplasm.<sup>6-8</sup>

Physicians' inexperience in clinically identifying precursor lesions or early lesions of SCC of the penis and patient delay in seeking medical attention for fear, shame or even ignorance, in addition to difficult access to health services in our country, cause delays in diagnosing most cases of the disease.

Cancer of the penis can cause high morbidity because of both the disease itself and the treatment, which includes partial or total amputation of the organ.<sup>4</sup> The mortality rate related to this neoplasm varies from 26.7 to 41%.<sup>9</sup> Early diagnosis reduces this rate and allows for less aggressive treatment, contributing to these men's better quality of life. Training physicians for early detection of this type of cancer and instructing the lay population will certainly improve this scenario.

This study aimed to describe the clinicopathological features of the cases of SCC of the penis registered at the Hospital from its inauguration in March 1978 to July 2004.

## MATERIAL AND METHODS

**Ethical considerations:** After approval of the Research Ethics Committee of the Hospital (protocol no. 098/01), the study was initiated and the patients evaluated in person signed the consent form.

**Design:** Cross-sectional observational study.

**Participants:** The study included cases of SCC *in situ* and invasive SCC of the penis histopathologically confirmed at the Hospital between March 1978 and July 2004.

## METHODS

The cases were selected among patients seen at the Outpatient Clinic of Genital Dermatology from January 2001 to July 2004 and from the nosological files at the Anatomic Pathology Service (APS) of the Hospital covering the period 1978-2004. At the APS, we crossed the SNOMED (Systematized Nomenclature of Medicine - 1980) codes corresponding to possible synonyms for SCC *in situ* and invasive SCC of the penis and to possible locations of the penile neoplasm (penis, glans and foreskin) (Chart 1).

We investigated the following variables in all cases: histological variant of SCC of the penis (*in situ* or invasive), patient age at diagnosis, location and clinical morphology of the lesion, risk factors for SCC of the penis (history of genital warts and other sexually transmitted diseases - STDs), lichen sclerosus, phimosis, co-factors related to carcinogenesis (history of neoplasms, smoking and immunosuppression) and treatment performed. Regarding invasive SCC of the penis, we also investigated histological features of the tumor related to prognosis, staging (according to the criteria established by the Union Internacional Contre le Cancer / 1997 - TNM) and death related to the neoplasm.<sup>3</sup>

Patients who were not undergoing regular fol-

**Chart 1:** Terms used in the investigation on cases of penile cancer in the Division of Anatomic Pathology of the Hospital, according to the SNOMED (Systematized Nomenclature of Medicine - 1980)

M.7400/8	Severe dysplasia
M.8000/3	Malignancy - unclassified tumor
M.8010/2	Intraepithelial carcinoma in situ
M.8010/3	Malignant epithelial carcinoma
M.8070/2	Squamous cell carcinoma in situ
M.8070/3	Squamous cell carcinoma
M.8071/3	Non-keratinizing squamous cell carcinoma
M.8072/3	Non-keratinizing large-cell squamous cell carcinoma
M.8073/3	Non-keratinizing small-cell squamous cell carcinoma
M.8076/2	Squamous cell carcinoma in situ with questioned stromal invasion
M.8076/5	Micro-invasive squamous cell carcinoma
M.8080/2	Erythroplasia of Queyrat
M.8081/3	Bowen's disease

low-up at the Outpatient Clinic of Genital Dermatology were invited to participate in the study by letter and/or telephone. The patients available for the study were interviewed and clinically examined. Those interviewed before undergoing surgery had their clinical lesion photographed. As for the remaining patients, the data were obtained from medical records.

Histological slides related to biopsies and/or surgical specimens of all cases included in the study were reviewed. The cases of SCC were classified as *in situ* - when the neoplasm was confined to the epidermis, which is usually acanthotic, consisting of depolarized keratinocytes with hyperchromatic nuclei and pleomorphism of variable intensity, sometimes vacuolated, basically present along the entire thickness of the epithelium - or invasive, when the neoplasm was present in the stroma in general as irregular masses or clusters of squamous cells more or less differentiated, with varying degrees of dyskeratosis, manifesting individual cell keratinization and/or horn pearl formation (Figure 1). In all cases, we investigated the presence of peritumoral changes suggestive of other dermatoses and analyzed the quality and intensity of the associated inflammatory response, classified as mild, moderate or severe. In case of invasive SCC, we also investigated the degree of tumor differentiation and presence of vascular invasion. To assess the degree of differentiation, we used a modified Broder's classification, which includes three levels instead of the four original classification levels: well-differentiated tumor (grade I), when less than 25% of the cells are undifferentiated; moderately differentiated (grade II), when

