






Review

Penile Cancer—A Preventable Cause of Death in Elderly Men

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Abstract

Penile cancer (PeCa) is a rare but preventable malignancy that predominantly affects elderly men. Incidence is rising in high-income countries, and mortality is particularly high in those aged 75 years and older. The major, synergistic risk factors are male genital lichen sclerosus (MGLSc) and persistent infection with high-risk human papillomavirus (HPV). This narrative review examines the peer-reviewed evidence on PeCa's epidemiology, aetiopathogenesis, diagnosis, management, and prevention, with a focus on MGLSc and high-risk HPV, and their implications for disease in older men. Priority was given to high-impact studies, and recent advances relevant to clinical practice. PeCa develops via two principal pathways: an HPV-dependent route, typically leading to undifferentiated penile intraepithelial neoplasia (uPeIN) and related squamous cell carcinoma (SCC) subtypes; and an HPV-independent route, driven by chronic inflammation and scarring from MGLSc, leading to differentiated PeIN (dPeIN) and SCC. Additional modifiable risk factors include phimosis, smoking, and poor genital hygiene. Diagnosis relies on careful clinical examination, dermatoscopy, and histopathology. Management ranges from topical therapy and circumcision to organ-sparing surgery, lymphadenectomy, systemic chemotherapy, and emerging immunotherapies. Prognosis is closely related to lymph node involvement. Preventive strategies, particularly early diagnosis and treatment of MGLSc and PeIN, HPV vaccination, circumcision, and smoking cessation, could substantially reduce disease burden. PeCa remains an under-recognised malignancy in older men despite being largely preventable. Improved public awareness, timely diagnosis of precursor conditions, and broader uptake of preventive interventions are essential to reverse current trends in incidence and mortality.

Keywords: skin cancer; penile cancer; dermatology

1. Introduction

Penile cancer (PeCa) is a rare but increasingly important malignancy, particularly in older men. One-third of new UK cases occur in men aged 75 or older, with incidence and mortality rising with age [1]. Global incidence varies, with rates of up to 10% of all male malignancies in low-income countries [2]. Although rare, PeCa is associated with poor outcomes, and its public health burden is growing [3].

This review aims to provide an up-to-date synthesis of the literature on PeCa, highlighting evolving insights into its importance in the elderly and its aetiopathogenesis, particularly focusing on the roles of male genital lichen sclerosus (MGLSc) and human papillomavirus (HPV). We also discuss diagnosis, histology, treatment, and public health strategies to better inform clinical practice and prevention efforts [4,5].

2. Epidemiology and Public Health Impact

In high-income countries, PeCa is rare (0.1–1/100,000 men). However, it contributes substantially to morbidity and mortality among older men. In the UK, 42% of PeCa-

related deaths occur in men aged 75+, and incidence is projected to rise by 20% in the next 15 years [1]. The condition is more prevalent in low-resource settings, indicating a role for socioeconomic factors [2].

The public health burden of PeCa is especially significant in low- and middle-income countries, where it can account for up to 10% of all male malignancies. Contributing factors include poor genital hygiene, limited access to healthcare, lower circumcision rates, and a lack of HPV vaccination programmes. Preventive strategies such as public education, early diagnosis of premalignant conditions, improved hygiene, and wider implementation of gender-neutral HPV vaccination could markedly reduce disease burden in these settings. International public health policies should prioritise these interventions to help mitigate global disparities in PeCa incidence and outcomes [6].

3. Risk Factors

Key risk factors for PeCa include:

- Uncircumcised state: Data from a meta-analysis showed that childhood/adolescent circumcision reduces invasive PeCa risk (odds ratio [OR] = 0.33). Data from a sys-



tematic review and meta-analysis pooling results from multiple observational studies showed that childhood or adolescent circumcision reduces the risk of invasive PeCa (OR = 0.33) [7]. However, the included studies varied in design and quality, and most were retrospective, which may limit the strength of the conclusions. Circumcision mitigates key contributory mechanisms by resolving chronic inflammation, improving genital hygiene, and creating a local environment less conducive to persistent HPV infection [8,9].

- **Increasing age:** Most men diagnosed with penile cancer are older than 50. In the UK between 2017 and 2019, on average each year, around a third of new cases (32%) were in males aged 75 and over. Only 3% of cases occur in men under 40 [1].

