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REVIEW ARTICLE

Penile carcinoma: what dermatologists need to know

Carcinoma do pénis: o que os dermatologistas devem saber

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Abstract

Penile cancer is a rare disease in developed countries and is frequently underrecognized by clinicians leading to delays in diagnosis and treatment. Squamous cell carcinoma (SCC) is the predominant pathological entity, representing 95% of all penile cancers. The most important risk factor for penile SCC is human papillomavirus (HPV) infection, with an estimated prevalence of 50%. Other major risk factors include phimosis, chronic inflammatory dermatosis, and poor genital hygiene. Two major pathophysiologic pathways have been proposed, one linked to HPV and another to chronic inflammation. Penile SCC usually presents as an erythematous area of induration or an ulcerating lesion, although changes can be more subtle in premalignant lesions [PeIN]. Confirmation of the diagnosis by biopsy and histopathological examination should be followed by staging. For localized diseases, namely PeIN, topical immunotherapy, chemotherapy, and epithelial ablative techniques are treatment options. For localized SCC, the mainstay of treatment is complete excision. Radiotherapy can be considered an organ-sparing alternative. The role of chemotherapy in penile SCC remains under discussion. The estimated 5-year overall survival is 66%, varying from 90% for T1N0M0 tumors to < 50% for patients with positive lymph nodes. Clarification of the role of HPV in premalignant lesions and penile SCC pathology has the potential to improve prevention and treatment regimens, namely through vaccination against HPV. Given its rarity and low levels of awareness by both patients and clinicians, penile SCC represents a diagnostic challenge. Prompt diagnosis is key to effective treatment since prognosis in the early stages is excellent.

Keywords: Penile Cancer. Penile carcinoma. Penile intraepithelial neoplasia. HPV.

Resumo

O carcinoma do pénis é raro em países desenvolvidos e frequentemente subestimado, levando a atrasos no diagnóstico e tratamento. O carcinoma espinocelular (CEC) é a entidade patológica predominante, representando 95% das neoplasias penianas. O fator de risco mais importante para o CEC peniano é a infeção pelo papilomavírus humano (HPV), com uma prevalência estimada de 50%. Outros fatores de risco incluem fimose, dermatose inflamatória crónica e má higiene genital. Foram propostas duas vias etiopatogénicas principais, uma ligada ao HPV e outra à inflamação crónica. Clinicamente, o CEC peniano surge como uma área eritematosa endurecida ou ulcerada, embora em lesões pré-malignas (PeIN) as alterações possam ser mais subtis. A confirmação do diagnóstico por biópsia e exame histopatológico deve ser seguida de estadiamento. A base do tratamento na doença localizada é a excisão cirúrgica completa e nas lesões pré-malignas a imunoterapia ou técnicas ablativas locais.A radioterapia pode ser considerada como uma alternativa poupadora de órgão. O papel da quimioterapia no CEC peniano

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permanece em discussão. A sobrevida global estimada aos 5 anos é de 66%, variando de 90% para tumores T1N0M0, a menos de 50% para doentes com metástases ganglionares. A clarificação do papel do HPV nas lesões pré-malignas e no CEC peniano tem potencial para melhorar os regimes de prevenção e tratamento, nomeadamente através da vacinação contra o HPV. Considerando a raridade e falta de consciencialização por doentes e médicos, o CEC peniano representa um desafio diagnóstico. O diagnóstico precoce é fundamental uma vez que o prognóstico é excelente em estadios iniciais.

Palavras-chave: Cancro do pénis. Carcinoma do pénis. Neoplasia intraepitelial do pénis. Infeção por HPV.

Introduction

Despite its rising incidence in most European countries over the last decade, penile cancer is still considered a rare disease[1]. It is frequently underrecognized by clinicians leading to delays in diagnosis and treatment[2,3]. Additional reasons for delaying diagnosis are attributed to patient factors, as usually, patients defer seeking medical advice due to mild symptoms, feelings of embarrassment, guilt, fear, denial, and lack of awareness[1,4]. It is estimated that 15 to 60% of patients postpone clinical observation for at least 1 year after the first signs of the disease[2]. This underlines the importance of consciousness regarding the condition, particularly for dermatologists and urologists most sought by the patient for these lesions. Prompt diagnosis is key for appropriate and early treatment, reducing the morbidity and mortality from penile cancer.

