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Clinical relevance of HPV infection in penile cancer and penile intraepithelial neoplasia: a retrospective observational study

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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Clinical relevance of HPV infection in penile cancer and penile intraepithelial neoplasia: a retrospective observational study

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Faculdade de Medicina da Universidade do Porto, 23/03/2023

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“Recomeça...
Se puderes
Sem angústia
E sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro
Dá-os em liberdade.
Enquanto não alcances
Não descanses.
De nenhum fruto queiras só metade.”

Miguel Torga

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E por fim, dedico a minha dissertação aos meus avós porque ainda hoje me inspiram e motivam a ser uma pessoa melhor todos os dias.

Clinical relevance of HPV infection in penile cancer and penile intraepithelial neoplasia: a retrospective observational study

Key Words: Penile Cancer; Penile intraepithelial neoplasia, HPV infection

1446 words, 3 tables. 1 figure

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Ethics statement: This study was approved by the Centro Hospitalar Universitário de São João Ethics Committee. The patients in this manuscript have given written informed consent to publication of their case details.

Abstract:

Background: Penile cancer is rising in most European countries. Several risk factors have been identified, namely human papillomavirus (HPV) infection. However, the exact role of HPV in penile cancer carcinogenesis is still unknown. Clarifying the contribution of HPV in penile cancer is crucial as it may improve prevention and treatment strategies.

Objectives: The aim of this study is to describe the characteristics of patients with penile cancer and penile intraepithelial neoplasia (PeIN), evaluate the prevalence of HPV-DNA in tumor tissue, and identify differences between patients with and without HPV-DNA.

Methods: A retrospective observational study including patients with histological diagnosis of penile squamous cell carcinoma (SCC) or PeIN between 2012 and 2021 in a university hospital was carried out. HPV analysis was performed using CLART® Papillomavirus, for the detection and typing of 28 types of HPV in tissue specimens.

Results: A total of 25 patients were included. Most of the tumors identified were invasive SCC (n=11) and SCC *in situ* (PeIN 3) (n= 8). HPV-DNA was tested in all tissue specimens and was detected in 18 of them. High risk HPV DNA was identified in all positive HPV samples, except one. HPV types included in the nonavalent HPV vaccine were identified in 16 of the 18 samples positive for HPV-DNA. Stratifying patients according to HPV-DNA detection, we found that patients with HPV-DNA were younger (57.5 years vs. 70 years, p=0.047), less likely to have phimosis (5.8% vs. 42.9%, p=0.022) and more likely to have PeIN lesions than invasive SCC (85.7% vs. 27.8%, p=0.025).

Conclusion: This study shows a prevalence of HPV-DNA in penile SCC and premalignant lesions of 45.5% and 92.9%, respectively. Identifying HPV involvement in SCC and PeIN pathology has the potential to guide treatment and enhance follow-up strategies. The neutral-gender HPV vaccine impact assessment on penile cancer in ongoing.

Introduction

Penile cancer is a malignancy with a rising incidence in most European countries, even though still considered a rare disease[1]. With an estimated 5-year overall survival of 66%[2], penile cancer's prognosis is impacted by low medical awareness, lack of diagnostic biomarkers and delays in seeking medical attention[3].

Besides history of sexually transmitted infections, particularly human papillomavirus (HPV), major risk factors of penile cancer include phimosis, chronic inflammation, smoking and immunosuppression[4].

Most penile cancers are epithelial squamous cell carcinoma (SCC)[5]. Both SCC and penile intraepithelial neoplasia (PeIN), a precursor lesion for penile cancer, are classified as HPV-related and non-HPV-related, according to WHO classification[6]. PeIN is categorized according to the degree of atypia, from PeIN I (mild atypia) to PeIN III (carcinoma *in situ*)[7].

The involvement of HPV infection in penile cancer carcinogenesis is not fully understood. HPV prevalence in penile cancer was reported to be around 50%[8] and the relative risk of penile cancer is approximately 4.5 higher in HPV-seropositive males[9]. Recently, the immunohistochemical expression of $p16^{INK4a}$, a surrogate biomarker of high-risk HPV transcriptionally active infection, has been studied in penile cancer and it seems to be associated with a better prognosis[10].

Current research into the contribution of HPV in penile cancer and PeIN has the potential to improve prevention and treatment strategies. While HPV vaccination can potentially reduce the risk for these lesions, topical immune response modifiers and immunotherapy checkpoint inhibitors can constitute useful treatment options for PeIN and penile cancer respectively[11,12].

This retrospective observational study aims to describe the characteristics of patients with penile cancer and PeIN, evaluate the prevalence of HPV-DNA in tumor tissue and assess differences between patients with and without HPV-DNA identification.

Materials and Methods

This was a descriptive, retrospective, observational study including patients with a histological diagnosis of penile SCC or PeIN between 2012 and 2021 attending the Outpatient Dermatology/STD Clinic of Centro Hospitalar Universitário São João, Porto, Portugal (CHUSJ). The study was approved by the CHUSJ Ethics Committee. Patient data was obtained through revision of medical records. Histological diagnosis was made by certified dermatopathologists of the Department of Pathology of CHUSJ. All the patients were staged according to the 8th edition American Joint Committee on Cancer TNM system.

HPV analysis was performed using CLART® Papillomavirus, a commercial polymerase chain reaction (PCR) kit for the detection and typing of 28 types of HPV categorized as high risk (HR) (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73 and 82) and low risk (LR) (6, 11, 40, 42, 43, 44, 54, 61 and 70) according to the International Agency for Research on Cancer Risk. The specimens used were formalin-fixed paraffin-embedded tissue sections on which the histological diagnoses were based.

Statistical analysis was performed with SPSS® software v27 (IBM Corp., Armonk, NY, USA). Categorical variables were described by frequency and proportion; summary statistics (median, range) were used to report continuous data. Differences between the two groups were tested by Mann–Whitney U-test (for continuous variables), and by chi-squared test (for categorical variables), as appropriate. A two-sided P-value of <0.05 was considered statistically significant.

Results

Demographic characteristics of the study population

A total of 25 patients were diagnosed with penile SCC or PeIN during the 10-year study period. The median age at diagnosis was 61 years (25-78 years). (Table 1)

Most patients reported only having sex with women (n=22; 88%) and almost half of them reported one or no sexual partner the year prior to diagnosis (n=12, 48%).

Four patients had history of phimosis and three of them had been previously circumcised; the remaining 22 patients were uncircumcised. Furthermore, almost half of the patients were previously diagnosed with chronic genital dermatosis, namely lichen sclerosis and balanitis (without other specification). Five patients were living with HIV under

antiretroviral treatment at the time of diagnosis and had nadir CD4 counts ranging between 200 and 400 cells/mm^3. All of them but two had undetectable viral load. Fourteen patients (56%) had active or past history of sexually transmitted infection, mainly syphilis and anogenital warts. The glans was the most frequent tumor location, followed by the foreskin. (Table 1)

The most used treatment modality was excisional surgery (n=16), followed by cryosurgery (n=11). In two patients these two modalities of treatment were performed. Imiquimod was associated with cryosurgery in two patients. The median time of follow-up was 29 months (ranging from 6 to 84 months). Four patients had local recurrence, 1 to 7 years later (median=3 years). None of the patients were vaccinated against HPV prior to the neoplasia diagnosis.

Neoplasia characterization:

Most of the tumors identified were invasive SCC (n=11) and SCC *in situ* (PeIN 3) (n=8) (Fig.1). Regarding histologic type, the usual type SCC was the most frequent (14 out of 19 patients), followed by verrucous type and warty type (two patients each) and basaloid type SCC (one patient). Immunohistochemistry for p16 was performed in nine surgical specimens and overexpression was found in six of them (4 SCC in situ and 2 invasive SCC). Patients with invasive SCC were staged as T1N0M0 (Fig.1) except one with SCC T2N0M0.