- **Smoking:** Carcinogens excreted in the urine may contribute to penile carcinogenesis by becoming trapped under the foreskin in uncircumcised men—paralleling similar mechanisms proposed in bladder cancer pathogenesis [8,10,11].

- **HPV infection:** High-risk (HR) HPV, particularly types 16 and 18, is implicated in approximately 60% of PeCa cases [1]. These viral types integrate into host DNA, disrupt tumour suppressor pathways and drive the formation of undifferentiated penile intraepithelial neoplasia (uPeIN) [12], which serves as the precursor to HPV-related PeCa.

- **Human immunodeficiency virus (HIV):** Individuals living with HIV have a significantly elevated risk of developing PeCa, with relative risks reported between 3.7 and 5.8 [13]. This is thought to be driven by a higher prevalence and persistence of high-risk HPV infections, as well as a tendency for faster progression from PeIN to invasive carcinoma [14]. HIV-positive individuals also face worse outcomes, including a markedly increased risk of PeCa-related mortality [15].

- **MGLSc:** Chronic occlusion and prolonged contact with urine lead to persistent epithelial irritation, triggering local inflammation, fibrosis, and eventual sclerosis of the genital skin. This pathogenic process underpins the development of male genital lichen sclerosus (MGLSc), which not only causes significant structural and functional morbidity but is also strongly associated with the development of HPV-independent differentiated penile intraepithelial neoplasia (dPeIN) and invasive PeCa [16].

In practice, many patients have several pathogenic factors contributing to the ‘perfect storm’ of penis cancer. The highest risks are observed in old age and in uncircumcised individuals with MGLSc who are immunosuppressed, such as patients with human immunodeficiency virus (HIV) or organ transplant recipients [9,17].

4. HPV and Vaccination

HPV infection has been implicated in numerous cancers, including cervical cancer (90% of cervical tumour cells contain HPV DNA), oropharyngeal malignancies

(68% of tonsillar tumour cells contain HPV DNA), anal squamous cell carcinoma (SCC), and PeCa [12,18,19]. HPV is also a major driver of PeCa, particularly uPeIN and the basaloid, warty, and warty-basaloid subtypes of penile squamous cell carcinoma (PeSCC) [20,21].

The UK HPV vaccination program began in 2008 for girls aged 12–13, with the primary aim of preventing cervical cancer. By mid-2020, the program in England had prevented an estimated 687 cases of cervical cancer (an 83.9% reduction) and 23,192 cases of cervical intraepithelial neoplasia (CIN)—a 94.3% reduction [22]. In 2018, the program was expanded to include men who have sex with men aged 45 or younger, and in 2019, this was then expanded further to include prepubescent boys, establishing a gender-neutral approach. This shift reflects growing recognition of HPV’s role in a range of malignancies beyond cervical cancer, including oropharyngeal, anal, and penile squamous cell carcinomas. The United States was the first country to adopt a gender-neutral routine HPV immunisation policy in 2011 and has observed a decrease in the rate of genital warts in 16- to 26-year-old males from 3.6% to 2.9% [23]. The impact of HPV vaccination on PeSCC rates has not yet been formally evaluated; however, its established efficacy in preventing high-risk HPV infection suggests a likely benefit in reducing HPV-associated penile neoplasia.

There is also emerging evidence that post-exposure HPV vaccination could offer a safe and low-cost therapeutic benefit in HPV-driven disease. A 2022 meta-analysis identified eleven studies involving 21,472 patients addressing the efficacy of adjuvant HPV vaccination in patients treated for HPV-related disease. Adjuvant HPV vaccination was associated with a reduced risk of CIN recurrence (pooled OR: 0.28–0.45, CIN 1–3, $p \leq 0.001$), although there was limited data regarding its role in other HPV-related diseases [24]. Such use is not currently endorsed by clinical guidelines in the context of PeIN or PeCa. Nevertheless, in our clinical practice, we recommend HPV vaccination for all patients with HPV-associated PeIN and PeSCC. The ESMO–EURACAN (European Society for Medical Oncology–European Reference Network for Rare Adult Solid Cancers) Penis Cancer Clinical Practice Guidelines suggest that for high-risk unvaccinated individuals, it is an option that can be discussed; however, its efficacy requires further validation [25].

