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Penile squamous cell carcinoma – a retrospective study

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THESIS OUTLINE

This Master thesis in Medicine consists of an Original Scientific Article, written between September 2019 and May 2020, with bibliographic research until May 2020.

RESUMO

Introdução

O cancro do pénis é considerado ser um tumor raro, cuja variante mais frequente consiste no carcinoma de espinho-celular. Novos avanços foram realizados nesta temática, tanto na abordagem diagnóstica e clínica como no seu tratamento. O objetivo do trabalho consistiu na avaliação da clínica, comorbilidades, fatores de risco, técnicas imagiológicas, estadiamento, tratamento e sobrevivência destes doentes.

Métodos

Foi realizado um estudo retrospetivo a doentes diagnosticados com carcinoma de espinho-celular (CEC) do pénis no Serviço de Urologia e Transplantação Renal do Centro Hospitalar Universitário de Coimbra, Portugal, entre 1 de janeiro de 2006 e 31 de dezembro de 2017. Estudaram-se múltiplas características, nomeadamente comorbilidades, fatores de risco, sintomatologia inicial, ferramentas diagnósticas, tratamento e sobrevivência da doença. Sendo que, a frequência e etiologia deste tumor pode variar consoante a idade, os doentes foram agrupados consoante a idade.

Resultados

Foram incluídos um total de 54 doentes com CEC do pénis. A grande maioria dos doentes apresentava, ao diagnóstico inicial, fimose (46.3%). A prevalência de HPV (18.5%) foi inferior à expectável. O sinal inicial mais comum consistiu na presença de lesões macroscópicas (66.7%), sendo seguido pela obstrução do meato uretral (26.7%). Referente à utilização de técnicas imagiológicas, 66.7% dos pacientes realizaram TAC, enquanto 25.9% realizaram ecografia. A localização da lesão tumoral revelou ser variável. A maioria dos tumores foram classificados como T3 (42.0%), relativamente ao tumor primário, e N1 (66.7%), no que diz respeito às adenopatias.

Todos os doentes foram submetidos a cirurgia, em que 67.2% realizaram amputação parcial e 16.7% realizaram circuncisão radical. Apenas 5.6% realizaram amputação total. Complementarmente, 42.6% realizaram linfadenectomia inguinal radical e 9.3% realizaram linfadenectomia inguinal e pélvica. Quanto à necessidade de uma cirurgia durante o seguimento, 24.1% foram submetidos a amputação parcial. Em relação à realização de quimioterapia, foram utilizados diversos esquemas. Destas, 7.4% doentes realizaram 5 ciclos

de TIP. No que diz respeito à causa da morte, a mais frequente correspondeu a causa desconhecida (42.6%), sendo seguida pela doença cardiovascular (14.3%).

Conclusão

Os nossos resultados permitiram a obtenção de novas informações, que poderão ser aplicadas na prática clínica, tanto no que diz respeito à investigação como tratamento e prognóstico. Apesar de ser um carcinoma pouco frequente, este tem associado uma morbi-mortalidade importante.

Palavras-Chave:

Cancro do Pénis, Carcinoma Espinho-celular, Sinais Iniciais, Diagnóstico, Tratamento, Sobrevivência

ABBREVIATIONS

5-FU: 5- Fluorouracil

AIDS: Acquired Immunodeficiency Syndrome

BMI: body mass index

CT: computed tomography

HIV: human immunodeficiency virus

HPV: human papillomavirus

hrHPV: high-risk human papillomavirus

MR: Magnetic resonance imaging

MVAC: methotrexate, vinblastine sulfate, doxorubicin hydrochloride, and cisplatin

PET-CT: Positron emission tomography–computed tomography

SCC: Squamous Cell Carcinoma

TIP: paclitaxel, ifosfamide. cisplatin

ABSTRACT

Introduction

Penile cancer is a rare malignant disease in which squamous cell carcinoma (SSC) account for its vast majority. In recent years there has been advances in its management and overall interventions. Therefore, we sought to describe clinical features, comorbidities, risk factors, imaging techniques, staging, treatment and overall survival.

Methods

We conducted a retrospective study of patients admitted to the Urology and Renal Transplantation Department of Coimbra University and Hospital Center, Portugal, between 1st January of 2006 and 31st of December 2017, diagnosed with penile squamous cell carcinoma of penis. We collected multiple variables comprising comorbidities, risk factors, initial signs, diagnostic tools, treatment approach and survival. Since the frequency and etiology of SCC may vary according to age, patients were compared by age groups for initial clinical signs, treatment, and overall survival.

Results

A total of 54 patients with SCC were included. A vast majority of our patients had phimosis present (46.3%), although the prevalence of HPV (18.5%) was lower than expected. The most common initial sign determined was the presence of macroscopic lesions (66.7%), followed by meatus obstruction (26.7%). Regarding radiological imaging, 66.7% of patients performed CT, while 25.9% performed ultrasonography. At the moment of diagnosis, tumor lesion location was variable. The most common location was the glans (88.9%) and the least common was the entire penis affected (1.7%). Most of patients' tumor were classified as pT3 (42.0%), concerning primary tumor, and N1 (66.7%), concerning regional lymph nodes. The most common metastasis site revealed to be ganglia metastasis (33.3%).

All patients were submitted to surgery, where 67.2% underwent partial amputation, and 16.7% underwent wide circumcision. Only 5.6% underwent total amputation. Consequently, 42.6% performed radical inguinal lymphadenectomy and 9.3% performed inguinal and pelvic lymphadenectomy. As for the need of follow-up surgery, 24.1% carried out one, being partial amputation the most recurrent. In terms of chemotherapy, there were several types of

regiments, where 7.4% underwent 5 cycles of TIP. The death cause, it was unknown (42.6%), followed by cardiovascular disease (14.3%).