Squamous cell carcinoma (SCC) is the predominant pathological entity, representing 95% of all penile cancers. The estimated 5-year overall survival is 66%[5]. Delay in diagnosis impacts prognosis[1].

Epidemiology

Penile SCC had a global estimated burden of 36,068 cases in 2020[3]. Incidence rates have marked geographical variability[2,5,6]. Whereas the prevalence in developed countries is less than < 1/100,000, it can reach 10% of all cancers in men in low and middle-income regions, explained by many social, hygienic, and cultural factors[3,4,7]. In developed countries, namely in Europe, a rise in penile cancer incidence has been reported[7]. Penile SCC usually occurs in men aged between 50 and 70 years[1,8]. Nevertheless, it can also occur in younger patients, especially if associated with HPV[1,7].

Risk factors

The most important risk factor for penile cancer is HPV infection, especially by oncogenic subtypes, such as HPV 16 or 18 and eventually 31, 33, 45, 56, and 65[9]. HPV prevalence is estimated at around 50%[9], and the relative risk for penile cancer is approximately 4.5 higher in HPV-seropositive patients[10]. However, the impact of HPV infection on penile cancer diagnosis, prognosis and prevention still warrants further research.

Although genital warts are generally associated with infection with low-risk HPV types, premalignant and malignant lesions have been found within genital warts[11,12]. Genital warts can constitute risk markers for the development of other HPV infections, as they indicate high-risk sexual behaviors[10]. Thus, close follow-up of patients with sexually transmitted infections (STIs), namely anogenital warts, should be considered to assess the risk of developing malignant lesions.

Besides a history of STIs, other major risk factors for penile cancer include phimosis, chronic inflammatory dermatoses such as lichen sclerosus, poor genital hygiene, ultraviolet A phototherapy, obesity, smoking, immunosuppression, low socioeconomic status, and low educational level[13,14].

Basically, two major pathogenic pathways have been proposed, one linked to HPV and another linked to chronic inflammation[1,6]. Based on this, the 2022 World Health Organization classification recommends the subdivision of penile SCC into HPV-dependent and HPV-independent types[15]. This classification recognizes an association between histological variants and HPV: basaloid, papillary-basaloid, warty, warty-basaloid, clear cell and lymphoepithelioma-like carcinomas are considered HPV related; common type, carcinoma cuniculatum, verrucous, papillary, pseudohyperplastic, pdeudoglandular, adenosquamous and sarcomatoid carcinomas are considered HPV-independent[5,15,16]. However, diagnosis based solely on morphological criteria may be misleading in a small proportion of tumors, and HPV deoxyribonucleic acid (DNA) testing and/or p16 immunostaining is required to classify SCC as HPV-associated or HPV-independent[5] properly. The expression of p16 is correlated with the integration of HPV's viral genome into the intracellular host genome[17]. Therefore, currently, p16 expression found in penile intraepithelial neoplasia (PeIN) or invasive SCC is considered a surrogate marker for high-risk HPV infection[17,18]. Additionally, the role of p16 as a prognostic marker is currently under investigation, as some works have shown that men with HPV or p16-positive penile cancer have a survival advantage[17,18].

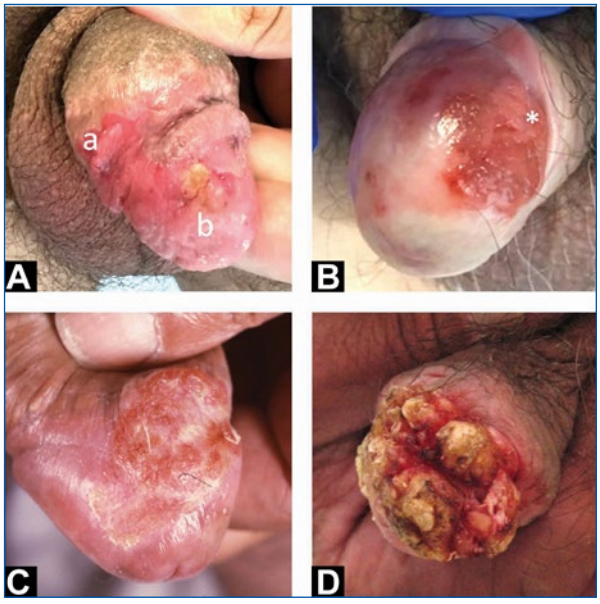

Figure 1. A: erythematous infiltrated plaque corresponding to PeIN 2 (a) and invasive SCC (b); **B:** erythroplasia of Queyrat (SCC *in situ*) with an area (*) of invasive SCC; **C:** area of induration in a patient with lichen sclerosus, corresponding to invasive SCC; **D:** invasive SCC manifested by a verrucous exophytic lesion distorting normal anatomy of glans and prepuce. PeIN2: penile intraepithelial neoplasia grade 2; SCC: squamous cell carcinoma.