5. Male Genital Lichen Sclerosus

MGLSc is a chronic, inflammatory and sclerosing dermatosis that creates sexual and urological morbidity. MGLSc is thought to result from microincontinence and the exposure of a susceptible epithelium to the irritant effects of chronically occluded urine under the prepuce [26,27]. It is the principal cause of phimosis, not only in adults but also in children [16,28].

The age-related incidence of MGLSc is triphasic, with one peak occurring in infancy and two additional peaks at

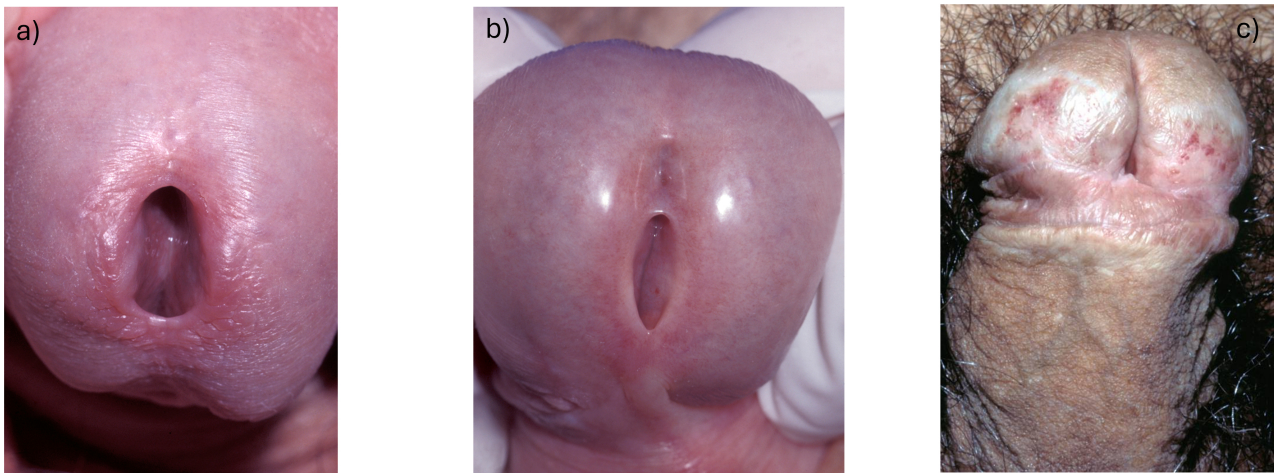


Fig. 1. Examples of a dysfunctional navicular fossa and valve, which may lead to urinary microincontinence. (a) Deep pitted Navicular fossa. (b) Embryogenic *forme fruste* of hypospadias. (c) Hypospadias associated with lichen sclerosus.

the end of the third and sixth decades of life [29]. Poorly controlled MGLSc is a significant risk factor for HPV-independent, dPeIN and PeSCC [9]. This risk likely increases synergistically in the presence of HR HPV infection [12].

5.1 Occlusion and MGLSc

Patients with MGLSc are frequently observed to possess architectural abnormalities of the meatus or navicular fossa, ranging from *forme fruste* to frank hypospadias, that facilitate urine microdribbling (Fig. 1). The distribution of MGLSc is typically localised to areas of direct urine occlusion. The proximal aspect of the prepuce usually exhibits the most advanced changes due to maximal contact with occluded urine [27].

MGLSc can also develop following urological instrumentation or trauma, such as genital piercing, which may damage the naviculomeatal valve and result in microincontinence [30]. In circumcised individuals, obesity can lead to the formation of a buried penis and pseudoforeskin, creating a new potential for urinary occlusion and triggering MGLSc [31].

Although a genetic predisposition to the irritant effects of urine has been proposed, no conclusive findings have been reported. Furthermore, nuclear magnetic resonance spectroscopy studies have not identified an altered urinary constituent profile in individuals with MGLSc compared to unaffected individuals [32]. We have shown that the balanopreputal sac and urine in MGLSc patients exhibit a distinct bacterial microbiome, suggesting a strong association with dysbiosis in its aetiopathogenesis [33].