Conclusion

Our results have implications for clinical practice concerning the investigation, treatment, and prognosis of patients with SCC. Besides being relatively infrequent, SCC entails a considerable morbidity and mortality burden. Therefore, it is important to further investigate new approaches to SCC management, to obtain a better quality of life and reduce its social impact.

Keywords:

Penile Cancer, Squamous Cell Carcinoma, Initial Signs, Diagnosis, Treatment, Survival

INTRODUCTION

Penile cancer is a rare malignant disease in Europe and North America, with an overall incidence of 1 case per 100.000 men. In Europe, about 4.000 cases are diagnosed every year, which comprises less than 0,5% of all cancers(1). However, the incidence is higher in the developing countries, such as Africa, Asia and South Africa, with 2 to4 cases per 100.000 men.(2) This diagnosis increases with age, mainly appearing between 50 to 70 years. The most common histology is the squamous cell carcinoma (SCC), representing over 95% of penile tumors. Around 80% occur on the glans or prepuce.

The etiology is multifactorial and there have been several studies that identified prognostic factors and risk factors, such as phimosis, smoking, chronic inflammatory states, number of sexual partners and human papillomavirus (HPV) infection (3). A protective factor could be circumcision during childhood. However, the exact mechanism for penile cancer development is still unknown (1).

Penile cancer is common in regions with high HPV, which explains the geographic variation in its incidence. However, no data links penile cancer to HIV (4). About one-third of cases could be attributed to HPV-related carcinogenesis. Studies have suggested a functional role of high-risk (hr) HPV for a subset of penile SCC (5). Penile carcinomas with basaloid features and those of the warty subtype displayed the highest hr-HPV prevalence (up to 100%) (2,6,7). On the other hand, keratinizing or not-otherwise-specified penile SCCs, which represent the most common histotypes in the developed countries, generally showed a lower HPV prevalence (30%-40%) (1).

Social stigma among patients have created an environment where most patients with penile cancer present with metastatic disease.(8,9) This tumor has a metastatic progression that follows a predictable and stepwise pattern of invasion from the primary tumor to inguinal lymph nodes before spreading to pelvic nodes and reaching systemic dissemination. Despite being potentially curative in half of patients, the treatment is associated with a considerable impact on patients' physical and psychological wellbeing.(8)

The objective of this study is to evaluate the incidence, risk factors, symptoms, clinical and imagiological features, and mortality of squamous cell carcinoma in Coimbra University and Hospital Center from 2006 to 2017.

METHODS

Study population

We conducted a retrospective study of consecutive patients admitted to the Urology and Renal Transplantation Department of Coimbra University and Hospital Center, Portugal, between 1st January of 2006 and 31st of December 2017, diagnosed with penile squamous cell carcinoma of penis. Out of the 58 patients selected, only 4 were excluded since their information was inconclusive.

Patients' clinical files were carefully reviewed, including etiological factors, presence of phimosis, HIV, HPV, and circumcision, pre-neoplastic lesions, initial clinical signs and symptoms, radiological imaging, the tumor localization, stage of diagnosis, treatment, and mortality.

The diagnosis of SCCP was documented based on clinical presentation and pathology. There was also assessed the presence of metastases and lymphatic invasion by ultrassonography, computed tomography scan (CT), magnetic resonance (MR), positron emission tomography-computed tomography (PET-CT) and lymphoscintigraphy.

All treatment modalities and duration were recorded. Since the frequency and etiology of SCC may vary according to age, patients were compared by age groups for initial clinical symptoms, and treatment. Patients were divided into 2 categories: group 1 (<70 years) and group 2 (≥70 years).

The study followed the Helsinki Declaration. Consent was not collected as it was a retrospective study. All patient information was kept anonymous, respecting all ethic and deontological aspects

Statistical Methods

Continuous data were summarized as mean ± standard deviation or median with interquartile range. Categorical data were presented as frequency and percent. Categorical data were analyzed by using Pearson chi-square or likelihood ratio test statistics. Independent sample t-test was used to compare groups for continuous variables.

RESULTS

Baseline characteristics of population

A total of 55 patients were diagnosed with penile squamous carcinoma between 1st January 2006 and 31st December 2017. A total of 54 patients were enrolled ([35-90] years, OR: 14.0), and one patient was excluded, as its data was inconclusive.

Table 1 Baseline characteristics and clinical information of study population

Characteristics and Comorbidities

Patients, n	54
Age, years (mean ± SD)	69±10
Smoking (%)	3.7
Arterial hypertension (%)	35.2
Dyslipidemia (%)	22.2
Diabetes mellitus type 2 (%)	22.2
BMI > 25 kg/m^2 (%)	16.7
Stroke (%)	5.6
Prostate adenocarcinoma (%)	5.6
Dysrhythmias (%)	14.8
Neurologic disorders (%)	7.4
Alcoholism (%)	11.1
Hyperuricemia (%)	11.1

BMI denotes body mass index.

Risk Factors and Pre-neoplasic Lesions

HIV (%)	3.7
HPV (%)	18.5
Phimosis (%)	46.3
Circumcision (%)	3.7
Queyrat Erythroplasia (%)	3.7
Balanitis Xerotica Obliterans (%)	11.1
Bowen Disease (%)	1.9

Clinical and Imaging Features

On most patients, there was no information from the time of the onset of symptoms until diagnosis.

The most common sign was macroscopic lesion (N=21 cases; 38.9%), followed by the meatus obstruction (N=5, 9.3%), urinary tract infection(N=2, 3.7%) and the least common was pruritus (N=1, 1.9%) (Table II and Figure 1).