Precursor lesions and HPV

Penile intraepithelial neoplasia (PeIN), a precursor lesion for penile cancer, is usually classified according to the degree of dysplasia, namely PeIN I if mild dysplasia is present, PeIN II in moderate dysplasia and PeIN III when dysplasia is severe or carcinoma *in situ*[19]. Like SCC, PeIN can also be classified as HPV-related or non-related[15]. Although these lesions are clinically similar, the association with HPV can be relevant as it could potentially guide treatment and enhance follow-up strategies. The pooled HPV DNA prevalence in PeIN was 79.8%[19], higher than its prevalence in invasive SCC, suggesting that HPV infection may be associated with a less aggressive evolution and with a more predictable carcinogenic path[20].

Clinical aspects

Around > 50% of penile SCC arises in the glans, followed by the prepuce, both glans and prepuce, coronal sulcus and the shaft[2]. Clinical presentation can vary, but SCC usually manifests as an erythematous area of induration or an ulcerating infiltrative lesion (Fig. 1)[16]. In premalignant lesions, changes can be more subtle, such as an erythematous patch with variable degrees of infiltration (Fig. 2)[16]. Bowenoid papulosis, Bowen's disease and erythroplasia of Queyrat are three clinically recognized manifestations of carcinoma *in situ*[21]. The former is characterized by multiple red-brown papules, sometimes coalescing into a plaque. Bowen's disease presents as a pink plate with white scales, and erythroplasia of Queyrat manifests as an eroded erythematous plaque with well-demarcated borders usually arising in the glans or prepuce[21]. Early suspicion and biopsy are necessary to prevent delays in diagnosis and treatment[1]. This is particularly relevant in patients with chronic genital dermatosis, like lichen sclerosus. Faced with a persistent suspicious lesion, particularly one with little or no response to corticosteroids, one should have a low threshold to perform a biopsy[16].

Diagnosis and staging

Confirmation of the diagnosis by biopsy of the suspected lesion and histopathological examination should be followed by staging[1]. Penile SCC should preferably be staged according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) eighth edition tumor, nodes, and metastases classification (Table 1).

Physical examination should include inguinal LN palpation[16]. In obese patients, the limitations of clinical evaluation can be overcome through ultrasound examination of inguinal LN[6]. When enlarged, LN is detected on physical examination; LN metastases can be diagnosed by percutaneous fine-needle aspiration cytology[4].

In clinically unremarkable inguinal LNs, management is particularly challenging because, in up to 25% of cases, inguinal lymphatic micrometastases are present[1,6]. In these cases, a dynamic sentinel node biopsy (DSNB) is recommended in intermediate (T1G2) or high-risk (T1G3 or worse) disease[4]. The sensitivity of DSNB is approximately 90-95% for micrometastases detection, with low associated morbidity[6]. In centers where DSNB is not available, modified inguinal lymphadenectomy is a safe and appropriate alternative[6,22].

When positive LN is detected, staging for systemic metastases is recommended through computed tomography of the thorax, abdomen, and pelvis[16]. A positron emission tomography scan is an acceptable alternative with high sensitivity and specificity in the detection of