5.2 Symptoms and Signs of MGLSc

MGLSc can be asymptomatic. However, it may also present with itching, soreness, bleeding, splitting, or tightness of the foreskin spontaneously or with sexual activity

(dyspareunia). There may also be a history of secondary infection with *Candida* species or bacterial pathogens, which can exacerbate inflammation and contribute to diagnostic confusion.

The clinical signs are diverse and include lichenoid inflammation, waxy pallor (pre-sclerotic changes) of the prepuce, sclerosis of the glans and frenulum, effacement of the coronal sulcus and frenulum, foreskin tears, adhesions, etiolation (a dull, greyish, washed-out appearance of the glans), purpura, ecchymoses, and angiokeratomas (Fig. 2). A constrictive posthitis, also referred to as “waisting” or “hourglass penis”, may result from a circumferential sclerotic band on the prepuce. If not addressed, this can lead to progressive tightening and ultimately phimosis. Hyperpigmented macules are frequently observed and may occasionally develop years after successful treatment of MGLSc. Careful dermatoscopic examination of these is essential to exclude in situ or invasive melanoma [34,35]. The loss of pearly penile papules can also occur [16], as can urethral stenosis [34]. Zoonoid inflammation, characterised by bright red, shiny macular erythema, is a well-documented but often underrecognized feature of MGLSc. It is a component of MGLSc rather than a distinct diagnosis [36]. In some cases, the Zoonoid component may be more pronounced than other features, potentially diverting the clinician’s attention from the underlying diagnosis (Fig. 3).

Pseudoepitheliomatous keratotic and micaceous balanitis (PEKMB) is a clinicopathological syndrome that typically presents in middle-aged men and represents a rare manifestation of chronic, undiagnosed or misdiagnosed, inadequately treated and unstable MGLSc. Clinically, it is characterised by thin or thick, micaceous scales on the glans and poses a significant risk of progression to multifocal PeIN and penile SCC [37,38].