HPV-DNA detection and typing were performed in all 25 tissue specimens. HPV-DNA was detected in 18 samples and in three of them there were more than one HPV type. We found HR-HPV DNA in all positive HPV samples, except one as genotyping was not possible. In 2 tissue samples concurrent LR-HPV was identified. The most common HPV was HPV 16 (n=8), followed by HPV 18, 33 and 6 (n=2 of each). Notably, we found HPV types included in the nonavalent HPV vaccine in 16 of the 18 samples positive for HPV-DNA. (Table 2)

Comparison between patients with penile tumor positive for HPV-DNA and patients without HPV-DNA in penile tumor

Stratifying patients according to HPV-DNA detection in penile tumor, we found that patients with HPV-DNA were younger (median 57.5 years vs. 70 years, p=0.047), less likely to have phimosis (5.8% vs. 42.9%, p=0.022) and more likely to have PeIN lesions than invasive SCC (85.7% vs. 27.8%, p=0.025). We found other marginally significant differences regarding chronic genital dermatosis which tends to be more likely in patients with neoplasia

without HPV-DNA detection. These patients were less likely to have a history of STIs and none had anogenital warts. (Table 3)

Discussion

Carcinogenic mechanisms in penile cancer are still unclear. However, two major pathways have been proposed, one linked to HPV and another linked to chronic inflammation[10]. In our study, we found HPV-DNA in most PeIN (92.9%) and in about half of penile invasive carcinoma (45.5%). Similarly, in a systematic review and meta-analysis with global data, authors found an HPV prevalence of 79.8% in PeIN and 50.8% in SCC[8].

The finding that HPV-DNA is more prevalent in PeIN than invasive SCC critically suggests that HPV infection may be associated with a less aggressive evolution and with a more predictable carcinogenic path[13]. On the other hand, this study indicates that penile neoplasia associated to chronic inflammation, usually HPV-DNA negative tumors, tend to have an unpredictable progression with a higher risk of invasive SCC. Therefore, we suggest a lower threshold for biopsy in these patients.

Like other studies, we found that penile cancer linked to HPV affect younger patients, whereas tumors without HPV-DNA arise more frequently in elderly men with phimosis and chronic genital dermatosis[14]. Nevertheless, HPV-DNA was identified in half of our patients with penile chronic inflammatory disease. In these cases, the role of HPV as another triggering factor should not be underestimated.

Although associated with LR-HPV 6 and 11, genital warts could harbor HR-HPV as well as premalignant and malignant tumors[9,15]. As expected, we found that the presence or history of anogenital warts seems to be associated with positive HPV-DNA neoplasia.

Currently, immunohistochemical expression of p16 should be included in the pathological report as it seems to be associated with prognosis[16]. Several tissue and serum biomarkers have been studied in recent years, aiming to improve early diagnosis, identify therapeutic targets and support prognosis evaluation. More research is needed to decipher the potential clinical implications of each marker[17].

Concerning HPV types, in almost all positive HPV penile neoplasia, the identified genotypes were covered by the nonavalent vaccine. The impact of neutral-gender HPV vaccination on penile cancer is ongoing, but promising results are expected[18].

This study shows a prevalence of HPV-DNA in penile SCC and premalignant lesions of 45.5 and 92.9%, respectively. Identifying HPV involvement in PeIN pathology has the potential to guide treatment and enhance follow-up strategies. The use of topical immune response modifiers such as toll-like receptor agonists in early PeIN is a recommended

organ-preserving treatment[16]. Additionally, immunotherapy checkpoint inhibitors aiming specific areas of the HPV pathway are currently being studied and outline a future achievement[11,12].

References

1. Fu L, Tian T, Yao K, et al. Global Pattern and Trends in Penile Cancer Incidence: Population-Based Study. JMIR Public Health Surveill. 2022 Jul 6;8(7):e34874.
2. Djajadiningrat RS, Graafland NM, van Werkhoven E, et al. Contemporary Management of Regional Nodes in Penile Cancer—Improvement of Survival? Journal of Urology. 2014 Jan;191(1):68–73.
3. Lucky MA, Rogers B, Parr NJ. Referrals into a dedicated British penile cancer centre and sources of possible delay. Sex Transm Infect. 2009 Dec 1;85(7):527–30.
4. Skeppner E, Andersson SO, Johansson JE, Windahl T. Initial symptoms and delay in patients with penile carcinoma. Scand J Urol Nephrol. 2012 Oct 1;46(5):319–25.
5. Hakenberg OW, Dräger DL, Erbersdobler A, Naumann CM, Jünemann KP, Protzel C. The Diagnosis and Treatment of Penile Cancer. Dtsch Arztebl Int. 2018 Sep 28;
6. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016 Jul;70(1):93–105.
7. Hoekstra RJ, Trip EJ, Kate FJ, Horenblas S, Lock MT. Penile intraepithelial neoplasia: Nomenclature, incidence and progression to malignancy in the Netherlands. Int J Urol. 2019 Mar 3;26(3):353–7.
8. Olesen TB, Sand FL, Rasmussen CL, et al. Prevalence of human papillomavirus DNA and p16INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. Lancet Oncol. 2019 Jan;20(1):145–58.
9. Catalfamo CJ, Brown HE, Dennis LK. Evaluating the Strength of Association of Human Papillomavirus Infection With Penile Carcinoma: A Meta-Analysis. Sex Transm Dis. 2022 May;49(5):368–76.
10. Mannweiler S, Sygulla S, Winter E, Regauer S. Two major pathways of penile carcinogenesis: HPV-induced penile cancers overexpress p16ink4a, HPV-negative cancers associated with dermatoses express p53, but lack p16ink4a overexpression. J Am Acad Dermatol. 2013 Jul;69(1):73–81.
11. Sali AP, Prakash G, Murthy V, et al. Updates in staging of penile cancer: the evolution, nuances, and issues. Hum Pathol. 2022 Jun;

12. McGregor B, Sonpavde G. Immunotherapy for advanced penile cancer — rationale and potential. Nat Rev Urol. 2018 Dec 30;15(12):721–3.
13. Lont AP, Kroon BK, Horenblas S, et al. Presence of high-risk human papillomavirus DNA in penile carcinoma predicts favorable outcome in survival. Int J Cancer. 2006 Sep 1;119(5):1078–81.
14. Moguelet P, Compérat EM. Les néoplasies intraépithéliales peniennes. Ann Pathol. 2022 Jan;42(1):15–9.
15. Cerejeira A, Cunha S, Coelho R, et al. Perianal warts as a risk marker for anal high-risk-human papillomavirus (HPV) detection and HPV-associated diseases. J Eur Acad Dermatol Venereol. 2020 Nov 1;34(11):2613–9.
16. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5. Available at: https://uroweb.org/guidelines/penile-cancer/publications-appendices (last accessed 22 January 2023)
17. Pekarek L, Ortega MA, Fraile-Martinez O, et al. Clinical and Novel Biomarkers in Penile Carcinoma: A Prospective Review. J Pers Med. 2022 Aug 24;12(9):1364.
18. Paulo J, da Silveira GG, Soave DF, et al. Human Papillomavirus Infection and Penile Cancer: Past, Present and Future. In: Human Papillomavirus and Related Diseases From Bench to Bedside A Diagnostic and Preventive Perspective. 1st ed. InTech; 2013. p.325.

Table 1. Demographic and clinical characteristics of 25 patients with penile cancer and penile intraepithelial neoplasia

		N	%
Age (y), median (minimum; maximum)	61 (25; 78)		
Sexual behavior			
Heterosexual		22	88
MSM		3	12
One or no sexual partner in previous year		13	52
Tobacco users		9	36
Uncircumcised		22	88
Phimosis		4	16
Previous chronic genital dermatosis		11	44
Balanitis (nonspecific)		4	16
Lichen sclerosis		3	12
Psoriasis		2	8
Leukoplakia		1	4
Zoon balanitis		1	4
Immunosuppressive treatment		2	8
HIV infection		5	20
STIs (other than HIV)		14	56
Anogenital warts		7	28
Syphilis		9	36
Chlamydia trachomatis		2	8
Gonorrhea		1	4
Location of Lesions			
Glans		11	44
Foreskin		9	36
Penile shaft		3	12
Glans + Foreskin[a]		2	8

Table 2. Distribution of HPV infection according to LR/HR and HPV genotypes in tissue specimens

	N	%
HPV		
Negative	7	28
Any HPV	18	72
HR-HPV	17	94.4 [c]
Only HR-HPV	15	83.3 [c]
LR-HPV	2	11.1 [c]
Only LR-HPV	0	0
HPV genotypes [a]		
6	2	11.1 [c]
11	1	5.6 [c]
16	8	44.4 [c]
18	2	11.1 [c]
31	1	5.6 [c]
33	2	11.1 [c]
45	1	5.6 [c]
51	1	5.6 [c]
56	1	5.6 [c]
58	1	5.6 [c]
66	1	5.6 [c]
At least one of the following 6, 11, 16, 18, 31, 33, 45, 52 and 58 [b]	16	88.9 [c]

Table 3. Selected characteristics of patients stratified by HPV-DNA detection in tissue samples.