Table II. Initial signs and symptoms by age group

		Age Group					
		< 70 years			>70 years		
		N	%	p	**N**	%	p
Initial signs	Macroscopic Lesion	**10**	66,7%	0,12	**11**	76,5%	0,11
	Meatus Obstruction	**4**	26,7%	0,11	**1**	7.1%	0,07
	Urinary Tract Infection	**1**	6,7%	0,06	**1**	7.1%	0,07
	Pruritus	**0**	0,0%	.	**1**	7.1%	0,07

Differences between each initial sign and both age groups.

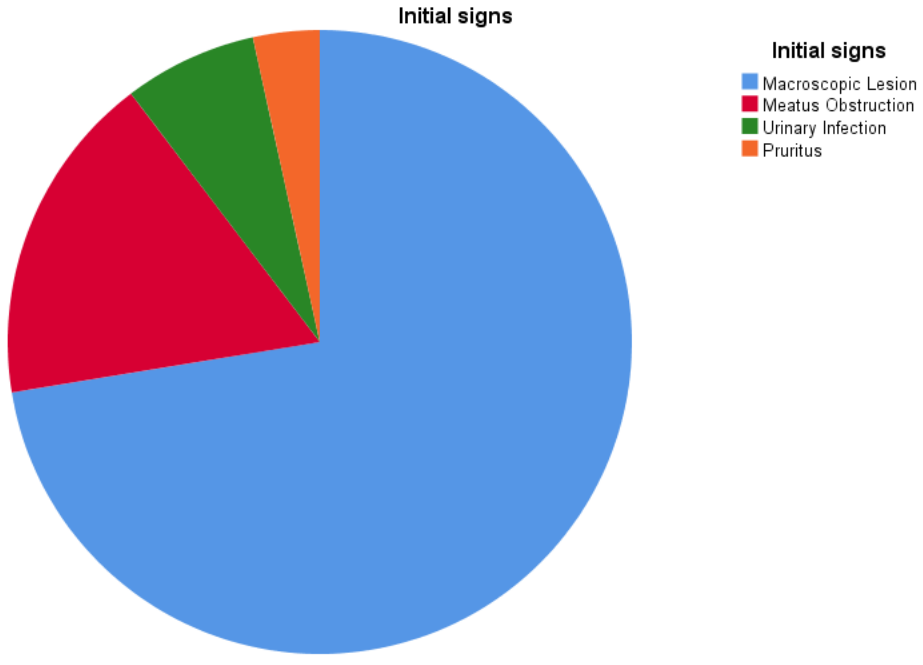

Figure 1. Initial signs of SCC

Radiological imaging was performed, specifically by CT (N=36, 66.7%), ultrasonography (N=14, 25.9%), MRI (N=9, 16.7%), PET-CT (N=17, 31.5%) and by lymphoscintigraphy (N=11, 20.4%).

Tumor Characterization

At the moment of the diagnosis, tumor lesion location was variable: glans (N=48, 88.9%), prepuce (N=16, 29.6%), retroglandular sulcus (N=8, 14.8%), penile shaft (N=6, 11.1%), penile base (N=1, 1.9%), and involving the entire penis (N=1, 1.9%).

There were more than one location in some patients: glans and prepuce (22.2%, N: 12), glans and retroglandular sulcus (13.0%, N: 7), glans and penile shaft (7.4%, N: 4), prepuce and penile shaft (1.9%, N: 1) and glans, prepuce and sulcus (1.7%, N: 1) (Table III).

Table III. Tumor location

	N	%	Cumulative %
Glans	**24**	44,4	44,4
Glans + Prepuce	**12**	22,2	66,6
Glans + Retroglandular sulcus	**7**	13,0	79,6
Glans + Shaft	**4**	7,4	87,0
Prepuce	**2**	3,7	90,7
Shaft	**2**	3,7	94,4
Base	**1**	1,9	96,3
Prepuce + Shaft	**1**	1,9	98,1
Glans + Prepuce + Retroglandular sulcus	**1**	1,9	100
Total	**54**	100	

Single and multiple tumor locations. N denotes number; %, percentage; Cumulative %, cumulative percentage