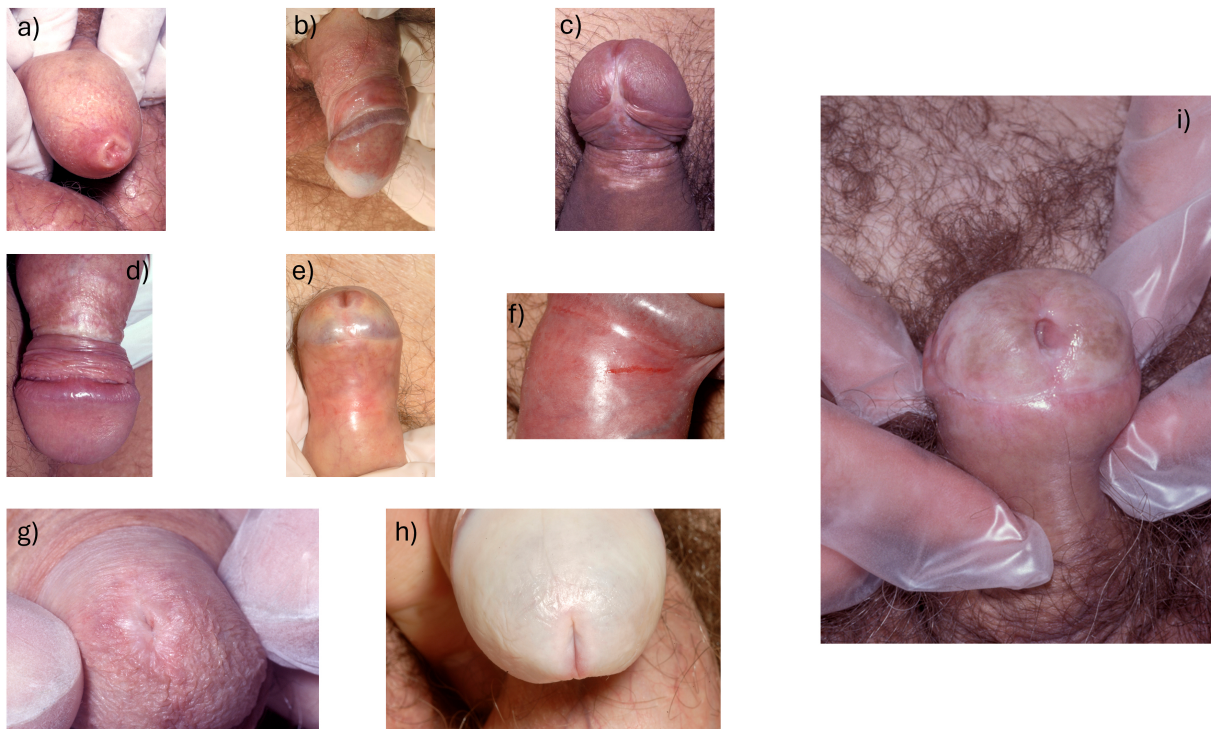


Fig. 2. Clinical features of male genital lichen sclerosus. (a) Phimosis. (b) 'Zoonoid' inflammation. (c) Frenulum disease. (d) 'Constrictive posthitis'. (e) 'Effacement' and loss of pearly penile papules of the coronal sulcus. (f) Splits in skin. (g) Urinary meatal stenosis. (h) 'Etioiation' (pallor) of the glans. (i) Coronal adhesions and benign penile melanosis of the glans.



Fig. 3. Lichen sclerosus with zoonoid balanoposthitis.

5.3 Management of MGLSc

Topical corticosteroids (TCS) and barrier preparations are first-line treatments for MGLSc. Ultrapotent TCS (e.g., clobetasol propionate 0.05%) is typically used daily for 1–2 months to quench inflammation. Additionally, soap substitutes help limit external irritation caused by detergents,

and barrier preparations reduce contact with urine. Herpes simplex virus (HSV) or HPV reactivation is rare but should be discussed. If symptoms persist, moderate-potency TCS, such as clobetasone butyrate 0.05%, can be used intermittently [16,39].

Circumcision is advised in refractory cases, phimosis, or when there is significant anatomical distortion.

Complete removal of the foreskin is preferred over preputioplasty or partial circumcision, as these procedures may temporarily relieve symptoms, but fail to address the underlying pathogenesis of MGLSc [16].

Weight loss should be recommended in obese patients with a buried penis as part of a multidisciplinary approach that may include medical or surgical interventions [31].

With appropriate management, most cases resolve with topical therapy [34], though up to half may require circumcision [16].

5.4 Melanoma and MGLSc

Primary penile malignant melanoma (PeMM) is an exceedingly rare malignancy. However, recent evidence suggests a notable association between PeMM and MGLSc [40]. In a 2023 retrospective study, we reported that approximately 80% (n = 11) of PeMM cases over an 11-year period occurred in the context of concurrent MGLSc [41]. Similarly, a separate retrospective analysis found vulval lichen sclerosus in 64% of patients diagnosed with vulval melanoma (n = 11) [42]. A Finnish group identified that three of nine patients with vulvar melanoma were also diagnosed with lichen sclerosus (LS) [43].

These findings point toward a potential pathogenic link, with chronic melanocytic distress proposed as a unifying mechanism.

6. Penile Intraepithelial Neoplasia

PeIN is the precursor lesion to invasive PeSCC, characterised by dysplastic squamous epithelium with an intact basement membrane. It can be classified histologically into:

- uPeIN: Associated with HR HPV infection, p16^{INK4a}-positive, accounts for approximately 85% of PeIN.
- dPeIN: Not HPV-driven, associated with MGLSc [21,25].

Transformation rates to invasive SCC vary widely between studies from 2.6% to 30% [21,44].

6.1 Clinical Variants of PeIN

Clinical variants include Erythroplasia of Queyrat (EQ) (red, shiny plaque on moist epithelium, such as the uncircumcised prepuce and glans), Bowen's disease of the penis (BDP) (scaly plaques on keratinised epithelium, including the circumcised glans), and bowenoid papulosis (BP) (warty, pigmented, flat-topped papules, often in groups) (Fig. 4).

EQ is usually encountered in elderly men and carries the highest risk of progression to PSCC (approximately 30%). BP predominantly affects younger men, is always associated with HPV infection, and has a very low risk of transformation to PeSCC [17,21].

Lesions may be multifocal or paucifocal and may affect any part of the penis, including the inner and outer prepuce, glans, and shaft.

Histopathology and Immunohistochemistry (IHC) (p16, p53, Ki-67) confirm diagnosis and subtype. Dermatoscopy supports diagnosis and biopsy site selection. Although both dPeIN and uPeIN can present with a predominant pattern of dotted/coiled vessels—white lines, hyperkeratosis, and yellow structureless areas are specific to dPeIN [45].