	Patients		
	HPV-negative tumor n=7	**HPV-positive tumor n=18**	**p-value**
Age, median (years)	70	57.5	**0.047**
STIs			
No	5 (71.4%)	6 (33.3%)	0.085
Yes	2 (28.6%)	12 (66.7%)	
Anogenital warts			
No	7 (100%)	11 (61.1%)	0.052
Yes	0	7 (38.9%)	
Phimosis			
No	4 (57.1%)	17 (94.4%)	**0.022**
Yes	3 (42.9%)	1 (5.6%)	
Previous chronic genital dermatosis			
No	2 (28.6%)	12 (66.7%)	0.085
Yes	5 (71.4%)	6(33.3%)	
Histological diagnosis			
PeIN1/2	1 (14.3)%)	5 (27.8%)	**0.025**
SCC in situ (PeIN3)	0	8 (44.4%)	
SCC (invasive)	6 (85.7%)	5 (27.8%)	

Figure 1

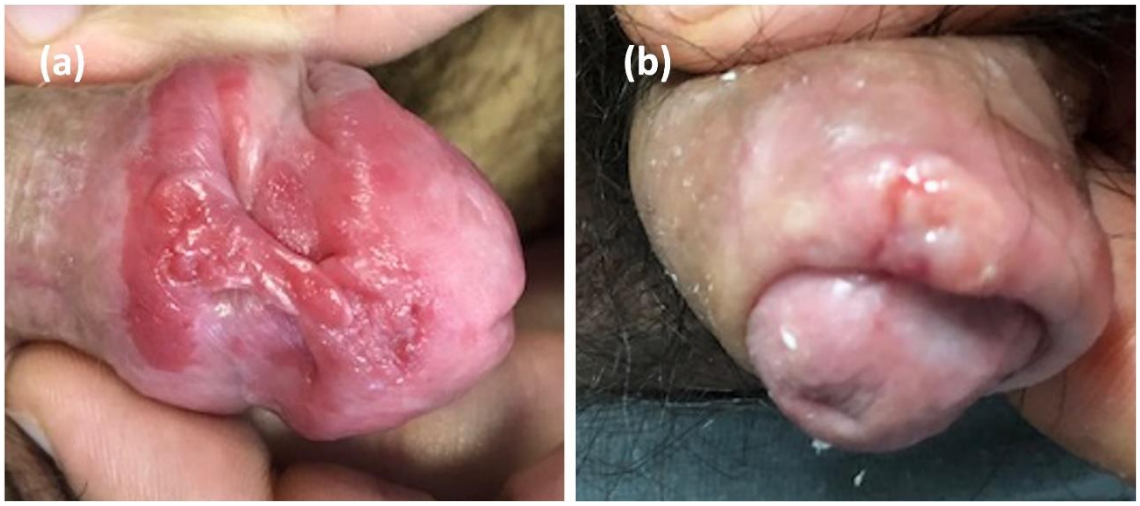

Table 1. Demographic and clinical characteristics of 25 patients with penile cancer and penile intraepithelial neoplasia

Abbreviations: HIV, Human Immunodeficiency virus; MSM, men who have sex with men; STIs, Sexually Transmitted Infections

Immunosuppressive treatments- methotrexate and systemic corticosteroids.

[a]Location of neoplasia-two patients had lesions in both glans and foreskin.

Table 2. Distribution of HPV infection according to LR/HR and HPV genotypes in tissue specimens.

Abbreviations: HPV, Human Papillomavirus; HR, High Risk -HPV; LR, Low Risk. In 1 patient the tissue specimen had an unqualified HPV.

[a] Because in some tissue specimens more than 1 HPV was identified, the total number of genotypes is greater than the number of cases.

[b] HPV types covered by the nonavalent HPV vaccine (Gardasil 9).

[c] percentage of different genotypes of HPV calculated in relation to total HPV-DNA positive tissue specimens (n=18)

Table 3. Selected characteristics of patients stratified by HPV-DNA detection in tissue samples.

Abbreviations: STIs, Sexually Transmitted Infections; PeIN, Penile intraepithelial neoplasia; SCC, squamous cell carcinoma

p bold, statistically significant (<0.05) calculated by Mann–Whitney U-test (for age), and by chi-squared test (for STIs, anogenital warts, phimosis, histological diagnosis)

Figure 1. Penile squamous celular carcinoma (SSC).

(a) A 27-year-old imunocompetent man with *in situ* SCC in glans and prepuce; HPV 33 DNA was detected in tissue sample.

(b) A 70-year-old man suffered from penile lichen sclerosus for several years. He presented invasive SSC (T1N0M0); HPV DNA in tissue sample was not detected

Apêndices

PROCESS 2020 Checklist			
Topic	**Item**	**Checklist Item Description**	**Page Number**
Title	**1**	- The phrase ‘case series’ and the area of focus should appear in the title (e.g. patient population, diagnosis, intervention or outcome).	Pág.6 Estudo foi caracterizado no título como estudo observacional retrospetivo. População e diagnóstico: Homens com cancro do pénis.
Key Words	**2**	- Include three to six keywords that identify what is covered in the case series (e.g. patient population, diagnosis, intervention or outcome). - Include ‘case series’ as one of the keywords.	Pág.6 Palavras-chave incluem a exposição (HPV infection) e o diagnóstico (Penile Cancer, Penile intraepithelial neoplasia)
Abstract	**3a**	Introduction and Importance - Describe what is unique or educational. - What is the overarching theme of the case series?	Pág.7 Com o aumento da incidência do cancro do pénis torna-se imperativo esclarecer o papel da infeção do HPV nesta patologia, de forma a melhorar as estratégias de prevenção e tratamento. Assim sendo, o objetivo deste estudo foi descrever e caracterizar os doentes com CEC do pénis e PeIN, avaliar a presença de infeção de HPV nas amostras e identificar as diferenças entre doentes HPV positivos e HPV negativos. “the exact role of HPV in penile cancer carcinogenesis is still unknown. Clarifying the contribution of HPV in penile cancer is crucial as it may improve prevention and treatment strategies.”

	3b	Methods - Describe what was done, how and when was it done and by whom.	Pág.7 Informação clínica recolhida através dos registos médicos de todos os doentes com diagnóstico de CEC do pénis ou PeIN no período de 2012-2021. A analise histopatológica do HPV foi realizada utilizando o CLART papillomavirus, e a análise estatística foi realizada com recurso ao SPSS. "A retrospective observational study including patients with histological diagnosis of penile squamous cell carcinoma (SCC) or PeIN between 2012 and 2021 in a university hospital was carried out. HPV analysis was performed using CLART® Papillomavirus, for the detection and typing of 28 types of HPV in tissue specimens."
	3c	Outcomes - Describe the outcomes of the intervention and management strategy.	N/A Estudo observacional, não foi realizada nenhuma intervenção.
	3d	Conclusion - Describe the take home message(s), including what has been learnt? - How will this impact future clinical practice?	Pág.7 Este estudo revelou uma prevalência de HPV-DNA no CEC e no PeIN de 45,5% e de 92,9%, respetivamente Este estudo demonstrou também que a maioria dos doentes HPV-positivos (n=16/18) tinham serotipos cobertos pela vacina; que os doentes HPV-positivos eram mais novos, tinham menos fimose, e uma maior probabilidade de ter lesões in situ. "This study shows a prevalence of HPV-DNA in penile SCC and premalignant lesions of 45.5% and 92.9%, respectively. Identifying

			HPV involvement in SCC and PeIN pathology has the potential to guide treatment and enhance follow-up strategies. The neutral-gender HPV vaccine impact assessment on penile cancer in ongoing.”
Introduction	**4**	- Describe the background of the case series and specify the overarching theme (e.g. common disease, intervention, or outcome). - The introduction should explain what is unique or educational about the case series. - Relevant scientific literature should be referenced. - Introduction should be 1-2 paragraphs in length.	Pág.8 O cancro do pénis, apesar de ser uma doença rara, a sua prevalência tem vido a subir. É uma doença com uma mortomorbilidade significativa, impactada pelo atraso do diagnóstico. Vários fatores de risco estão identificados, sendo dos mais relevantes a infeção por HPV. Esta série de casos reúne uma coorte significativa de doentes com diagnóstico de cancro do pénis/PeIN, e tem como objetivo caracterizar e descrever as diferenças dos doentes HPV-positivos e HPV-negativos. Vários artigos de relevo são citados, incluído 2 meta-analises a descrever a prevalência do HPV no cancro do pénis e a sua associação. Por motivos de estruturação do texto a introdução tem mais de 2 parágrafos. “This retrospective observational study aims to describe the characteristics of patients with penile cancer and PeIN, evaluate the prevalence of HPV-DNA in tumor tissue and assess differences between patients with and without HPV-DNA identification”