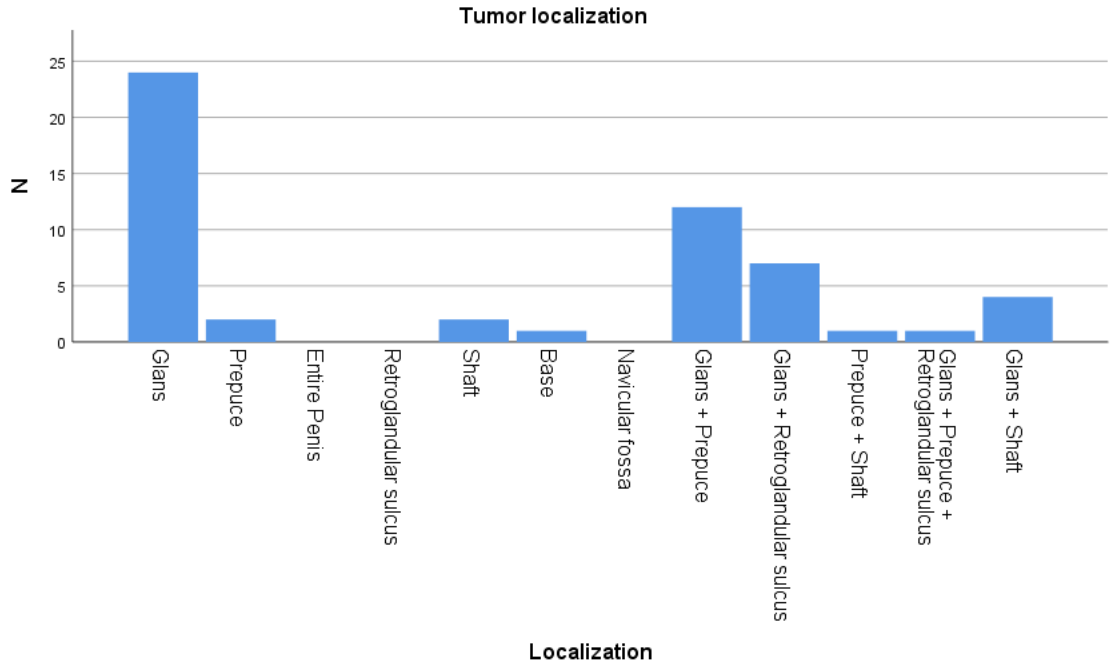

Figure 2. Tumor localization

Applying the TNM classification, in terms of size of the tumor and any regional spread, most patients were pT3 (N=21, 42%), tumor invading corpora cavernosum with or without urethral invasion, followed by pT1 (N=17, 34%), tumor invades subepithelial connective tissue, dermis or lamina propria, as in Table IV.

Table IV. Classification T

		N	%
T	is	**1**	2,0%
	1	**17**	34,0%
	1_a	**17**	31,5%
	1_b	**0**	0,0%
	2	**11**	22,0%
	3	**21**	42,0%
	x	**0**	0,0%

Primary tumor classification. Is denotes “in situ”; x, primary tumor cannot be assessed, N, number of cases; %, percentage.

Concerning other characteristics, it was realized that they had: corpus spongiosum invasion (N=27, 50.0%), urethral invasion (N=21, 38.9%), corpus cavernosum invasion (N=19, 35.2%),

vascular invasion (N=12, 22.2%), lymphatic invasion (N=11, 20,4%) and perineural invasion (N=4; 7.4%).

Comparatively, in terms of lymph nodes invasion: N1 (N=31, 66.7%), not more than two unilateral inguinal metastases and no extranodal extension; N2 (N=12, 25.0%), at least three unilateral inguinal metastases or bilateral metastasis; N3 (N=4, 8,3%). None of the results were inconclusive (Table V).

Table V. Classification N

		N	%
N	1	32	66,7%
	2	12	25,0%
	3	4	8,3%
	x	0	0,0%

Regional lymph nodes classification. X denotes lymph node metastasis cannot be establish; N, number of cases, %, percentage.

In terms of metastatic disease, on a total of 25 (46.3%) patients, it was realized: retroperitoneal ganglia metastases (N=18, 33.3%), bone metastases (N=6, 11.1%), pulmonary metastases (N=5, 9.3%), skin metastases (N=2, 3.7%) and hepatic metastases (N=1, 1.9%).

Treatment

All patients were submitted to surgery: 39 (67.2%) patients underwent partial amputation, 9 (16.7%) underwent wide circumcision, 3 (5.6%) underwent local excision, 3 (5.6%) underwent total amputation, 1 (1.9%) underwent urethrectomy and 1 (1.9%) underwent emasculation.

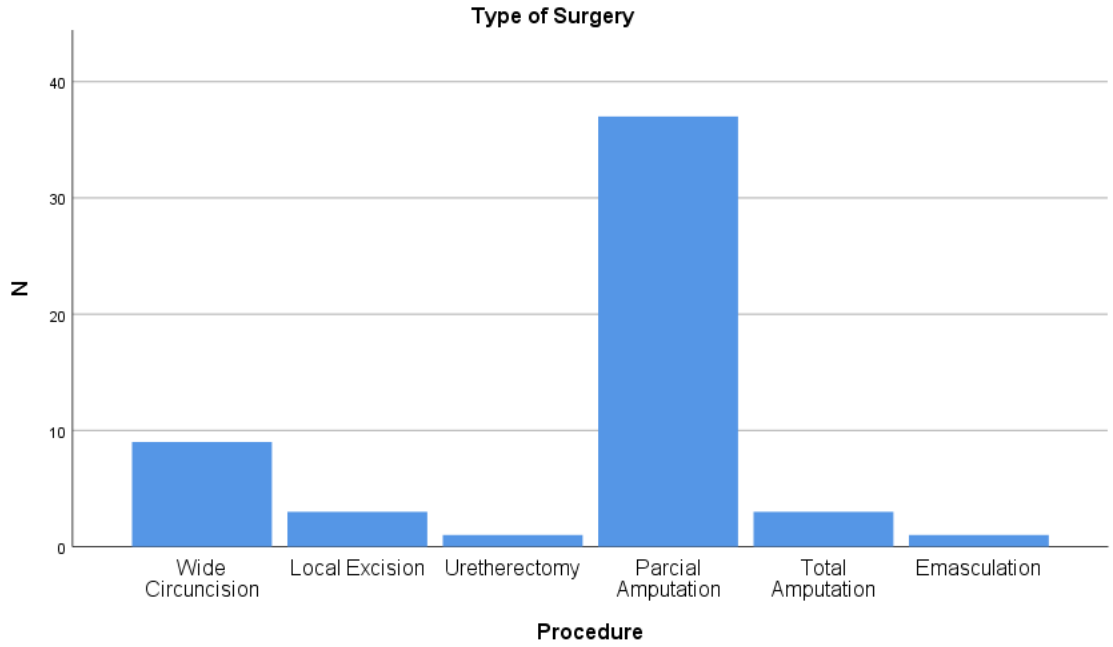

Figure 3. Types of surgery. N denotes for number of cases.

Comparing the procedures between both age groups, there were no statistical differences.