6.2 Management of PeIN

Management of PeIN treatment depends on severity, location, and subtype. Topical therapies (5-Fluorouracil [5-FU], imiquimod, podophyllotoxin), curettage and cauterization, and cryotherapy are options for early or multifocal disease. Circumcision is curative in many cases. More invasive surgery (glans resurfacing, wide local excision) is reserved for extensive or persistent disease [17,21,46].

7. Penile Squamous Cell Carcinoma

PeSCC accounts for 95% of PeCa cases worldwide [25]. Incidence rates of PeSCC have increased by 28% since the early 1990s, and 18% over the last decade. Furthermore, both PeSCC incidence and mortality are projected to rise further in the UK and reach 1100 new cases and 250 deaths per year by the year 2040 [1].

7.1 Clinical Features of PeSCC

PeSCC usually presents as an exophytic or ulcerated tumour (Fig. 5). Associated symptoms include irritation, pain, discharge or bleeding. There is often a history suggestive of MGLSc, such as dyspareunia, balanoposthitis, or phimosis. On examination, features of MGLSc may be present, as well as clinical variants of PeIN. In patients with phimosis, the tumour may be concealed, and inguinal metastases may be the presenting feature [17,47,48].

The diagnosis of PeSCC is confirmed histologically. In patients with a high index of suspicion and negative biopsies, close follow-up and repeat biopsies are advisable [17].

7.2 Histological Variants of PeSCC

Based on the histological morphology, PeSCC can be divided into several subtypes. Basaloid, warty (or condylomatous), warty-basaloid, and clear cell types are associated with HPV infection. Usual, verrucous, papillary, pseudo-hyperplastic, pseudoglandular, and sarcomatoid types are non-HPV-related and are thought to be linked to MGLSc [21,48].

7.3 Management of PeSCC

Surgical excision is the cornerstone of treatment. However, due to the rarity of PeSCC, there are no randomised controlled trials or observational comparative studies for the approach to surgical treatment [49].

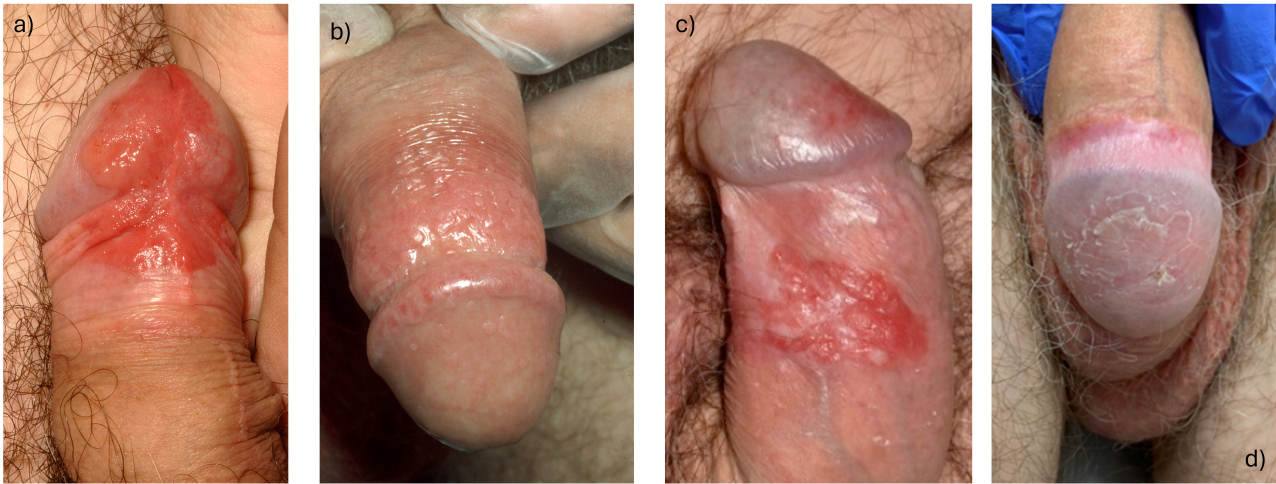


Fig. 4. Clinical variants of penile intraepithelial neoplasia. (a) Erythroplasia of Queyrat. (b) Bowenoid papulosis. (c) Bowen's disease. (d) Pseudoepitheliomatous keratotic and micaceous balanitis.