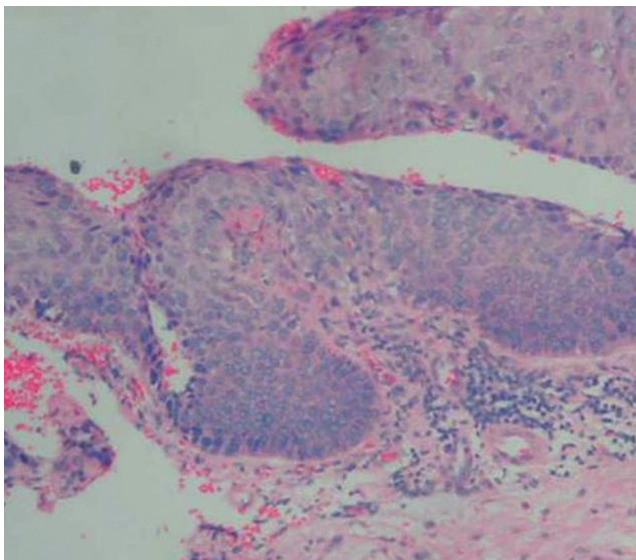


FIGURE 1: Squamous cell carcinoma *in situ*: acanthosis with vacuolated keratinocytes occupying the entire thickness of the epithelium

25 to 75% of the cells are undifferentiated; and undifferentiated (grade III), when more than 75% of the cells are undifferentiated.<sup>10</sup>

## RESULTS

In the 26 years covered by the study (March 1978 to July 2004), 34 cases of SCC of the penis were registered at the Hospital, of which 11 were diagnosed at the Outpatient Clinic of Genital Dermatology between January 2001 and July 2004 (4 SCC *in situ* and 7 invasive SCC). The 34 cases of SCC were classified into 2 groups according to the histological variant: *in situ* (8 cases) and invasive (26 cases).

In relation to age at diagnosis, the patients with SCC *in situ* were between 21 and 80 years old (mean =  $54.7 \pm 22.4$ ) and those with invasive SCC were between 38 and 86 years old (mean =  $64.7 \pm 12.5$ ).

Among the risk factors and co-factors studied, smoking was the most frequent, seen in two patients with SCC *in situ* and in 15 with invasive SCC. Previous history or presence of phimosis at diagnosis was verified in 5 patients with invasive SCC. Circumcision was performed in only 2 patients with invasive SCC during adulthood, 11 patients denied having undergone this procedure, and this information could not be confirmed for the remaining 21 patients.

History of STDs was registered among patients with SCC *in situ* (3 cases of genital warts associated with HIV infection and 1 case of syphilis) and patients with invasive SCC (1 case of genital warts and gonorrhea, 1 case of syphilis and 1 case of gonorrhea). On clinical examination, warts were observed in 6 patients (4 SCC *in situ* and 2 invasive SCC). On histopathological examination, we identified changes consistent with HPV infection in 9 cases: 5 had been clinically suspected (3 SCC *in situ* and 2 invasive SCC) and 4 cases of invasive SCC had not been suspected on clinical examination (Figure 2).

Changes suggestive of lichen sclerosis on clinical examination were investigated in the 11 patients diagnosed at the Outpatient Clinic of Genital Dermatology, and four cases were confirmed: two SCC *in situ* and 2 invasive SCC, while features suggestive of this disease were not mentioned in the medical records of the remaining 23 patients (Figures 3 to 6). Changes consistent with lichen sclerosis were not detected in the histopathological examination of any of the cases of SCC *in situ*, but were found in the 2 cases of invasive SCC that also showed clinical changes suggestive of this disease as well as in a patient with invasive SCC previously submitted to circumcision due to phimosis, but who had no changes clinically suggestive of lichen sclerosis at diagnosis of a neoplasm located in the glans.