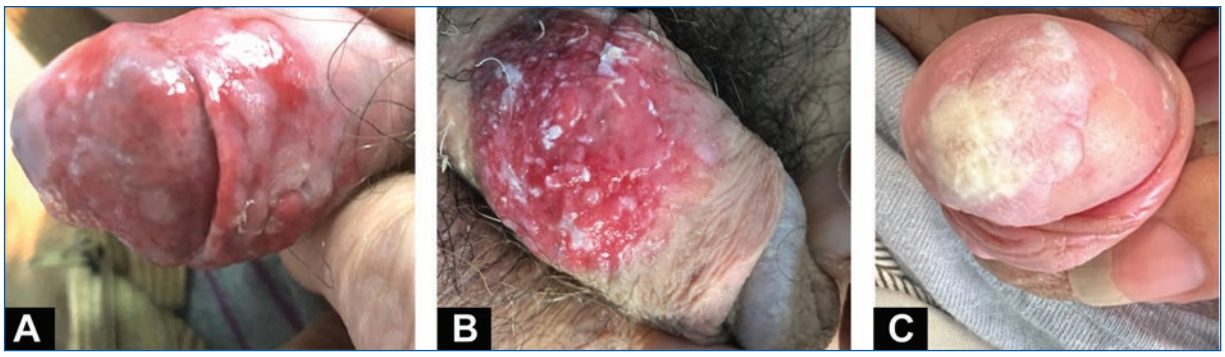

Figure 2. A: erythematous patch corresponding to SCC *in situ* (Erythroplasia of Queyrat); **B:** SCC *in situ* on penile shaft; **C:** verrucous whitish patch on glans corresponding to SCC *in situ*. SCC: squamous cell carcinoma.

distant metastases; however, limited spatial resolution reduces its acuity for small metastases. Additionally, false positives may occur due to inflammation[23].

Treatment

Given the lack of randomized controlled trials, multidisciplinary care in experienced centers is crucial for improving outcomes[16].

Previously, the mainstay of treatment in localized disease was excision with wide margins (2 cm)[1]. However, current recommendations allow narrow tumor margins as long as complete excision is achieved[1]. For carcinoma *in situ*, topical immunotherapy or chemotherapy (imiquimod applied once daily or on alternate days, 5-fluorouracil applied on alternate days for 6 weeks[24]), as well as epithelial ablative techniques (cryosurgery, CO_2 laser, neodymium-doped yttrium aluminum garnet laser or photodynamic therapy) are treatment options[1]. For low and intermediate-grade T1 lesions, circumcision, wide local excision or partial glansectomy are recommended[16]. However, high-grade T1 or T2-T3 disease requires more extensive surgical interventions, with partial or total penectomy[1,16]. Mohs surgery could play a role in smaller lower-grade tumors, achieving a superior esthetic and functional result[1,25]. Its use in larger, stage II or above tumors should be discouraged since these cases are not suitable for penile-sparing therapy[25].

Squamous cell carcinomas (SCCs) are generally radiosensitive tumors[1]. Thus, radiotherapy, particularly brachytherapy, can be considered an organ-sparing alternative[16]. This modality is reserved as the initial treatment for invasive T1 and T2 cancers. Despite local recurrence rates ranging to 20% after 5–10 years, secondary control could be achieved by salvage surgery in 85% of cases[4]. Radiotherapy is also advocated as an adjuvant treatment to the inguinal lymphatic area when histopathological examination reveals more than one metastatic LN or extranodal extension[4].

The role of chemotherapy in penile SCC remains under discussion, as most available evidence comes from small prospective or retrospective studies[4]. Further high-quality prospective studies are required. Cisplatin has been the cornerstone of the combination regimens used[4]. Neoadjuvant chemotherapy (NC) is recommended in patients with fixed or bulky inguinal LN, bilateral LN involvement, or pelvic node involvement[16]. Similarly, adjuvant chemotherapy is advocated for patients that had not received NC in pN2-pN3 disease[4,16].

Palliative therapy is the standard of care in patients with unresectable locally advanced or metastatic disease[16]. Studies show that palliative chemotherapy can achieve limited survival benefits[1].

Prognosis

The overall 5-year survival rates are above 90% for pT1 tumors, decreasing to 55% for pT3 and under 50% for patients with positive LN pN1-N3[1]. Patients with metastatic disease have a poor prognosis, with a median overall survival of 7–8 months[16]. Around > 90% of recurrences occur in the first 5 years, so patients should be carefully followed in this period, with follow-up visits every 3 months in the first 2 years and every 6 months in the remaining 3 years[4]. The recommended follow-up depends on nodal involvement, varying from physical examination alone to regular imaging, such as CT, MRI or ultrasound with fine needle cytology[1].