Table VI. Types of surgery by age group

		Age Group			
		< 70 years		≥70 years	
		N	%	N	%
Procedures	Partial Amputation	16	64,0%	21	72,4%
	Wide Circumcision	4	16,0%	5	17,2%
	Local Excision	2	8,0%	1	3,4%
	Ureterectomy	1	4,0%	0	0,0%
	Total Amputation	1	4,0%	2	6,9%
	Emasculation	1	4,0%	0	0,0%

Different procedures by age group. N denotes number; %, percentage.

Regarding lymphadenectomy, we only have data from 28 (51.9%) patients. From this total: 23 (42.6%) underwent inguinal lymphadenectomy, 5 (9.3%) underwent inguinal lymphadenectomy plus pelvic lymphadenectomy and 5 (9.3%) were unresectable. Also, there were 9 (16,7%) sentinel lymph node biopsies.

Table VII. Types of lymphadenectomy

		N	%
Lymphadenectomy	Total	28	51.9%
	Missing	26	48,1%
	Radical Inguinal Lymphadenectomy	23	42,6%
	Inguinal + Pelvic lymphadenectomy	5	9.3%
	Unresectable	5	9.3%

Management of regional lymph nodes. N denotes number; %, percentage.

Follow-up surgery

There was a total of 16 (29.6%) tumor relapse. While 13 (24.1%) underwent a second procedure, 2 (3.7%) died before it could be done.

On a total of 13 (24.1%) cases, there was a need of a second surgery: partial amputation (13%, N: 7), total amputation (9.3%, N: 5) and emasculation (1.9%, N: 1).

Table VIII. Types of second surgery

		N	%	Cumulative %
Surgery	Parcial Amputation	**7**	13,0	53,8
	Total Amputation	**5**	9,3	92,3
	Emasculation	**1**	1,9	100,0
	Total	**13**	24,1	

Number of follow-up surgeries. N denotes number; %, percentage; Cumulative %, cumulative percentage.

The mean time between both surgeries was about 6,5 ± 9 months ([1-35] months), varying with each surgery performed (Table IX).

Table IX. Time between both surgeries

		Time between 1st and 2nd surgery (months)							Total
		1	2	4	6	7	8	35	
Procedure	Parcial amputation	1	2	0	1	1	1	1	**7**
	Total amputation	0	3	1	0	1	0	0	**5**
	Emasculation	0	0	0	1	0	0	0	**1**
Total		1	5	1	2	2	1	1	**13**

Time between first and second surgeries.1st denotes first; 2nd, second.

Chemotherapy

In terms of chemotherapy, there were diverse regiments: 4 cycles of TIP (N=4, 7.4%), 3 cycles of TIP (N=1, 1.9%), 5 cycles of MVAC (N=1, 1.9%), 2 cycles of 5-FU (N=3, 5.6%) and cisplatin (N=1, 1.9%). There were 3 (5,6%) patients who were not suitable for chemotherapy, 2 (3.7%) for intolerance and 1 (1.9%) for its worsening general condition.

Some patients did more than one type of chemotherapy: 2 cycles of 5-FU and cisplatin (N=1, 1.9%) and TIP (4 cycles) and 5-FU (N=1, 1.9%).

Table X. Types of Chemotherapy

		N	%	Cumulative %
Regiments	TIP regiment (4 cycles)	**3**	5,6	37,5
	TIP regiment (3 cycles)	**1**	1,9	50,0
	MVAC regiment (5 cycles)	**1**	1,9	62,5
	5-FU regiment (2 cycles)	**1**	1,9	75,0
	5-FU + Cisplatin	**1**	1,9	87,5
	TIP (4 cycles) + 5-FU	**1**	1,9	100,0
	Total	**8**	14,8	

Different regiments of chemotherapy, and its prevalence. TIP denotes paclitaxel, ifosfamide and cisplatin; MVAC, methotrexate, vinblastine sulfate, doxorubicin hydrochloride, and cisplatin; 5-FU, 5-fluorouracil.

Survival

At the end of study, 31 patients (57.4%) had died from different causes: cardiovascular disease (N=4, 7.4%), non-related neoplastic etiology (N=3, 5.6%), febrile neutropenia (N=1, 1.9%), respiratory failure (N=2, 3.7%) and unknown cause (N=23, 42.6%). (Figure 4).

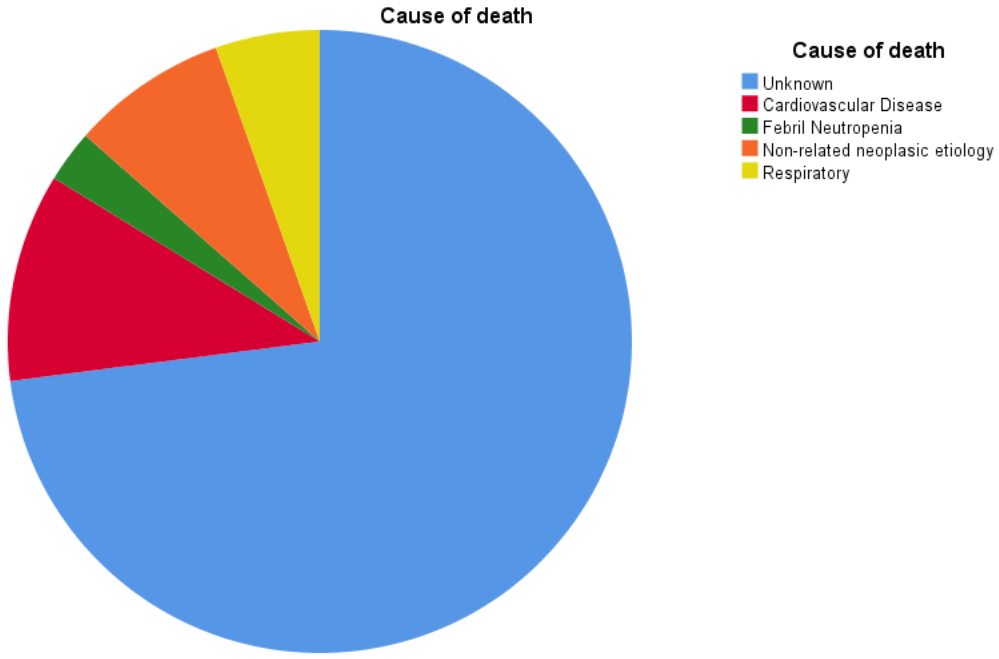

Figure 4. Cause of death

We also compared the cause of death between both age groups (Table XI).