Chart 2 shows the findings of the clinical exami-

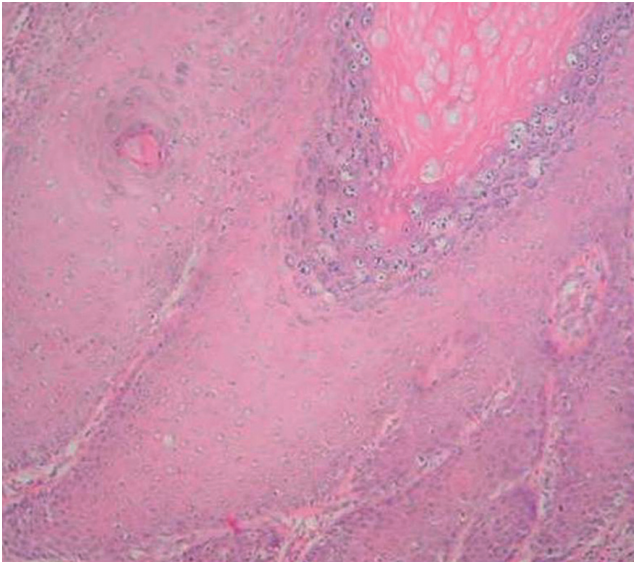


FIGURE 2: Invasive squamous cell carcinoma: signs suggestive of associated infection with HPV (hypergranulosis, koilocytosis) in keratinocytes located in the higher portions of the Malpighian layer

nation: location of the neoplasm, predominant elementary dermatological lesion, number and size of lesions. Regarding local symptoms, 8 patients (3 SCC *in situ* and 5 invasive SCC) were asymptomatic, while 21 reported pain (2 SCC *in situ* and 10 invasive SCC), pruritus (3 SCC *in situ* and 3 invasive SCC) and pain and pruritus (3 invasive SCC). This information was not found in the medical records of the other five remaining cases.

From a histopathological point of view, the inflammatory response was observed in all patients in varying degrees: mild (6 cases of SCC *in situ* and 7 cases of invasive SCC), moderate (1 case of SCC *in situ* and 10 cases of invasive SCC) and intense (1 case of SCC *in situ* and 9 cases of invasive SCC). Regarding the degree of differentiation of invasive SCC, 21 (80.8%) were well differentiated and 5 (19.2%) were moderately differentiated; only 2 showed images of lymphatic emboli (Figure 7).

There was no reference to palpation of the inguinal lymph nodes in the medical records of 2 of the 26 patients with invasive SCC. Of the 24 remaining patients, 13 had inguinal lymphadenopathy at diagnosis and the 7 patients who had undergone lymphadenectomy had metastatic lymphadenopathy revealed by histopathological examination. Among the patients with SCC *in situ*, no inguinal lymphadenopathy was detected on physical examination.

There was insufficient data about 3 patients so that staging could be determined. The other patients were distributed as follows: 13 patients in stage I, 3 in stage II, 4 in stage III and 3 in stage IV.

Among the 8 patients with SCC *in situ*, the type

CHART 2: Distribution of the number of cases of squamous cell carcinoma of the penis according to the clinical features observed

Characteristics of the lesions	Number of cases	
	SCC <i>in situ</i> (N = 8)	Invasive SCC (N = 26)
<b>Location of tumor</b>		
Glans	3	16
Foreskin	1	2
Glans + foreskin	2	6
Glans + foreskin + body of the penis	2	1
Glans + body of the penis	0	1
<b>Predominant elementary lesion</b>		
Macule	1	0
Papule	3	0
Erosion	1	0
Macule + erosion	2	0
Ulceration	1	1
Vegetation	0	5
Nodule	0	1
Vegetation + ulceration	0	18
Uninformed	0	1
<b>Lesion size (cm)</b>		
< 0.5	1	0
0.6 to 2.0	4	5
2.1 to 5.0	0	14
> 5.1	0	3
uninformed	3	4
<b>Number of lesions</b>		
1	3	18
2 to 5	2	3
6 to 10	0	0
>10	1	0
uninformed	2	5

of treatment established was as follows: circumcision in 1 case, simple excision in 1 case, cryosurgery in 1 case; local chemical treatment (trichloroacetic acid 90%, 5-fluorouracil and imiquimod) in 3 cases; treatment not reported in the records of two cases. Among the 26 patients with invasive SCC, 2 underwent circumcision, 16 underwent partial amputation of the penis and 5 underwent total amputation, complemented in some by lymphadenectomy, radiotherapy and/or chemotherapy; the medical records of 3 cases did not give any information about the treatment established. There were 3 deaths related to the neoplasm: one case in stage III and two cases in stage IV.