Table 1. AJCC/UICC 8th edition for clinical and pathological staging

Primary tumor (T)	
T-category	T criteria
Tx	Primary tumors cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma *in situ* (PeIN)
Ta	Noninvasive localized SCC
T1	Glans: tumour invades lamina propria Foreskin: Tumor invades dermis, lamina própria or dartos fáscia Shaft: Tumor invades connective tissue between epidermis and corpora
T1a	Without lymphovascular or perineural invasion and is not high grade (G3 or sarcomatoid)
T1b	With lymphovascular and/or perineural invasion or is high grade (G3 or sarcomatoid)
T2	Tumour invades corpus spongiosum with or without urethral invasion
T3	Tumour invades corpus cavernosum with or without urethral invasion
T4	Tumour invades adjacent structures (scrotum, prostate, pubic bone)
Regional nodes (N)	
Clinical N category	Clinical N criteria
cNx	Regional LNs cannot be assessed
cN0	No palpable or visibly enlarged inguinal LNs
cN1	Palpable mobile unilateral inguinal LN
cN2	Palpable mobile ≥ 2 unilateral inguinal LN or bilateral
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
Pathological N	Pathological N criteria
pNx	LN metastasis cannot be established
pN0	No LN metastasis
pN1	≤ 2 unilateral inguinal metastases, no extranodal extension
pN2	≥ 3 unilateral inguinal metastases or bilateral metastases, no extranodal extension
pN3	Extranodal extension of LN metastases or pelvic LN metastases
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis present
Histopathological grading (G)	
Gx	The grade of differentiation cannot be assessed
G1	Well-differentiated
G2	Moderately differentiated
G3	Poorly differentiated/high grade

AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control; T: primary tumor; SCC: squamous cell carcinoma; N: regional nodes; M: distant metastasis; G: histopathological grade of differentiation.

Future perspectives

The protective effect of HPV vaccination against cervical cancer is reported in various studies; however, in penile cancer, its impact is inconsistently described[26–28]. Vaccination in males is recommended by several international scientific societies and is now being implemented in many countries, including Portugal[29,30]. The impact of this preventive measure is promising and expected to be clarified in the next few years[31].

To improve early diagnosis, identify therapeutic targets and support prognosis evaluation; recent research has identified several tissue and serum biomarkers. Nevertheless, significant gaps still exist in understanding the potential clinical implications of each biomarker[8].

Several novel therapies are under investigation for the treatment of advanced-stage disease[16]. Phase II studies, including targeted therapies (e.g., EGFR inhibitors and immune checkpoint inhibitors), are ongoing with promising preliminary results[16]. A basic understanding of penile SCC at a molecular level holds promise in developing novel therapeutic approaches[16].