Table XI. Cause of death between age groups.

		Age Group			
		< 70 years		≥70 years	
		N	%	N	%
Cause of death	Unknown	12	75,0%	15	71,4%
	Cardiovascular disease	1	6,3%	3	14,3%
	Febrile neutropenia	1	6,3%	0	0,0%
	Non-related neoplasic etiology	1	6,3%	2	9,5%
	Respiratory failure	1	6,3%	1	4,8%

Relation between the different causes of death between both age groups.

DISCUSSION

In this study, data was obtained from 54 patients that were admitted to the Urology and Renal Transplantation Department of Coimbra University and Hospital Centre, and evaluated risk and epidemiological factors, initial clinical signs and symptoms, imagiological findings, tumor characterization, different types of treatment and survival.

In Europe and North America, penile cancer has low incidence that increases with age, with a peak in the sixth decade, but also occurring in younger men. In our population, the mean age of affected man is around 69 years, which presents in that range (4).

The etiology of penile SCC appears multifactorial, with a history of smoking, phimosis, poor hygiene, and lack of circumcision during childhood commonly associated with this tumor (1,10,11). EAU Guidelines shows that one-third of cases can be attributed to HPV-related carcinogenesis. However, our study found that only 18.5% of our patients were HPV positive, which is slightly lower than the correlation known between the presence of this virus and the development of this tumor. The fact that the center region of Portugal has a lower HPV prevalence might, however, explain these findings (12). Concerning phimosis (46.3%), its strong association with SCC carcinogenesis is likely related to a chronic inflammatory state and underlying balanitis (4,13). Circumcision during childhood significantly reduces the prevalence of the condition (14). Our results showed a low prevalence of circumcised patients, corroborating the present data. Cigarette smoking has demonstrated a 4.5% increased risk of SCC (13), however it was only present in 3.7% of patients. On the other hand, several studies did not show any link between penile cancer and HIV. Our study also did not show any evidence supporting a relation between HIV and the SCC, due to the percentage of patients' HIV positive being non-significant (3.7%, p=0.363) (4,15).

Finally, we also analyzed the presence of pre-neoplastic lesions, that showed a farewell number of patients presented with Balanitis Xerotic Obliterans (11.1%). Both Queyrat Erythroplasia and Bowens Disease were not very common in our population, despite being premalignant lesions associated with SCC of the penis (4,16).

Unfortunately, there was no information on the onset of symptoms, nor the time between the appearance of the first symptom and the moment of the diagnose. It would be an important factor to investigate since it is known to be a late diagnose. Researchers seem to believe that the delay in seeking medical help, in these cases, is due to social stigma (17).

Initial symptoms were analyzed according to its frequency between the two age groups, under and above 70 years old. When comparing both groups, there was not a significant difference between them. The most common signal was the presence of macroscopic lesion, 38.9%.

These results were expected, since several studies demonstrated that the most common finding is usually an area of induration next to an ulcer or a warty exophytic growth(16). The only noticeable difference was in the number of patients with meatus obstruction, being more common in the first group.

Due to a wide variety of presentations, it is important to do, to a certain extent, some complementary exams, being the radiological imaging one of greater importance. Therefore, it is necessary to understand which exams were more frequently done, which, in this case, was CT (N: 36, 66.7%). The second most requested exam was ultrasonography (N: 14, 25.9%). PET-CT (N: 17, 31.5%) was also performed to confirm metastases in palpable inguinal lymph nodes, even though its limitations are characterized by its poor diagnostic accuracy in patients with impalpable nodes (4,8,18). Magnetic Resonance (MR) was done on a total of 16.7% of patients, with the purpose of characterizing the functional anatomy of inguinal lymph nodes (8). Finally, lymphoscintigraphy was done in 20.4% of patients, demonstrating nuclear tracer present in sentinel lymph node (8).

SCC usually originates from inner prepuce or the glans (4). With continued neglect, the lesion progresses until a purulent discharge is seen from beneath a phimotic, nonretractile prepuce. Finally, the disease extends along the penile shaft and involves the corpora cavernosa(16). The tumor location was analyzed in our patients: a vast majority had the tumor localized in the glans (88.9%), followed by the prepuce (29.6%). Only a minority of patients had the entire penis affected (1.7%). Most patients had more than one location affected: glans and prepuce (22.2%) and glans and retroglandular sulcus (13.0%).