FIGURE 3: Squamous cell carcinoma *in situ* and lichen sclerosus: poorly defined erythematous area with some erosion at the distal portion of the penis up to the balanopreputial sulcus, which shows a slightly waxy aspect



FIGURE 5: Invasive squamous cell carcinoma and lichen sclerosus: opaque achromic lesion in the distal third of the penis, with blurring of the balanopreputial sulcus, erythematous areas and ulceration surrounded by exuberant keratosis around the urethral meatus;



FIGURE 4: Squamous cell carcinoma *in situ* and lichen sclerosus: hypochromic area with thin keratosis affecting much of the glans and about 2 cm above the balanopreputial sulcus, where there is a slight erythema and a phimotic ring



FIGURE 6: Invasive squamous cell carcinoma: ulcer with approximately 3 cm, dirty base and hypertrophic borders in the body of the penis. Phimosis exposing the tip of the glans, which is achromic and waxy, with dotted hemorrhage on the surface of a small paraurethral ulcer

## DISCUSSION

The motivation to conduct this study arose after some difficulties in relation to managing patients with penile cancer were observed at the Outpatient Clinic of Genital Dermatology of the Hospital. Some of these difficulties were the nonspecific clinical aspect (Figures 2 and 3) of many cases of carcinoma *in situ* not suspected by assistant physicians, the advanced state at which many patients with invasive SCC arrived at the hospital (Figures 4 to 6), lack of protocols to

standardize and guide the full medical care of these patients, in addition to controversies regarding concepts and nomenclatures.

SCC of the penis is a rare tumor. Over the 26 years studied, since the inauguration of the Hospital in March 1978, only 34 cases were registered (8 SCC *in situ* and 26 invasive SCC). The concentration of cases diagnosed (n=11), especially cases of SCC *in situ* (n=4), in 4½ years of data collection at the



FIGURE 7: Invasive squamous cell carcinoma: ulcerovegetating lesions surrounded by keratosis, deforming the region of the glans and balanopreputial sulcus in a 43-year-old man

Outpatient Clinic of Genital Dermatology was remarkable. This outpatient clinic inaugurated in 1985, initially as an outpatient clinic of Vulvar Pathology, became a reference for referral of patients with cutaneous lesions in the genital area, especially lichen sclerosus and HPV-related lesions. Starting in 1999, its service was extended to male patients. At that time, the exchange between the outpatient clinic of Genital Dermatology and the Urology Service was intensified. Since penile cancer appears as a skin lesion, detection of cases, especially those at an early stage, depends on the accuracy of clinical examination and, therefore, training on skin lesions of this region is essential.

As in most national and international articles, “penile cancer” is used as a general term in the records of cancer cases of the Brazilian Ministry of Health, with no regard to the tumor cell line. However, as squamous cell carcinoma accounts for nearly 95% of these cases, much of the information found in these studies can be compared with the results of this one.<sup>12</sup> Nonetheless, even among cases of squamous cell carcinoma, the nomenclature used by the different authors is not standardized. This is even more evident with regard to SCC *in situ* of the penis, with articles on “Bowen’s disease”, “erythroplasia of Queyrat,” “bowenoid papulosis” and “penile intraepithelial neoplasia” (PIN), which histologically correspond to the same neoplasm - squamous cell carcinoma *in situ* - but with possibly different clinical features.<sup>11</sup> The term “intraepithelial neoplasia” has been used for lesions of the cervix since 1966 and was gradually adopted for other epithelia.<sup>11</sup> In relation to SCC of the penis, the PIN designation for cases of SCC

*in situ* has been used only recently.<sup>12</sup> Standardization of the nomenclature for SCC *in situ* of the penis would certainly facilitate comparability between studies, increasing the level of knowledge on the subject. In this study, we used only the name “SCC *in situ*”, because it is a broader term, which identifies the squamous intraepithelial neoplasia, regardless of the clinical features.