Conclusion

Given its rarity and low levels of awareness by both patients and clinicians, penile SCC represents a diagnostic challenge. Prompt SCC diagnosis is critical for effective treatment since prognosis in the early stages is excellent. Furthermore, clarification of the role of HPV in premalignant lesions and penile SCC pathology has the potential to improve prevention and treatment regimens.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Hakenberg OW, Compérat E, Minhas S, Necchi A, Protzel C, Watkin N, et al. EAU Guidelines on Penile Cancer. In: Edn presented at the EAU Annual Congress Amsterdam 2022. Arnhem: EAU Guidelines Office; 2022.
2. Li K, Le X, Wang J, Fan C, Sun J. Tumor location may independently predict survival in patients with M0 squamous cell Carcinoma of the Penis. Front Oncol. 2022;12:927088.
3. Yu YB, Wang YH, Yang XC, Zhao Y, Wang ML, Liang Y, et al. The relationship between human papillomavirus and penile cancer over the past decade: a systematic review and meta-analysis. Asian J Androl. 2019;21(4):375-80.
4. van Poppel H, Watkin NA, Osanto S, Moonen L, Horwich A, Kataja V. Penile cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013;24:vi115-24.
5. Manzotti C, Chulo L, López del Campo R, Trias I, del Pino M, Saúde O, et al. Penile squamous cell carcinomas in Sub-Saharan Africa and Europe: differential etiopathogenesis. Cancers (Basel). 2022;14:5284.
6. Hakenberg OW, Dräger DL, Erbersdobler A, Naumann CM, Jünemann KP, Protzel C. Diagnostik und therapie des Peniskarzinoms. Deutsches Arzteblatt Int. 2018;115:646-52.
7. Fu L, Tian T, Yao K, Chen XF, Luo G, Gao Y, et al. Global pattern and trends in penile cancer incidence: population-based study. JMIR Public Health Surveill. 2022;8:e34874.
8. Pekarek L, Ortega MA, Fraile-Martinez O, García-Montero C, Casanova C, Saez MA, et al. Clinical and novel biomarkers in penile carcinoma: a prospective review. J Pers Med. 2022;12:1364.
9. Olesen TB, Sand FL, Rasmussen CL, Albieri V, Toft BG, Norrild B, 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;20:145-58.
10. 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;49:368-76.
11. Pennycook KB, McCready TA. Condyloma Acuminata. Stat Pearls Publishing, Treasure Island (FL). 2022.
12. Cerejeira A, Cunha S, Coelho R, Macedo G, Barkoudah E, Azevedo F, 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;34:2613-9.
13. Vieira CB, Feitoza L, Pinho J, Teixeira-Júnior A, Lages J, Calixto J, et al. Profile of patients with penile cancer in the region with the highest worldwide incidence. Sci Rep. 2020;10:2965.
14. Skeppner E, Andersson SO, Johansson JE, Windahl T. Initial symptoms and delay in patients with penile carcinoma. Scand J UrolNephrol. 2012;46:319-25.
15. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs—part a: renal, penile, and testicular tumours. Eur Urol. 2022;82:458-68.
16. Stecca CE, Alt M, Jiang DM, Chung P, Crook JM, Kulkarni GS, et al. Recent advances in the management of penile cancer: a contemporary review of the literature. Oncol Ther. 2021;9:21-39.
17. Sand FL, Rasmussen CL, Frederiksen MH, Andersen KK, Kjaer SK. Prognostic significance of HPV and p16 status in men diagnosed with penile cancer: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2018;27:1123-32.
18. Djajadiningrat RS, Jordanova ES, Kroon BK, van Werkhoven E, de Jong J, Pronk DTM, et al. Human Papillomavirus prevalence in invasive penile cancer and association with clinical outcome. J Urol. 2015;193:526-31.
19. Hoekstra RJ, Trip EJ, Kate FJ, Horenblas S, Lock MT. Penile intraepithelial neoplasia: nomenclature, incidence and progression to malignancy in the Netherlands. Int JUrol. 2019 Mar 3;26(3):353-7.
20. Lont AP, Kroon BK, Horenblas S, Gallee MPW, Berkhof J, Meijer CJLM, et al. Presence of high-risk human papillomavirus DNA in penile carcinoma predicts favorable outcome in survival. Int J Cancer. 2006;119:1078-81.
21. Soyer HP, Rigel DS, McMeniman E. 108 Actinic Keratosis, Basal Cell Carcinoma, and Squamous Cell Carcinoma. In: Bolognia J, Schaffer J, Cerroni L, editors. Dermatology. 4th ed.Philadelphia: Elsevier Saunders; 2017. p. 1872-92.
22. Nerli RB, Sharma M, Patel P, Ghagane SC, Patil SD, Gupta P, et al. Modified inguinal lymph node dissection in groin-negative patients of penile cancer: our experience. Indian J Surg Oncol. 2021;12:229-34.
23. Ottenhof SR, Vegt E. The role of PET/CT imaging in penile cancer. Transl AndrolUrol. 2017;6:833-8.
24. Hegarty PK, Shabbir M, Hughes B, Minhas S, Perry M, Watkin N, et al. Penile preserving surgery and surgical strategies to maximize penile form and function in penile cancer: recommendations from the United Kingdom experience. World J Urol 2009;27:179-87.
25. Marchionne E, Hui A, Perez C, Khachemoune A. Penile squamous cell carcinoma: a review of the literature and case report treated with Mohs micrographic surgery. An Bras Dermatol. 2017;92:95-9.
26. Mix JM, van Dyne EA, Saraiya M, Hallowell BD, Thomas CC. Assessing impact of HPV vaccination on cervical cancer incidence among women aged 15–29 years in the United States, 1999-2017: an ecologic study. Cancer Epidemiol BiomarkersPrev. 2021;30:30-7.
27. Medeiros R, Vaz S, Rebelo T, Figueiredo-Dias M. Prevention of human papillomavirus infection. Beyond cervical cancer: a brief Review. Acta Med Port. 2020;33:198-201.
28. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68:698-702.
29. Colzani E, Johansen K, Johnson H, Pastore Celentano L. Human papillomavirus vaccination in the European Union/European Economic Area and globally: a moral dilemma. Eurosurveillance. 2021;26:2001659.
30. Bleeker MCG, Heideman DAM, Snijders PJF, Horenblas S, Dillner J, Meijer CJLM. Penile cancer: epidemiology, pathogenesis and prevention. World J Urol. 2009;27:141-50.
31. Oliveira-Costa JP, da Silveira GG, Soave DF, Castilho-Fernandes A, Roberto Oliveira L, Ribeiro-Silva A, 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. InTech; 2013.