Classification of penile cancer uses TNM clinical and pathological classification, which is divided in T (primary tumor), N (regional lymph nodes) and M (distant metastasis). The classification is important, allowing to choose the most adequate treatment modality.(4,19) Regarding the presentation of the primary tumor, most of our patients were T3 (42.0%), since invasion of corpus cavernosum ,with or without urethral invasion, was present. Secondly, some of our patients were T1a (31.5%), with invasion of the subepithelial connective tissue, dermis, or lamina propria. There were also T2 patients (22.0%) with invasion of corpus spongiosum, with or without urethral invasion. Finally, only one case of Tis (1.9%), carcinoma in situ, was present. Concerning the presence of regional lymph nodes, 66.7% were N1, had palpable mobile unilateral inguinal lymph node, 25.0% were N2, had palpable mobile multiple unilateral or bilateral inguinal lymph nodes, and only 8.3% were N3, had fixated inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral. Inguinal lymph nodes are the first site of metastasis followed by the pelvic nodes and, sometimes, the retroperitoneal nodes. Metastatic sites that are rarely involved include liver, lungs, and bones, usually between 1-10% (16). Our

results revealed that 33.3% had retroperitoneal ganglia metastasis, 11.1% had bone metastasis, 9.3% had pulmonary metastasis, 3.7% had skin metastasis and 1.9% had hepatic metastasis.

All patients were submitted to surgery. Treatment choice was based on tumor size, histology, stage and grade, location relative to the meatus, and patient preference. It was guided by the following principle: as much organ preservation as possible and as much radicality as necessary (14). For small invasive lesions (Ta/T1a), a penis-preserving strategy is recommended. Circumcision should be performed as it may be sufficient for tumors confined to the prepuce (4). Poorly differentiated carcinomas or more deeply infiltrative tumors involving the cavernous bodies and the distal shaft are best managed by partial penectomy, excising 0.5–1 cm of normal tissue proximal to the margin of the tumor (16). Total penectomy with perineal urethrostomy should be performed for bulky T3 or T4 tumors involving the base of the penis (16). According to this, 16.7% of our patients underwent wide circumcision, 5.6% underwent local excision, 67.2% underwent partial amputation and 5.6% underwent total amputation. Comparing the procedures between both age groups, there were no statistical differences.

Radical inguinal lymphadenectomy is indicated in patients with surgical removal and histologic confirmation if, by intraoperative frozen-section analysis, the results are positive. (14). If at least two lymph nodes are positive on the same side, it is necessary to perform additional ipsilateral pelvic lymphadenectomy. Although this tumor is characterized by bilateral inguinal lymphatic spread, metastasis from inguinal to pelvic lymph nodes is strictly unilateral. Consequently, it is sufficient to perform unilateral radical pelvic lymph node dissection in these cases (14). Finally, it is important to denote that locally advanced tumor stages can be treated with palliative intention, either by radical surgery or radiation therapy (14). During our study, we were only able to gather data from 51.9% of patients about their lymphadenectomy realization. For the remaining patients (49.1%) the data was missing. From this group, 42.6% underwent radical inguinal lymphadenectomy and 9.3% underwent radical inguinal lymphadenectomy and pelvic lymphadenectomy. Unfortunately, 9.3% of our patients were unresectable. This type of dissection is associated with considerable morbidity in the form of lymphedema, lymphoceles and complications of wound healing. Therefore, it should be evaluated on a future study.

It was also investigated the need for a second surgery, being that a total of 24.1% of our patients underwent one. Among them, 13.0% underwent partial amputation, 9.3% underwent total amputation and 1.9% underwent emasculation. Some studies defend that a local

recurrence as such is not a threat to the life of the patient, as it is curable by renewed treatment. Consequently, the strategy will conceive in trying to narrow the margins, ensuring optimum quality of life is maintained (14,20).

In terms of chemotherapy, there were diverse regiments applied in our study. There were 5 different types of chemotherapy regiment, from TIP, MVAC, 5-FU to cisplatin regiment. A total of 7.4% of our patients received 4 cycles of TIP, 1.9% received 3 cycles of TIP, 1.9% received 5 cycles of MVAC, 5.6% received 2 cycles of 5-FU and 1.9% received a cycle of cisplatin. Also, there were 5,6% patients who were not suitable for chemotherapy: 2 (3.7%) were intolerant to the procedure and 1(1.9%) had a poor health condition. Several chemotherapeutic agents are effective. In Europe, the most common used is the combination of paclitaxel, cisplatin and 5-fluoruracil, while in the United States the TIP regiment is preferred.(14,19,21)

As for overall survival, it was found that 57.4% of our patients had died from different causes, namely 7.4% died from cardiovascular disease, 5.6% died from non-related neoplasic etiology, 1.9% died from febrile neutropenia and 3.7% died from respiratory failure. The cause of death was unknown in 42.6% of patients. Correlating the cause of death to different age groups, we found that in the first group (<70 years) the most common cause was unknown, and there were no differences in the remaining patients. In the second group the most common cause was also unknown. However, it was followed by cardiovascular disease (14.3%) and non-related neoplasic etiology (9.5%).

Strengths of the study include its considerably sample, whereas it is a rare disease, and the involvement of patients from only one country. This allowed us to better understand the clinical and etiological features and outcome of the. Also, the selection of our patients is not biased. Out of the 58 patients selected, only 4 were not included in the study since their information was inconclusive. SCC was confirmed in all cases with current technology, and established consensus criteria.

Nevertheless, our study has several limitations that warrant comment. Firstly, our analysis is limited by the nature of the retrospective study. Secondly, the sample could have been even larger, but given that the disease is rare, and the fact that the data came from a single hospital, it is justifiable. Besides, some patients did not have all the necessary information on their clinical files, and, for that reason, we did not collect all relevant variables. Being a central hospital, Coimbra's university Hospital takes charge of several SCC cases, most coming from all central region. In addition, we only took Portuguese population, mainly from the central region, so, even though it covers a board demographic area, our results may not apply to other populations.

Our results have implications for clinical practice concerning the investigation, treatment, and prognosis of patients with SCC. Soon, more studies should be performed, with a larger amount of population, in different hospitals, and with a prospective design. Raising awareness to the prevalence of SCC, even in its small numbers, within the medical community and reinforcing the need to not overlook the management of this disease is an important goal of this project. Although this is an observational study, its results will improve current knowledge about SCC.