A study, also carried out in Rio de Janeiro, gathered 80 cases of penile SCC between 1995 and 2000 from three hospitals: Instituto Nacional do Câncer (National Cancer Institute), Hospital Universitário Pedro Ernesto (Pedro Ernesto University Hospital) and Hospital do Câncer Mário Kröeff (Mario Kröeff Cancer Hospital) (7). Possibly, the participation of cancer hospitals helped collect three times the number of cases in our study in the same city in a period five times shorter than that of our study. This frequency of invasive penile SCC is much higher than that found in developed countries. A study conducted in a urological hospital in Madrid, covering a period of 23 years (1981-2004), detected only 16 cases of invasive penile SCC, showing the rarity of this cancer type in Europe.<sup>13</sup> In another investigation involving 62 pathology laboratories in France (1990-1992), 11 cases of invasive SCC were detected, contrasting with the higher frequency of intraepithelial neoplasms of the penis: 60 of low grade (PIN I) and 41 of high grade (PIN II and PIN III, the latter corresponding to SCC *in situ*).<sup>14</sup>

In an epidemiological study on penile cancer (invasive) in Brazil, published in 2007 by the Brazilian Society of Urology, the highest incidence rates were found in the states of Sao Paulo (24.26%), Ceará (12.87%), Maranhao (10.66%) and Rio de Janeiro (9.19%), and the lowest incidence rates were found in Rio Grande do Sul, Santa Catarina and Paraná (0.37%).<sup>15</sup> There has been an increase in incidence rates in developing countries and underdeveloped countries, and the North and Northeast of Brazil follow this trend.<sup>9,15</sup> In contrast, the incidence of penile cancer has been decreasing in developed countries over the years, which can be explained, at least in part, by better socioeconomic conditions, higher levels of education and higher efficacy of the health system.<sup>2,5</sup>

Since 2007, the Brazilian Society of Urology has developed a national educational campaign in order to eradicate penile cancer by disseminating the signs and symptoms most commonly found and by examining the population in different cities in the interior of the country.<sup>15</sup> Measures such as this one contribute to making men less embarrassed and seek medical care, allowing early diagnosis of cancer of the penis in seemingly innocent lesions.

In this study, in general, patients with SCC *in*

*situ* (mean age  $54.7 \pm 22.4$ ) were younger than those with invasive SCC (mean age  $64.7 \pm 12.5$ ). SCC *in situ* affected individuals in all age groups between 21 and 80 years old, while invasive SCC, although covering a wide age range, showed to be predominant among older patients (69.2% were between 61 and 80 years old). The youngest patient with SCC *in situ* was 21 years old at diagnosis and had genital warts, besides being HIV positive, which illustrates the contribution of the immunodeficiency both to the risk of acquiring an oncogenic HPV type and to initiation and progression of a tumor.<sup>6,16</sup> The youngest patient with invasive SCC was 38 years old at diagnosis and had phimosis associated with histopathological changes suggestive of lichen sclerosus, another risk factor for this neoplasm. According to the manual of the Ministry of Health on cancer of the penis, this neoplasm affects men over 50 years old, which corroborates our findings, according to which 80.7% of the cases of invasive SCC and 62.5% of the cases of SCC *in situ* belonged to this age group. In the European studies cited above, the mean ages of patients with invasive SCC were similar to ours:  $71.7 \pm 10.2$  years in the Spanish study and 68 years in the French study.<sup>3,13,14</sup> In the Brazilian study conducted in Rio de Janeiro, the mean age was 57.6 years (36-86 years).<sup>7</sup> In relation to SCC *in situ*, the mean age in the French study was 33 years, which is much lower than ours, and it is probably more representative of the diagnosable cases, because of the larger sample size of that study.<sup>14</sup>

In our study, the duration of the disease at diagnosis reported by the patients was  $18.4 \pm 27.9$  months in SCC *in situ* and  $19.8 \pm 18.8$  months in invasive SCC. This information is subject to various biases, such as memory, patients' inability to correlate precursor lesions with current lesion and even patients' embarrassment in admitting faults with their own health care. In the Spanish study mentioned above, the mean duration of cases of invasive SCC at diagnosis was 18 months, comparable to our study.<sup>13</sup>

Although some factors have been linked to penile SCC since the first publications on the subject and repeated throughout much of the literature researched, it is likely that they just coexist with the real risk factors, which currently seem to be persistent infection with oncogenic types of HPV, especially HPV 16, and lichen sclerosus.<sup>12</sup> Thus, lack of hygiene, smegma accumulation and presence of phimosis could actually be related to lichen sclerosus. Phimosis may be present in up to 53% of the adults with lichen sclerosus.<sup>17</sup> In this study, although insufficient information in the medical records has hampered the analysis of putative risk factors, occurrence of some of these factors can be noticed.