Methods	**5a**	Registration - State the research registry number in accordance with the Declaration of Helsinki - "Every research study involving human subjects must be registered in a publicly accessible database". This can be obtained from, for example, ResearchRegistry.com, ClinicalTrials.gov, or ISRCTN. - If a protocol already exists, state the corresponding registration number and access directions (e.g. website or journal, and include a hyperlink that is publicly accessible). It must be written in the English language.	Pág.9 O estudo foi aprovado pela comissão de ética Projeto de investigação n.º 273/22. “The study was approved by the CHUSJ Ethics Committee.”
	5b	Study Design - State that the study is a case series. - State whether the case series is: (1) prospective/ retrospective, (2) single/multi-centre, and if (3) cases are consecutive/non-consecutive.	Pág.9 É constatado que o design do estudo é observacional retrospetivo e que este inclui doentes com cancro do pénis/PeIN, estando subentendido que se trata de uma série de casos. O estudo é unicentrico. “This was a descriptive, retrospective, observational study including patients with a histological diagnosis of penile SCC or PeIN between 2012 and 2021 attending the Outpatient Dermatology/STD Clinic of Centro Hospitalar Universitário São João, Porto, Portugal (CHUSJ).”

	5c	Settings and Time-Frames - Describe the setting(s) in which the patient was managed (e.g. research institution, teaching/district general hospital, community, or private practice). - Document any relevant dates (e.g. recruitment, intervention, follow-up, and data collection time-frames).	Pág.9 Foram incluídos no estudo todos os doentes com diagnóstico de CEC ou PeIN seguidos na consulta externa de Dermatologia/Doenças Sexualmente Transmissíveis do CHUSJ, durante o período entre 2012 e 2021. "This was a descriptive, retrospective, observational study including patients with a histological diagnosis of penile SCC or PeIN between 2012 and 2021 attending the Outpatient Dermatology/STD Clinic of Centro Hospitalar Universitário São João, Porto, Portugal (CHUSJ)."
	5d	Participants - Describe the relevant characteristics (e.g. demographics, comorbidities, tumour staging, smoking status) and if relevant, exposure(s) of the participants. - Describe the method of participant recruitment, if relevant. - State any subsequent inclusion or exclusion criteria, and how the participants were selected. - Methods used to ensure the de-identification of patient information.	Pág.9 e 16 As características demográficas e clínicas encontram-se descritas nos Resultados e na Tabela 1, como por exemplo, a idade, a orientação sexual, o número de parceiros no último ano, presença de circuncisão, fimose, dermatoses genitais crónicas, tratamentos imunossupressores, infeção por HIV ou outras ISTs e localização das lesões. O método de recrutamento já foi mencionado no ponto 5c). Sem critérios de inclusão ou exclusão de pacientes. O anonimato da informação colhida foi garantido pela codificação dos doentes.

	5e	Pre-Intervention Patient Optimisation - Lifestyle (e.g. weight loss). - Medication review (e.g. anticoagulation, oral hypoglycemics/insulin). - Pre-surgical stabilisation/preparation (e.g. treating hypothermia/hypovolemia/hypotension, ICU care for sepsis, nil by mouth, or enema). - Other (e.g. psychological support).	N/A Não foi realizado nenhuma intervenção.
	5f	Interventions - Describe the type(s) of intervention(s) used (e.g. pharmacological, surgical, physiotherapy, psychological, preventative). - Describe any concurrent treatments (e.g. antibiotics, analgesia, antiemetics, venous thromboembolism prophylaxis).	N/A Não foi realizado nenhuma intervenção.
	5g	Intervention Details - Describe the rationale behind the treatment offered, how it was performed and time to intervention. - For pharmacological therapies, include information on the formulation, dosage, strength, route, and duration. - For surgery, include details such as anaesthesia, patient position, preparation used, use of other relevant equipment, sutures, devices, and surgical stage. - The degree of novelty for a surgical technique/device should be	N/A Não foi realizado nenhuma intervenção.

		mentioned (e.g. 'first in human' or 'first in this context'). - Medical devices should have manufacturer and model specifically mentioned.	
	5h	Operator Details - Where applicable, include operator experience and position on the learning curve, any relevant training, and specialisation (e.g. 'junior trainee with three years of surgical specialty training in Plastic Surgery and seven similar cases completed previously under direct supervision').	N/A Não foi realizado nenhuma intervenção.
	5i	Quality Control - What measures were taken to reduce inter- or intra-operator/operation variation, to ensure quality, and to maintain consistency between cases (e.g. independent observers, lymph node counts, standard surgical technique). - State any specific disparities between cases.	N/A Não foi realizado nenhuma intervenção.
	5j	Follow-Up - When (e.g. how long after discharge, frequency, maximum follow-up length at the time of submission). - Where (e.g. home via video consultation, primary care, secondary care). - How (e.g. telephone consultation, clinical examination, blood tests, imaging).	Pág.9 Não foi realizado nenhuma intervenção. Reviu-se os dados clínicos e o seu follow-up após diagnóstico e tratamento do carcinoma do pénis e PeIN. "Patient data was obtained through revision of medical records."

		- Any specific long-term surveillance requirements (e.g. imaging surveillance of endovascular aneurysm repair or clinical exam/ultrasound of regional lymph nodes for skin cancer). - Any specific post-operative instructions (e.g. post-operative medications, targeted physiotherapy, psychological therapy). - State if any participants were lost to follow-up and why.	
Results	**6a**	Participants - Please state the number of patients involved, the patient characteristics (e.g. demographics, comorbidities, smoking status, and if applicable, tumour staging (e.g. TNM)).	Pág.10 Nº de Participantes: 25 "Most of the tumors identified were invasive SCC (n=11) and SCC *in situ* (PeIN 3) (n=8) (Fig.1). Regarding histologic type, the usual type SCC was the most frequent (14 out of 19 patients), followed by verrucous type and warty type (two patients each) and basaloid type SCC (one patient). Immunohistochemistry for p16 was performed in nine surgical specimens and overexpression was found in six of them (4 SCC in situ and 2 invasive SCC). Patients with invasive SCC were staged as T1N0M0 (Fig.1) except one with SCC T2N0M0."

	6b	Deviation from the Initial Management Plan - State if there were any changes in the planned intervention(s) (e.g. what was changed and why). - Please include a suitable schematic diagram if appropriate.	N/A Não foi realizado nenhuma intervenção.
	6c	Outcomes and Follow-Up - Expected versus attained clinical outcome as assessed by the clinician. Reference literature used to inform expected outcomes. - When appropriate, include patient-reported measures (e.g. questionnaires including quality-of-life scales). - Describe and explain the percentage of patients lost to follow-up.	N/A Não foi realizado nenhuma intervenção.
	6d	Intervention Adherence and Compliance - Where relevant, detail how well the patient adhered to and tolerated the advice provided (e.g. avoiding heavy lifting for abdominal surgery, or tolerance of chemotherapy and pharmacological agents). - Explain how adherence and tolerance were measured.	N/A Não foi realizado nenhuma intervenção.