In conclusion, we were able to enroll a number of patients which corroborated the results of previous studies regarding epidemiology, risk factors, clinical signs and symptoms, diagnostic tools, therapeutic approaches, and overall survival. Additionally, it is important to investigate further new treatments that are being studied, to obtain a better management of SCC and overall improve quality of life and reduce social impact. Besides being relatively infrequent, SCC entails a considerable morbidity and mortality burden and, therefore, an early and accurate diagnosis of these conditions will certainly help to prevent long-lasting deterioration of sexual disfunction and, in severe cases, death. Nevertheless, in order to clarify all these multicentered studies with different designs and a higher number of patients, will have to be made.

REFERENCES

1. Heideman DAM, Waterboer T, Pawlita M, Delis-Van Diemen P, Nindl I, Leijte JA, et al. Human papillomavirus-16 is the predominant type etiologically involved in penile squamous cell carcinoma. J Clin Oncol. 2007;25(29):4550–6.

2. Li K, Sun J, Wei X, Wu G, Wang F, Fan C, et al. Prognostic value of lymphovascular invasion in patients with squamous cell carcinoma of the penis following surgery. BMC Cancer. 2019;19(1):1–11.

3. Chipollini J, Chaing S, Azizi M, Kidd LC, Kim P, Spiess PE. Advances in understanding of penile carcinogenesis: The search for actionable targets. Int J Mol Sci. 2017;18(8).

4. Hakenberg OW, Compérat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. Eur Urol. 2015;67(1):142–50.

5. Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. Med Microbiol Immunol. 2004;193(1):35–44.

6. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WGV, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: Evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol. 2001;159(4):1211–8.

7. Hansen BT, Orumaa M, Lie AK, Brennhovd B, Nygård M. Trends in incidence, mortality and survival of penile squamous cell carcinoma in Norway 1956–2015. Int J Cancer. 2018;142(8):1586–93.

8. O'Brien JS, Perera M, Manning T, Bozin M, Cabarkapa S, Chen E, et al. Penile Cancer: Contemporary Lymph Node Management. J Urol [Internet]. 2017;197(6):1387–95. Available from: http://dx.doi.org/10.1016/j.juro.2017.01.059

9. Skeppner E, Andersson SO, Johansson JE, Windahl T. Initial symptoms and delay in patients with penile carcinoma. Scand J Urol Nephrol. 2012;46(5):319–25.

10. Dillner J, Von Krogh G, Horenblas S, Meijer CJLM. Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl. 2000;34(205):189–93.

11. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Penile cancer: Importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer. 2005;116(4):606–16.

12. Graça B, Reis J, Ilgenfritz R, Lopes SP, Serrão V. Consensos HPV Masculino. Soc Port Andrologia, Med Sex e Reprodução [Internet]. 2018;1–25. Available from: http://www.spandrologia.pt/pdfs/Consensos HPV Masculino SPA 2018.pdf

13. Diorio GJ, Leone AR, Spiess PE. Management of Penile Cancer. Urology [Internet]. 2016;96:15–21. Available from: http://dx.doi.org/10.1016/j.urology.2015.12.041

14. Hakenberg OW, Dräger DL, Erbersdobler A, Naumann CM, Jünemann KP, Protzel C. übersichtsarbeit: Diagnostik und therapie des Peniskarzinoms. Dtsch Arztebl Int. 2018;115(39):646–52.

15. Binny B, Tambe S, Nayak C. Metastatic squamous cell carcinoma of penis in an HIV-infected man presenting with cutaneous manifestations. Int J STD AIDS. 2019;30(6):613–6.

16. Kroon BK, Horenblas S, Nieweg OE. Contemporary management of penile squamous cell carcinoma. J Surg Oncol. 2005;89(1):43–50.

17. Attalla K, Paulucci DJ, Blum K, Anastos H, Moses KA, Badani KK, et al. Demographic and socioeconomic predictors of treatment delays, pathologic stage, and survival among patients with penile cancer: A report from the National Cancer Database. Urol Oncol Semin Orig Investig [Internet]. 2018;36(1):14.e17-14.e24. Available from: http://dx.doi.org/10.1016/j.urolonc.2017.09.014

18. Schlenker B, Scher B, Tiling R, Siegert S, Hungerhuber E, Gratzke C, et al. Detection of inguinal lymph node involvement in penile squamous cell carcinoma by 18F-fluorodeoxyglucose PET/CT: A prospective single-center study. Urol Oncol Semin Orig Investig [Internet]. 2012;30(1):55–9. Available from: http://dx.doi.org/10.1016/j.urolonc.2009.10.012

19. Mannweiler S, Sygulla S, Tsybrovskyy O, Razmara Y, Pummer K, Regauer S. Clear-Cell differentiation and lymphatic invasion, but not the revised TNM classification, predict lymph node metastases in pT1 penile cancer: A clinicopathologic study of 76 patients from a low incidence area. Urol Oncol Semin Orig Investig [Internet]. 2013;31(7):1378–85. Available from: http://dx.doi.org/10.1016/j.urolonc.2012.01.017

20. Leijte JAP, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence Patterns of Squamous Cell Carcinoma of the Penis: Recommendations for Follow-Up Based on a Two-Centre Analysis of 700 Patients. Eur Urol. 2008;54(1):161–9.

21. Bermejo C, Busby JE, Spiess PE, Heller L, Pagliaro LC, Pettaway CA. Neoadjuvant Chemotherapy Followed by Aggressive Surgical Consolidation for Metastatic Penile

Squamous Cell Carcinoma. J Urol. 2007;177(4):1335–8.