Genital warts were registered in 7 (14.2%) of

our patients with invasive SCC and in 5 (60%) of the patients with SCC *in situ*. The latter were co-infected with HIV, illustrating the role of immunodeficiency in carcinogenesis.<sup>6,16</sup> It is accepted that HPV is implicated in the pathogenesis of some cases of penile SCC, since the HPV DNA is detected by PCR in 30.5% to 81.8% of the cases.<sup>6,7</sup> In the study conducted in Rio de Janeiro, Brazil, HPV-16 was the most prevalent type (52% of the cases).<sup>7</sup> However, HPV infection is not sufficient to determine cancer, considering the high prevalence of the viral infection and the rarity of the neoplasm. Genetic and environmental factors seem to be necessary. The time interval between HPV infection and emergence of SCC of the penis may be decades, which reinforces the hypothesis of the synergistic action of other agents, such as smoking.<sup>5</sup> In our study, current or past smoking was identified in 6 (33.4%) of the patients with SCC *in situ* and in 20 (75%) of the patients with invasive SCC.

A history of phimosis or current phimosis was detected in 5 (19.2%) of our patients with invasive SCC, but this information was only obtained in 7 cases of invasive SCC and in 3 cases of SCC *in situ*. Clinical changes suggestive of lichen sclerosus were observed in 4 (50%) of the cases of SCC *in situ* and in 7 (28.6%) of the cases of invasive SCC. The frequency of SCC in patients with lichen sclerosus of the penis varies from 4 to 8%, while 32 to 50% of the cases of SSC of the penis coexist with lichen sclerosus.<sup>18</sup> Although neonatal circumcision is considered a protective factor against cancer of the penis by some authors, there are reports of penile cancer in these individuals.<sup>19</sup>

In this study, we found that some cases of clinically suspected lichen sclerosus and genital warts were not confirmed histopathologically. On the other hand, some cases of those same dermatoses diagnosed in the histopathological examination did not show the clinical changes expected. These differences can be partially explained by the lack of information in the medical records of the patients evaluated retrospectively. However, it is possible that the tumor growth changed the specific clinical and histopathologic features of these diseases. Koilocytosis, a marker of HPV infection, is often not observed in malignant lesions due to the fact that, when the viral DNA integrates into the genome of the host cell, it stops producing virions, which are responsible for the cytopathic effect.

In this study, the predominant location of SCC, *in situ* or invasive, was the glans, alone (55.9%) or associated with other regions of the penis (91.1%). It was followed by the foreskin, which was affected alone in 8.8% of the cases and in association with other regions in 41.1%. In the literature investigated, the glans was also the predominant region affected

(48%), but at a proportion much lower than that found in our study, followed by the foreskin (21%), glans and foreskin (9%), balanopreputial sulcus (6%) and body of the penis (less than 2%).<sup>5,20,21</sup>