	6e	Complications and Adverse Events - Precautionary measures taken to prevent complications (e.g. antibiotic or venous thromboembolism prophylaxis). - All complications and adverse or unanticipated events should be described in detail and ideally categorised in accordance with the Clavien-Dindo Classification (e.g. blood loss, length of operative time, wound complications, re-exploration or revision surgery, impact on length of stay). - If relevant, was the complication reported to the relevant national agency or pharmaceutical company. - Specify the duration of time between completion of the intervention and discharge, and whether this was within the expected timeframe (if not, why not). - Where applicable, the 30-day post-operative and long-term morbidity/mortality may need to be specified. - State if there were no complications or adverse outcomes.	N/A Não foi realizado nenhuma intervenção.
Discussion	**7a**	- Summarise the key results.	Pág.12 e 18 -Os doentes HPV-positivo são mais jovens que os doentes HPV-negativo e tem uma maior prevalência de PeIN, sugerindo um evolução carcinogénica menos agressiva. Por sua vez os doentes HPV-negativos têm uma maior prevalência de dermatose crónica

			inflamatória, fimose e um maior risco de CEC invasivo. -Os condilomas, apesar de estarem associados a infeções de HPV de baixo risco são um potencial marcador de risco de neoplasia HPV-positiva. -A maioria das lesões eram positivas para HPV coberto pela vacina. Resultados sumáriados na tabela 3.
	7b	Relevant Literature and Placing the Results in Context - Include a discussion of the relevant literature and, if appropriate, similar published studies. - Describe the implications for clinical practice guidelines (e.g. NICE) and any relevant hypotheses generated.	Pág.12 e 18 Discussão e contextualização com artigos com resultados semelhantes: "In our study, we found HPV-DNA in most PeIN (92.9%) and in about half of penile invasive carcinoma (45.5%). Similarly, in a systematic review and meta-analysis with global data, authors found an HPV prevalence of 79.8% in PeIN and 5 0.8% in SCC[8]."; "Like other studies, we found that penile cancer linked to HPV affect younger patients, whereas tumors without HPV-DNA arise more frequently in elderly men with phimosis and chronic genital dermatosis." Resultados com impacto na prática clínica: "…this study indicates that penile neoplasia associated to chronic inflammation, usually HPV- DNA negative tumors, tend to have an unpredictable progression with a higher risk of invasive

			SCC. Therefore, we suggest a lower threshold for biopsy in these patients.”
	7c	Strengths - Describe the relevant strengths of the study. - Detail any multidisciplinary or cross-speciality relevance. Weaknesses and Limitations - Describe the relevant weaknesses or limitations of the study. - For novel techniques or devices, outline any contraindications and alternatives, potential risks and possible complications if applied to a larger population.	Os pontos fortes deste artigo é o facto de ter reunido uma coorte significativa de doentes com cancro do pénis, visto que é uma neoplasia rara. Outros pontos fortes consistem em todos os doentes terem pesquisa da infeção de HPV nas amostras e o facto de existir uma boa correlação clínico laboratorial. Os pontos negativos deste estudo são todos aqueles inerentes ao tipo de estudo utilizado, ou seja um estudo retrospetivo observacional, e o facto de este ser unicentro.
	7d	Directions for Future Research - State how the methodology and findings discussed can impact future research and clinical practice. Describe the questions that have arisen as a result of this study. - State the alternative study design(s) best suited to address these questions.	Pág.12 Os resultados de demonstram a importância de avaliar a infeção por HPV nas lesões de PeIN e CEC do pénis. “The finding that HPV-DNA is more prevalent in PeIN than invasive SCC critically suggests that HPV infection may be associated with a less aggressive evolution and with a more predictable carcinogenic path[13]. On the other hand, this study indicates that penile neoplasia associated to chronic inflammation, usually HPV- DNA negative tumors, tend to have an unpredictable progression with a higher risk of invasive SCC. Therefore, we suggest a lower threshold for biopsy in these patients.” Os resultados demonstram a importância da vacinação de todas as pessoas independentemente do

			sexo. “Concerning HPV types, in almost all positive HPV penile neoplasia, the identified genotypes were covered by the nonavalent vaccine. The impact of neutral-gender HPV vaccination on penile cancer is ongoing, but promising results are expected[18].” É discutida a importância de pedir a expressão imunohistoquímica de p16 pois esta pode ser importante para definir o prognóstico. “Currently, immunohistochemical expression of p16 should be included in the pathological report as it seems to be associated with prognosis[16]. Several tissue and serum biomarkers have been studied in recent years, aiming to improve early diagnosis, identify therapeutic targets and support prognosis evaluation. More research is needed to decipher the potential clinical implications of each marker[17].”
Conclusions	**8a**	Key Conclusions - Outline the key conclusions from this study.	Pág.12 e 13 Conclusão sobre a importância de avaliar a infeção de HPV nas lesões de PeIN e CEC do pénis. “This study shows a prevalence of HPV-DNA in penile SCC and premalignant lesions of 45.5 and 92.9%, respectively. Identifying HPV involvement in PeIN pathology has the potential to guide treatment and enhance follow-up strategies. The use of topical immune response modifiers such as toll-like receptor agonists in early PeIN is a recommended organ-preserving treatment[16]. Additionally, immunotherapy checkpoint inhibitors aiming specific areas of the HPV pathway are currently being

			studied and outline a future achievement[11,12].”
	8b	Rationale - Ensure that any of the conclusions made are supported by a strong rationale.	Pág. 12, 13, 14 e 15 As conclusões são suportadas por vários estudos citados. -EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5. Available at: https://uroweb.org/guidelines/penile-cancer/publications-appendices (last accessed 22 January 2023) - Sali AP, Prakash G, Murthy V, et al. Updates in staging of penile cancer: the evolution, nuances, and issues. Hum Pathol. 2022 Jun - McGregor B, Sonpavde G. Immunotherapy for advanced penile cancer — rationale and potential. Nat Rev Urol. 2018 Dec 30;15(12):721–3
	8c	Future Work - Briefly discuss any questions arisen from this study and any differences in approach to patient diagnosis or management which the authors might adopt in future similar studies.	Este estudo foi inovador em descrever as características dos doentes com CEC do pénis e PeIN e a prevalência de HPV nestas lesões, podendo este estudo ser replicado a outros centros.
Patient Perspective	**9**	- Where appropriate, the patients should be given the opportunity to share their perspective on the intervention(s) they received (e.g. sharing quotes from a consented, anonymised interview, or questionnaire).	N/A Não foi realizado nenhuma intervenção.

Informed Consent	**10**	- The authors must provide evidence of consent, where applicable, and if requested by the journal. - State the method of consent at the end of the article (e.g. verbal or written). - If not provided by the patients, explain why (e.g. death of patient and consent provided by next of kin). If the patients or family members were untraceable then document the tracing efforts undertaken.	Pág.6 O consentimento dos pacientes está contemplado na frase "Ethics statement: This study was approved by the Centro Hospitalar Universitário de São João Ethics Committee. The patients in this manuscript have given written informed consent to publication of their case details."
Additional Information	**11a**	- State any conflicts of interest.	Pág.6 "Disclosure of interest: The authors report no conflict of interest"
	11b	- State any sources of funding.	Pág.6 Funding source: None
	11c	Other Relevant Disclosures - Please state any author contributions, acknowledgments, and where required, institutional review board and ethical committee approval. - Disclose whether the case has been presented at a conference or regional meeting.	Pág.6 "M. J. Guimaraes1*, R. Macieira2*, F. Azevedo3, C. Lisboa2,3,4 1Department of Dermatology and Venereology, Hospital de Braga, Portugal 2Microbiology, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal 3Department of Dermatovenereology, Centro Hospitalar Universitário de São João, Porto, Portugal 4CINTESIS - Centre for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto,

			Portugal * These authors contributed equally to this work” “Ethics statement: The Centro Hospitalar Universitário de São João Ethics Committee approved this study. The patients in this manuscript have given written informed consent to publication of their case details.”
Clinical Images and Videos	**12**	- Where relevant and available, include clinical images to help demonstrate the cases pre-, peri-, and post-intervention (e.g. radiological, histopathological, patient photographs, intraoperative images). - Where relevant and available, include a link (e.g. Google Drive, YouTube) to the narrated operative video to highlight specific techniques or operative findings. - Ensure all media files are appropriately captioned and indicate points of interest to allow for easy interpretation.	Imagens anexadas na pág.19
Referencing the Checklist	**13**	- Include reference to the PROCESS 2020 publication by stating: 'This case series has been reported in line with the PROCESS Guideline' at the end of the methods section (and include citation in the references section).	Não se realizou referência à checklist PROCESS.

Regras de formatação da revista *Journal of the European Academy of Dermatology and Venereology* (*JEADV*)

1. AIMS & SCOPE

The *Journal of the European Academy of Dermatology and Venereology*(*JEADV*) is the official publication of the European Academy of Dermatology and Venereology (EADV). The *JEADV* is one of the leading international peer-reviewed journals in the field of Dermatology and Venereology. Our target audience is clinician dermatologists and venereologists in hospitals or in private practice, as well as researchers and everybody interested in understanding the management of skin disease to improve patient outcomes.

The aim of the *JEADV* is to deliver the highest level of dermatological knowledge to its readership, publishing clinical and translational research articles, clinical trial reports, and systematic and state of the art reviews. The Journal publishes original articles, review articles, short reports, and also welcomes submissions of Letters to the Editor expressing opinions on current and/or controversial issues as well as observations of general importance. With thought-provoking features like editorials, commentaries and the Historical Perspectives series, the Journal strives to be an engaging and relevant platform for dermatologists and venereologists in Europe and beyond.