Fig. 5. Examples of invasive penile squamous cell carcinoma.

Patients should ideally be managed by a specialist multidisciplinary team where a balance is struck between organ-sparing and oncological control [50]. Organ-sparing treatment (such as circumcision, wide local excision, glans resurfacing, or glansectomy) is preferred to partial or subtotal penectomy, which is typically reserved for more advanced disease where the tumour invades the proximal corpus cavernosum or the urethra.

The presence of metastatic disease in the inguinal lymph nodes is the most important prognostic indicator. For impalpable inguinal nodes, the risk of micro metastatic disease is 15–25% [25]. Dynamic sentinel lymph node biopsy can be offered for impalpable inguinal nodes, and radical inguinal lymphadenectomy is performed for metastatic inguinal lymph nodes.

PeSCC is relatively chemo-resistant, with response rates estimated to be approximately 50% in patients with bulky regional lymph node metastases [51]. Thus, chemotherapy is typically reserved for distant metastatic disease or palliation of advanced disease. Platinum-based chemotherapy is the first-line option; however, there is low-level evidence supporting its use [49]. There is also emerging evidence supporting the efficacy and safety of the immune checkpoint inhibitor cemiplimab in metastatic PeSCC [52], although prospective trials are needed to validate these findings.

7.4 Prognosis of PeSCC

The presence and extent of lymph node metastasis are the most important prognostic factors for survival of PeSCC. Approximately one-third of patients will present

with metastatic disease at diagnosis, and <5% of patients will have distant metastases [49,53].

Five-year cancer-specific survival rates are:

- N0: 95%
- N1: 80%
- N2: 65%
- N3: 35%

Patients with localised disease have the most favourable prognosis, with a 5-year survival of up to 81%. In contrast, distant metastases portend a poor prognosis (5-year survival approximately 16%) [3,49].

7.5 Diagnostic Delay and Increased Risk in Elderly Men

Penile lesions are associated with a significant psychosocial burden, stigma and fear, which can lead to delays in presentation [54]. Additional factors contributing to patient-related delays include being single, heavy alcohol consumption, and residing in rural areas [55]. Healthcare system-related delays may also occur due to limited access to specialist care and inappropriate referral pathways.

Elderly patients, who are more likely to live alone [56], are less sexually active [57], experience cognitive impairment, and are at particularly high risk of diagnostic delay.

Furthermore, urinary incontinence is common in older adults and increases with age [58], placing these individuals at higher risk of developing MGLSc, dPeIN, and ultimately PeCa. Immunosenescence in the elderly, characterised by impaired immune function and diminished response to novel or mutated pathogens, further increases their susceptibility to infections such as HPV and to malignancy [59].

8. Conclusion

PeCa is a rare but preventable malignancy, particularly affecting older men. MGLSc and HR HPV are critical, synergistic risk factors for PeIN and PeSCC. Early diagnosis and treatment of MGLSc and PeIN, combined with vaccination and circumcision, offer the best strategy for prevention. Public health campaigns must prioritise awareness, timely referral, and broader vaccine uptake.

Future directions include further exploration of post-exposure HPV vaccination, surveillance strategies for treated PeIN, and improved clinical pathways for older men at risk.

Key Points

- Penile cancer (PeCa) is a rare but preventable malignancy that is projected to rise by 20% over the next 15 years.
- PeCa affects elderly men and is associated with a high 5-year mortality rate.
- Male genital lichen sclerosus (MGLSc) and high-risk HPV are two critical and synergistic risk factors in the pathogenesis of PeCa.

- Penile intraepithelial neoplasia (PeIN) represents a histopathological precursor to invasive cancer and can be classified into MGLSc-driven differentiated PeIN and HPV-dependent undifferentiated PeIN.
- The early recognition and management of MGLSc and PeIN, coupled with the mitigation of other modifiable risk factors, offer the most effective strategy to prevent the development of PeCa.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

EU, GK, HA, AM and CB designed the work. EU was the lead author in drafting the article, revision, and project administration. GK made substantial contributions to article drafting. CB and GK provided overall supervision for the project, with CB providing leading supervision. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patients for the publication of the clinical images included in this article. The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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