Regarding clinical morphology, SCC *in situ* can present with nonspecific lesions such as macules, papules, keratoses, erosions and/or ulcerations and various colors (whitish, pink, red, violaceous, gray, brown, black).<sup>11</sup> In this study, despite the small number of cases of SCC *in situ*, we observed various clinical aspects, which could easily be confused with inflammatory lesions: erythematous macules, erosion, erythematous macules with erosion, papules and ulceration (Figures 3 and 4). The presence of erosions in these cases could be associated with the presence of other inflammatory or traumatic lesions, such as lichen sclerosus. It is worth noting that the only patient with an ulcerated lesion of SCC *in situ* complained of pruritus at the site of the lesion and scratching could have caused it. In relation to SCC *in situ* of the penis, differential diagnoses include dermatoses such as candidiasis, Zoon's plasma cell balanitis, psoriasis, contact dermatitis, lichen planus and lichen sclerosus. In contrast, the clinical presentation of invasive SCC, predominantly ulcerated and/or vegetating, readily refers to the possibility of malignancy (Figures 5, 6 and 8). Even though, these lesions are nonspecific and must be biopsied to rule out other causes of chronic ulcers in the genital area, such as donovanosis and chronic herpes simplex, as in cases of exuberant condylomata acuminata. The high prevalence (73%) of ulcerated lesions among invasive SCC reinforces the notion that ulceration indicates, in most cases, tumor invasion. In the Spanish study mentioned above, a greater variability in the clinical morphology of invasive SCC was observed: ulceration (53%), papule (33%), nodule (7%) and plaque (7%).<sup>13</sup> The description of skin lesions sometimes poses difficulties, especially among physicians who are not dermatologists. Both in that work conducted at a urology hospital and in our study, the accuracy of the description of dermatologic lesions is subject to criticism, because they were not always made by dermatologists and because the data were collected from medical records.

In relation to the number of lesions (similar to that found in the literature) among invasive SCC cases, single lesions prevailed. They were observed in 85.7% of the 21 invasive SCC cases in which this information was available, and there were up to 5 lesions in the remaining ones.<sup>13</sup> Among the 6 cases of SCC *in situ* with number of lesions reported, half showed a single lesion, two had less than 5 lesions and one had more than 10 lesions.

As regards the size of the lesions, invasive SCC lesions tended to be greater than SCC *in situ*. Of the

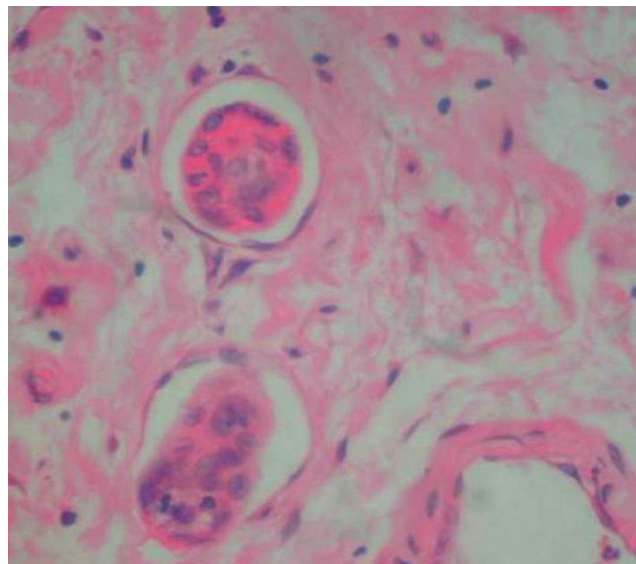


FIGURE 8: Invasive squamous cell carcinoma: lymphatic emboli

five cases of SCC *in situ* whose size was known, all measured less than 2 cm and even a lesion as small as 0.5 cm was detected. Of the 22 invasive SCC whose size was known, 77.2% measured more than 2 cm and 13.6% exceeded 5 cm; however, lesions smaller than 2 cm were observed in 22.7% of the cases.

The genital area is an area rich in nerve endings and it is not surprising that most patients presented pruritus and/or pain. In addition, a lesion of lichen sclerosus, occasionally combined with SCC, can be pruriginous. Pain was more frequent among patients with invasive SCC. Many patients self-medicate. Also, many doctors who offer primary care prescribe the use of antifungal agents, antibiotics and/or corticosteroids, assuming that this is one of the dermatoses that make differential diagnosis with neoplasm of the penis.

In this study, 50% of the cases of invasive SCC had inguinal lymphadenopathy at diagnosis; however, only 7 patients underwent lymphadenectomy, which revealed metastases in 38.4% of them. It should be noted that none of the patients with SCC *in situ* had palpable inguinal lymph nodes. Presence of inguinal lymphadenopathy may correspond to reactive inflammatory adenopathy or regional metastasis.<sup>2</sup> In relation to the degree of histological differentiation of invasive SCC, the results of this study are consistent with the literature investigated: 80.8% were well differentiated and 19.2% were moderately differentiated.<sup>6,10,22</sup> Only two patients had vascular invasion. Lymph node involvement, poorly differentiated tumors and vascular invasion are considered indicators of poor prognosis in penile cancer.<sup>10,23</sup>

Among the 23 cases of invasive SCC in which it was possible to determine staging according to the cri-



teria established by the *Union Internacional Contre le Cancer/ 1997 - TNM* (3), most (56.5%) were in stage I and the remaining cases were distributed in stage II (13%), III (17.4%) and IV (13%). The cases that evolved to death belonged to stage III (1 case) and IV (2 cases).