Furthermore, the *JEADV* is the place where the European Clinical Guidelines derived from cooperation between the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the Union Européenne des Médecins Spécialistes (UEMS), and other relevant subspecialty societies are published.

2. MANUSCRIPT CATEGORIES

JEADV invites the following types of submissions:

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Original Articles are the Journal's primary mode of communication. This type of manuscripts should report new data arising out of scientific research that may involve a wide range of empirical methods and study designs. Original articles must include a structured abstract (maximum 300 words), and should not exceed 3000 words of body text (that is, excluding the abstract, reference list and figure legends). The addition of tables and figures (with figure legends) is encouraged.

> **Clinical Trial Registration.** As of January 2020, JEADV requires that clinical trials are prospectively registered in a publicly accessible trials registry. We ask authors to provide the name of the trial register and the clinical trial registration number at the end of the abstract. The journal considers a trial for publication only if it has been registered prior to randomization of patients. If the trial is not registered, or was registered retrospectively, justification for this should be given when submitting the manuscript.

Reporting standards. Manuscripts reporting randomised controlled trials (RCTs) must follow the **CONSORT** statement. RCTs will not be considered by *JEADV* without submission of a completed **CONSORT checklist.** Checklists should be uploaded during manuscript submission using file designation 'Supplementary files for review'.

Review Articles. The Journal is particularly keen to publish concise, high-quality review articles identifying, synthesizing and summarizing available evidence about a focused topic pertaining to clinical practice and discussing recent advances in laboratory or clinical

research. The JEADV welcomes the submission of both systematic and narrative reviews. **Systematic reviews and meta-analyses** are published under the **Systematic Review subcategory** within Review Articles. Review articles may be submitted by authors for publication subject to peer review or may be solicited by the Editor-in-Chief. Review articles must include an unstructured abstract (maximum 300 words), and should not exceed 5000 words of body text. Use of tables and figures (with figure legends) is encouraged.

> **Systematic Review Registration.** Prospective registration of systematic reviews on **PROSPERO** or a similar database is recommended.
>
> **Reporting standards.** Reports of systematic reviews and meta-analyses must include a completed **PRISMA** (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram to accompany the main text. Checklists should be uploaded during manuscript submission using file designation 'Supplementary files for review'. Authors are encouraged to include an assessment of the methodological quality of the included studies.

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Book Reviews. The Journal publishes reviews of recent books in Dermatology and Venereology and in related fields. Book reviews are solicited by the Editor-in-Chief. Proposals with adequate information on the book may also be submitted by prospective book reviewers. All book reviews are subject to expert review.

3. SUBMISSION OF MANUSCRIPTS

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New users should first create an account. Once a user is logged onto the site, submissions should be made via the Author Dashboard. Authors must also supply:
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4. CONTACTING THE EDITORIAL OFFICE

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5. PREPARATION OF MANUSCRIPTS

Manuscripts must be submitted in grammatically correct English (American or British usage is accepted, but not a mixture of the two). Manuscripts that do not meet this standard cannot be reviewed. Authors for whom English is a second language may wish to consider having their manuscript professionally edited before submission to improve the English. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.
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Title page. A title page must be provided for all submissions regardless of the type of manuscript being submitted. Please note that without title page, the submission will not be sent to peer-review and will be instantly returned to the authors so they can update their submission. The first page of all manuscripts should contain the following information:

1. the title of the paper
2. a list of key words (2–6 article key words)
3. manuscript word, table and figure count
4. names of authors as initial(s) followed by surnames
5. names of the institutions at which the research was conducted, clearly linked to respective authors
6. name, address, telephone and fax number, and email address of corresponding author
7. a statement of all funding sources that supported the work
8. any conflict of interest disclosures (see sections 3 and 6).
9. a data availability statement
10. ethics statement

Number of authors. The JEADV does not have an upper limit concerning the number of authors of a manuscript.

Abstracts. Authors submitting original articles or short reports should note that structured abstracts are required. The structured abstract should adopt the format: Background, Objectives, Methods, Results, Conclusions.
Abstract should be included after the Title Page of the manuscript.

Text. The main text of a manuscript should in general, but not necessarily, be divided into sections with the headings: Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Legends and Figures.

Tables and figures. Tables and figures should not be inserted in the appropriate place in the text but should be provided as separate files and should be uploaded below the main text.
Tables and figures should be referred to in text as follows: Fig. 1, Figs 2–4; Table 1, Table 2. The place at which a table or figure is to be inserted in the printed text should be indicated clearly in the manuscript. A title should be provided for each table. Where a figure

has more than one panel, each panel should be labelled in the top left-hand corner using lower case letters in parentheses, i.e., (a), (b), etc., and a brief description of each panel given in the figure legend.
Colour illustrations are welcomed and all colour is published free of charge to the author. Authors are themselves responsible for obtaining permission to reproduce previously published materials (e.g. figures, diagrams, charts, tables, etc.), for which they do not own the copyright. Permissions must be obtained from the original publisher or copyright holder and the evidence must be provided to the Editorial Office. You must acknowledge the original source in the figure/table legends, as requested by the original publisher. When an individual is identifiable in a photograph or human neuroimaging data and brain scans are presented, written permission must be obtained (see section 6).

Figure legends. Each figure must have a legend that explains its purpose without reference to the text. Figure legends should be listed in numerical order, at the end of the text document, separate from the figure files. Please note that Figure legends are excluded from the word count.

Formats. Clinical photographs may be supplied in GIF, JPEG, PNG, or TIFF format at the time of submission, but only TIFF files (and exceptionally JPEG files, as original format) are suitable for production and printing. *JEADV* has a dedicated medical illustrator who works on accepted manuscripts to format/re-design the tables/figures to comply with the Journal's style. If a manuscript is accepted, the corresponding author will be contacted to provide high-quality photographs at their actual size, which is 100% of their print dimension in TIFF format, at a minimum resolution of 300 pixels per inch and in RGB color mode. Vector graphics (e.g. graphs, diagrams, histograms) should be provided in editable PPT, PDF, EPS, or AI files, either in greyscales or RGB at the appropriate resolutions: 300 dpi for color figures; 600 for black and white figures; 1200 dpi for line-art figure.

Tables should be supplied in a format compatible with Word, preferably as .DOC files. The authors are requested to ensure that the whole area of the tables is visible in the PDF proof of the manuscript.

Flow charts should be provided in an editable Word format.
Images and photographs destined to redesigns should not contain any added lettering (a,b,c,..), arrows or symbols.
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Patient consent. The journal requires confirmation of patient consent for publication for all clinical images, videos and health information - whether or not the patient is identifiable - acknowledging the potential of publication and the possible use in social media. The signed consent form should be filed securely in the patient's case notes and **the manuscript submitted to the journal should include this statement in the Ethics Statement section indicating that specific consent for publication was obtained: "The patients in this manuscript have given written informed consent to publication of their case details."** The Editorial Office will not collect or archive consent forms from authors, but reserves the right to enquire about or audit their presence.

Authors are encouraged to use the EADV Patient Consent form for Publication, which can be downloaded **here**. In case other patient consent form was used, the authors are required to indicate whether consent for social media usage was obtained.

References. References should be in Vancouver format and appear as consecutive, unbracketed superscript numbers in the text, e.g., 'in our previous reports[1,2] and those of Smith *et al*.[3–5] and should be listed numerically in the reference list at the end of the article.

Format references as below, using standard (Medline) abbreviations for journal titles. If more than six authors, include the first three authors followed by *et al*. If six or fewer authors, please include all authors' names.

1. de Berker DAR, Baran R, Dawber RPR. The nail in dermatological diseases. In: *Baran and Dawber's Diseases of the Nails and their Management*(Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds), 3rd edn. Oxford: Blackwell Science Ltd, 2001; 172–92.

2. Wollina U, Hansel G. The use of topical calcineurin inhibitors in lupus erythematosus: an overview. *J Eur Acad Dermatol Venereol*2008;**22**:1–6.

3. Graham-Brown R, Burns T. *Lecture Notes: Dermatology*. Oxford: Wiley-Blackwell, 2006.

4. British Lymphology Society. *Consensus Document on the Management of Cellulitis in Lymphoedema*. 2007.
Available
at: **http://www.lymphoedema.org/lsn/consensus_on_cellulitis_dec_06.pdf**(last accessed 28 November 2007).

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SÃO JOÃO

DELIBERAÇÃO DO CONSELHO DE ADMINISTRAÇÃO

Após apreciação e pareceres favoráveis da Comissão de Ética e do Centro de Epidemiologia Hospitalar, considerando que se encontram reunidos os requisitos e demais trâmites previstos no circuito para submissão de projetos de investigação no Centro Hospitalar Universitário de S. João e em conformidade com as disposições legais em vigor, o Conselho de Administração – ao abrigo das competências previstas no Artigo 71.º dos Estatutos dos hospitais, centros hospitalares, institutos portugueses de oncologia e unidades locais de saúde, aprovados pelo Decreto-Lei n.º 52/2022, de 4 de agosto – delibera:

1. Aprovar a realização do projeto de investigação:
   - "Clinical and epidemiologic relevance of HPV in Penile Cancer: A Retrospective Study".
   - Serviço(s) onde decorrerá o projeto de investigação: Dermatologia.
   - Investigador(a) principal: Cármen Maria Lisboa.
2. Remeta-se à Comissão de Ética para os procedimentos adequados e demais trâmites convenientes.

CONSELHO DE ADMINISTRAÇÃO DO CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE • REUNIÃO DE 2 DE FEVEREIRO DE 2023

Presidente do Conselho de Administração

Prof.ª Doutora Maria João Baptista

Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
Prof.º Doutor Roberto Roncon	Enfermeiro Paulo Emílio Mota	Dra. Sofia Leal	Dra. Fernanda Oliveira

› Comissão de Ética
› Centro de Epidemiologia Hospitalar
› Direção Clínica

CES 273/2022

Centro de Epidemiologia Hospitalar

Tomei conhecimento. Nada a opor. À DC.

27 de Janeiro de 2023

A Diretora do Centro de Epidemiologia Hospitalar

(Prof.ª Doutora Ana Azevedo)

DIRECÇÃO CLÍNICA
30 JAN 2023

n.º 273 / 22

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

CONSELHO DE ADMINISTRAÇÃO CHUSJ, EPE - REUNIÃO DE
Presidente do Conselho de Administração

(Prof.ª Doutora Maria João Baptista)

Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
Prof. Doutor Roberto Roncon	Enf.º Paulo Emílio Mota	Dra. Fernanda Oliveira	Dra. Sofia Leal

Exmo. Senhor Presidente do Conselho de Administração do Centro Hospitalar de São João

Nome do Investigador Principal:

Carmen Maria Lisboa

Título da Investigação:

Clinical and epidemiologic relevance of HPV in Penile Cancer: A Retrospective Study

Pretendendo realizar no(s) Serviço(s) de:

Dermatologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 14 *de* Outubro *de* 2022 .

assinatura

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
19 / 1 / 2023

SÃO JOÃO | Encarregado de Proteção de Dados
Data Protection Officer

Entrada 09/01/2023

CES-IM005-0

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Clinical and epidemiologic of HPV in Penile Cancer: A restrospective study

Nome da Investigadora Principal: Prof. Doutora Cármen Maria Lisboa

Onde decorre o Estudo: No Serviço de Dermatologia. Apresentou declaração da Dra. Filomena Azevedo.

Objetivos do Estudo:
O estudo tem como principal objetivo avaliar a associação entre infeção de HPV e cancro do pénis.

Conceção e Pertinência do estudo:
Coorte retrospetiva e transversal, de doentes seguidos na consulta de Dermatovenerologia do CHUSJ com diagnóstico de cancro ou neoplasia intraepitelial do pénis, no período de 2012 a 2021.
Estão definidos os critérios de inclusão, bem como as variáveis a recolher. *Deverá esclarecer a necessidade de recolher o nome dos participantes (indicada no pedido à CE, e omissa no documento para o EPD).*

Benefício/risco: Não aplicável

Confidencialidade dos dados:
Codificação dos dados recolhidos.
Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: dezembro de 2022

Conclusão: Proponho um parecer favorável à realização do estudo, após o esclarecimento da questão assinalada.

Porto, 18 de novembro de 2022

O Relator da CE, Doutor Pedro Brito

Pedro Brito

29/12/2022

Não serão recolhidos o nome dos participantes, pelo que proponho a sua aprovação.
Pedro Brito

273-22

230000146

Questionário eletrónico

SÃO JOÃO

SUBMISSÃO DE PROJETO DE INVESTIGAÇÃO PARA PARECER E AUTORIZAÇÃO

SÃO JOÃO

AUTORIZADO
RA: Responsável pelo Centro de Formação e Investigação do Hospital de São João
(Art. 9º, Lei: 26/2016, de 22/8)

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

05/01/2023

Preenchimento em formato digital obrigatório

IDENTIFICAÇÃO DO ESTUDO

Título do projeto: Clinical and epidemologic relevance of HPV in Penile Cancer: a retrospective study

Data prevista para início: ____ / 10 / 2022 Data prevista para o término: ____ / 12 / 2022

EQUIPA DE INVESTIGAÇÃO

1. Investigador principal

Nome: Carmen Maria Lisboa

Contacto telefónico: 966346770 Endereço eletrónico: carmenlisboa.derma@gmail.com

Afiliação institucional: ☒ CHUSJ ☒ FMUP Outro: ____

Serviço/ Departamento: Serviço Dermatologia- CHUSJ, Departamento de Patologia- FMUP

Grupo profissional: Médica Assistente Graduada Hospitalar Cédula Profissional n.º: 32444

Formação em Boas Práticas Clínicas (GCP): ☐ Não ☒ Sim

2. Co-investigadores

Nome: Maria José Guimarães

Contacto telefónico: 936995501 Endereço eletrónico: mjcunhaguimaraes@gmail.com

Afiliação institucional: Hospital de Braga

Grupo profissional: Médica Interna de Formação Específica Cédula Profissional n.º: 61551

Nome: Ana Rita Macieira

Contacto telefónico: 915009888 Endereço eletrónico: macieirarita@gmail.com

Afiliação institucional: FMUP

Grupo profissional: Estudante Medicina, 6º ano Cédula Profissional n.º: ____

(acrescentar nº de investigadores, se apropriado ao projeto de investigação)

3. Promotor *(se aplicável)*: ____

CARACTERIZAÇÃO DA INVESTIGAÇÃO

1. Metodologia da investigação

☐ Qualitativa ☒ Mista (qualitativa+quantitativa) ☐ Outra. Qual? ____

Se quantitativa:

☐ Experimental ☒ Observacional ☐ Sem intervenção ☐ Com intervenção

Se experimental ou observacional com intervenção, qual o tipo de intervenção?

☐ Algoritmo de decisão diagnóstica/terapêutica ☐ Comunicação

☐ Outra. Qual? ____

SÃO JOÃO Gabinete de Apoio ao I&I 04 01 2023 A Funcionária

CES-IM007-1

CARACTERIZAÇÃO DA INVESTIGAÇÃO

2. Aleatorização dos braços de intervenção: ☐ Não ☐ Sim

3. Se observacional, qual o desenho?

☐ Coorte prospetivo ☐ Coorte retrospetivo ☐ Caso-controlo

☐ Transversal ☐ Ecológico ☒ Outro. Qual? Série de Casos

REALIZAÇÃO DA INVESTIGAÇÃO

Local onde se realiza a investigação: ☒ CHUSJ ☐ FMUP ☐ Outro

Serviço/ Departamento: Serviço de Dermatologia

Existem outros Centros onde se realizará a investigação? ☒ Não ☐ Sim. Quais? _____

ENTIDADE(S) QUE TUTELA(M) A INVESTIGAÇÃO

1. CHUSJ – Serviço: Dermatologia

2. FMUP – Departamento: Patologia

3. Outra instituição. Qual? _____

ORIENTADOR *(se aplicável)*

Nome: _____

Afiliação: _____ Endereço eletrónico: _____

PROFISSIONAL DE LIGAÇÃO *(se aplicável - ver anexo)*

Nome: _____ Serviço: _____

ENQUADRAMENTO DA INVESTIGAÇÃO

Em trabalho académico? ☒ Não ☐ Sim Conferidor de grau? ☒ Não ☐ Sim

Síntese dos objetivos:

Esclarecer o papel da infeção de HPV no cancro de pénis e possível prevenção por Vacinação

Fundamentação ética *(incluir informação sobre o estado da arte, ganhos em conhecimento/inovação, ponderação geral sobre benefícios/risco)*:

O cancro do pénis é uma doença maligna cuja incidência tem vindo a aumentar em vários países Europeus. Este estudo observacional retrospetivo prevê clarificar relação entre a infeção de HPV e o cancro do pénis e a sua importância clínica na prevenção, diagnóstico e tratamento.