In this study, sixteen patients underwent partial or total amputation of the penis. The rarity of penile SCC and the lack of protocols implemented in the period covered by the study explain the heterogeneity of the adjuvant regimens adopted. Even today, the rarity of the disease limits the possibility of conducting randomized studies comparing different therapeutic approaches.<sup>4</sup> Treatment of SCC *in situ* of the penis can be through medication or surgery, depending on extent, location in the genitals and convenience of the patient and physician. Treatment of invasive SCC, however, is always surgical (circumcision, partial or total amputation of the organ) and, depending on the stage, may be associated with lymphadenectomy, radiotherapy and/or chemotherapy.<sup>24</sup> In any case, treatment of invasive SCC is aggressive and can leave physical and psychological sequelae.

The European Association of Urology established in 2009 the following recommendations for diagnosis and staging of penile cancer: physical examination and cytologic and/or histopathological examination of the primary tumor; physical examination of the inguinal regions: in case of impalpable lymph nodes, sentinel lymph node biopsy and in case the latter is not available, cytology of material aspirated with fine-needle guided by ultrasound; in case of palpable lymph nodes, cytology of material aspirated with fine-needle; in patients with metastasis to inguinal lymph nodes, pelvic CT and PET-CT scan; to investigate distant metastases, when PET-CT scan is not possible, abdominal CT and chest radiography; in symptomatic patients with distant metastasis, bone scan.<sup>23</sup> It is important to note that when the lesion is poorly defined or when different morphologies coexist, it is recommended to perform more than one biopsy. In case of ulcers, it is important to include the border of the lesion. In suspected cases of verrucous carcinoma, biopsy should be deep enough to go through the stratum corneum and include the entire thickness of the epidermis and dermis.

Academic controversies, such as the profusion of nomenclatures and conceptual inaccuracies about cancer of the penis, have repercussions on health

care. The need for protocols to guide the multiprofessional and interdisciplinary approach to cancer of the penis, from diagnosis to treatment and follow up, is evident. Initiatives such as those adopted by the Brazilian Society of Urology and the Ministry of Health, aimed at disseminating information about cancer of the penis to the general population, are fundamental to demystify the disease and overcome men's reluctance to seek medical attention for skin lesions in the genital area. These initiatives promote the early diagnosis of penile SCC, improving prognosis and patient's quality of life and reducing health care costs and economic and psychological damage resulting from work leave. On the other hand, they imply increased demand for medical care and the need for qualified health professionals.

This work highlights the importance of careful dermatological examination of the genital region as a step toward early detection of cancer of the penis and its precursor lesions. Implementation of multidisciplinary programs involving dermatologists, urologists, physicians of the family health care program, pathologists, psychologists and social workers, among others, would certainly contribute to that goal, providing a full service of better quality to these men.

## CONCLUSION

SCC of the penis is rare and well-differentiated invasive SCC predominated over SCC *in situ*. Invasive SCC was more frequent in patients over 60 years old, while SCC *in situ* was distributed more evenly among adults of all ages. Among the cases of invasive SCC, single lesions larger than 2 cm usually ulcerated or ulcero-vegetating prevailed. Among SCC *in situ*, lesions smaller than 2 cm and with various aspects simulating inflammatory diseases prevailed. Pruritus and/or pain were frequent. Lichen sclerosus and HPV infection coexisted in a small number of cases of SCC of the penis. Treatment of invasive SCC is aggressive: although most cases were in stage I, indication of the need for partial amputation could already be observed. Careful dermatological examination of the genital area favors early diagnosis of penile cancer as well as of possible precursor lesions. Dissemination of this information and implementation of protocols for diagnosis, treatment and follow up of patients with cancer of the penis can positively affect many men's quality of life. □

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