PARTICIPANTES PREVISTOS PARA A INVESTIGAÇÃO

Doentes? ☐ Não ☐ Sim

Pessoas incapazes do exercício de autonomia? ☐ Não ☐ Sim

Pessoas menores de 18 anos? ☐ Não ☐ Sim. Justifique:

Voluntários saudáveis? ☐ Não ☐ Sim. Justifique:

PARTICIPANTES PREVISTOS PARA A INVESTIGAÇÃO

Estão definidos critérios de inclusão / de exclusão de doentes? ☐ Não ☐ Sim

Onde e como serão recrutados os participantes no estudo?

Qual é o tamanho amostral?

Está prevista a recolha de material biológico específico para a investigação?

☐ Não ☐ Sim. Identifique e justifique:

BENEFÍCIO/RISCO DE CORRENTE DA PARTICIPAÇÃO

Descreva os benefícios previsíveis:

Estudo que analisa a associação entre a infeção de HPV e Cancro do Pénis, que será útil no futuro, na avaliação do papel protetor da vacina do HPV neste cancro.

Descreva os riscos/incómodos previsíveis:

Sem riscos e incômodos previstos.

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

Prevê a obtenção de consentimento informado? ☐ Sim ☒ Não. Justifique:

Estudo observacional retrospetivo com dados anonimizados de doentes seguidos pela Investigadora Principal

Se sim, prevê informação escrita para os participantes?

☐ Não. Justifique:

☐ Sim (se sim, enviar documento de informação a utilizar na investigação)

O modelo para obtenção de consentimento é o modelo institucional do CHUSJ? ☐ Não ☐ Sim

PROTEÇÃO DE DADOS PESSOAIS

Necessita consultar registos clínicos? ☐ Não ☒ Sim

Está previsto o tratamento de dados pessoais? ☐ Não ☒ Sim

Se sim, de que forma é garantida a pseudonimização dos dados recolhidos? *(codificação, uso de filtros, siglas...)*

Uso de codificação

Descreva o património informacional a que pretende ter acesso *(v.g.: nome, idade, data nascimento, idade, morada, diagnóstico, história clínica, tratamento...)*:

Nome, idade, diagnóstico, idade ao diagnóstico, escolaridade, orientação sexual, hábitos etílicos e tabágicos, diagnóstico de doenças sexualmente transmissíveis, imunossupressão iatrogénica, diagnóstico de dermatoses inflamatórias crónicas genitais, história de fimos

Está prevista a criação de um Banco de Dados? ☐ Não ☒ Sim

Está previsto o registo de som ou de imagem dos participantes? ☒ Não ☐ Sim

O estudo envolve investigação genética? ☒ Não ☐ Sim

PROPRIEDADE INTELECTUAL

De quem será a propriedade intelectual da investigação e seus resultados?

☒ Investigador ☐ Promotor ☐ Serviço ☐ Todos

DIVULGAÇÃO DOS RESULTADOS

Está prevista a divulgação dos resultados da investigação? ☐ Não ☒ Sim

Se sim, estão definidos critérios de publicação? ☐ Não ☒ Sim. Quais? Publicação numa revista científica indexada

CONTRAPARTIDAS PARA OS PARTICIPANTES

Estão previstas contrapartidas para os participantes?	☒ Não	☐ Sim
Pela participação?	☒ Não	☐ Sim
Pelas deslocações?	☒ Não	☐ Sim
Pelas perdas salariais?	☒ Não	☐ Sim
Por outras perdas e/ou danos?	☒ Não	☐ Sim

EXAMES COMPLEMENTARES DE DIAGNÓSTICO

Estão previstos exames complementares de diagnóstico, para além dos inerentes à rotina assistencial?

☒ Não ☐ Sim. Quais? _____

Por quem serão suportados estes custos?

_____

PROTOCOLO FINANCEIRO

Existe protocolo financeiro com o CHUSJ? ☒ Não ☐ Sim *(se sim, enviar documento)*

SEGURO

Este estudo prevê intervenção clínica que implique a existência de um seguro para os participantes?

☒ Não ☐ Sim *(se sim, junte cópia da respetiva Apólice)*

Data previsível para fim das credenciais de acesso: - / 12 / 2022

DOCUMENTOS ANEXOS *(em suporte digital)*

- ☒ Protocolo do estudo
- ☐ Caderno de recolha de dados (CRF)
- ☒ Declaração Diretor(es) Serviço(s)
- ☐ Informação Orientador
- ☐ Profissional de ligação
- ☐ Informação aos participantes
- ☐ Modelo de consentimento a utilizar
- ☐ Instrumentos de avaliação *(escalas...)*
- ☒ Curriculum vitae *(investigador/es)*
- ☐ Questionário para Encarregado de Proteção de Dados (EPD)
- ☐ Termo de Responsabilidade do Centro Académico Clínico *(para investigadores da FMUP que não pertençam ao CHUSJ)*
- ☐ Protocolo financeiro
- ☐ Outros

TERMO DE RESPONSABILIDADE

Aceitação dos termos e condições de reutilização

Cumulativamente com as obrigações decorrentes da *Lei n.º 26/2016, de 22 de agosto*, maxime dos *n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12*, ao submeter o presente pedido, concordo e fico ainda juridicamente vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a Lei 26/2016, de 22 de agosto, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e à qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar e respeitar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, poderá resultar no apuramento de responsabilidades disciplinares, civis e penais, e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

- Independentemente de requerer a Certidão de Reutilização, DAta REuse Certificate for Research (DARE), comprometo-me a citar as fontes, sempre que publicitar, no todo ou em parte, resultados da presente investigação.

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Eu, Carmen Maria Lisboa ,

abaixo assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes na Declaração de Helsínquia (1960, e sucessivas emendas), e da Organização Mundial de Saúde, da Convenção de Oviedo e das 'Boas Práticas Clínicas' (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CE de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CE o relatório final da investigação, assim que concluído.

Data: 14 / 10 /2022 Lisboa

assinatura

18/11/2022

Aguarda esclarecimentos.

·Centro Hospitalar **São João**·

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A). A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

02/01/2023

SÃO JOÃO

ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE
Paulo Alexandre Mota da Silva
Encarregado de Proteção de Dados do CHUSJ
epd@chsj.min-saude.pt

Ref.ª CES CHUSJ: **273/ 2022**

Título do Projeto	Clinical and epidemiologic relevance of HPV in Penile Cancer: A retrospective study

Responsável pelo tratamento	Carmen Maria Lisboa Silva		
Instituição	Centro Hospitalar Universitário São João (CHUSJ)		
	Faculdade de Medicina da Universidade do Porto (FMUP)		
Investigador	**Interno**	Externo	
Contacto telefónico	966346770	Endereço Electrónico	u006081@chsj.min-saude.pt
Profissional de Ligação	Não aplicável		
Amostra	20-30		

Análise de Risco: Tolerável | **Baixo** | Elevado | Muito Elevado

Parecer do EPD: Data: 18/01/2023

Finalidade: esclarecer a relação entre infeção de HPV e cancro do pénis e clarificar o papel da vacinação como medida preventiva.

Licitude: fundamento previsto no artigo **9(2)(j)**, com as garantias do **89(1)** do **RGPD**, e artigo **31(1)** da **LERGPD**.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 09/01/2023, **ponto 13**, tendo presente o **princípio da minimização dos dados.**

Conservação: os dados serão alvo de **pseudonimização**, armazenados em **local seguro**, em área restrita com acesso limitado ao Investigador Principal, com acesso a ficheiros protegido por **palavra-passe**, efetuando-se a conservação até a conclusão da investigação, durante o prazo máximo de **seis (6) meses**. Os dados recolhidos **serão destruídos** após a finalização do estudo.

Comunicação de Dados: **não há partilha** de dados pessoais.

Face ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o **tratamento é realizado em conformidade com o RGPD.**

Recomendações:

1. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (Laptop), nomeadamente através de medidas de cifragem e autenticação;
2. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão: ___/___/_____ ☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 273/2022
2. Parecer CES (29/12/2022)
3. AIPD (09/01/2023)
4. Protocolo de Investigação

Encarregado de Proteção de Dados
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**
Data: 2023.01.18 11:04:03+00'00'
Localização: CHUSJ

CARTÃO DE CIDADÃO