Penile Neoplasms

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1. Introduction

Malignant lesions of the penis may arise from the squamous epithelium of the prepuce, glans, and/or penile shaft. Penile cancers remain rare, with an estimate of 2,210 new cases in the United States for 2021.[1] The most prevalent histologic subtype is **squamous cell carcinoma**, although histologies types may occur (**Table 1**). These lesions principally occur in uncircumcised men, and most commonly develop from the mucosal surface of the glans penis or inner prepuce. Primary lesions are localized to the **glans**, **prepuce, and penile shaft in 60%**, **23%, and 9%** respectively, with the remaining lesions overlapping between these sites.[2] Similar to squamous tumors arising in other locations, these tumors have a propensity for progressive growth and infiltration, eventually leading to metastases through lymphatic dissemination. Multimodal management of this disease incorporates surgery, radiation, and chemotherapy, with durable survival occasionally seen in the setting of locally advanced and regional metastatic disease. In this review, we will discuss the epidemiologic, diagnostic, pathologic, staging, and therapeutic characteristics of penile cancer.

2. Epidemiology & Risk Factors

Table 1: Classification of Malignant Tumors of the Penis
Squamous cell carcinoma
Usual
Warty (condylomatous)
Verrucous
Papillary
Basaloid
Sarcomatoid
Adenosquamous
Pseudoglandular
Cuniculatum
Pseudohyperplastic
Mixed
Malignant epithelial tumors
Clear cell carcinoma
Extramammary Paget's disease
Malignant melanoma
Other
Sarcoma (Kaposi's, leiomyosarcoma)

Malignant lymphoma

Penile cancers most commonly occur after the fifth decade, with the highest incidence between **50-70 years of age**.[3] The annual incidence rates for penile cancer are consistently low among industrialized countries, such as Europe, Canada and the United States (US). Within the US, penile cancer is rare, with an average reported incidence of 1/100,000 men/year. [2] However, among non-industrialized countries in Asia, South America and Africa, prevalence rates are 5-10 times higher.[4] In general, this disease is exceedingly uncommon among children and young men; however, **higher rates of penile lesions have been reported among men with human immunodeficiency virus (HIV) (8-fold increase)[5] and human papilloma virus (HPV).**[6]

Several risk factors have been associated with the development of penile cancer, including (i) **lack of circumcision/phimosis** (ii) **HPV infection** (iii) **lower socioeconomic status** (iv) **chronic inflammatory conditions** (v) **smoking** and (vi) **poor genital hygiene.**[7] Among these, **the presence of an uncircumcised phallus remains the greatest risk factor for the development of this uncommon disease**. The lifetime risk of developing penile cancer among the **uncircumcised US male population is estimated at 1/400, as compared to ~1/100,000 for circumcised US men**, **resulting in a 22-fold risk reduction.**[8] The benefit of circumcision in penile cancer prevention seems to be maximized when performed in the neonatal period, with higher prevalence rates seen when performed after the newborn period. Accordingly, in countries where males routinely undergo circumcision in the newborn period, incidence rates are <0.1/100,000 men. [9] Some authors have demonstrated that neonatal circumcision can eliminate almost all invasive penile cancer from developing. [10] Among 50,000 cases and 10,000 deaths from penile cancer occurring between 1930-1990, only 10 were documented in circumcised patients, all of whom underwent circumcision after puberty. [11]

HPV infection has received greater attention in recent years, largely due to its role in the pathogenesis of several cancers (e.g., oropharyngeal, cervical, rectal) and the development of vaccines for the prevention of disease dissemination. **The pathogenesis of HPV-mediated penile carcinomas is felt to be mediated through alterations in the RB, p21, and p53 pathways, ultimately leading to overexpression of p16**.[12,13] It is estimated that up to 50% of penile cancers are associated with HPV. [14,15,16,17,18,19] **Among the basaloid and warty penile carcinomas, HPV infection is present in the majority.**[4] This is in contrast to keratinizing and verrucous penile carcinomas in which HPV infection is present among roughly one-third of cases. While several subtypes of HPV infection can be present, HPV serotypes 16 and 18 remain the most common risk factors for malignant degeneration.[20] **While HPV infection may occur in any patient, uncircumcised men have a 5 to 10-fold increased likelihood of infection as compared to circumcised individuals.**[21]

The association of penile cancer development and local environmental conditions resulting in chronic inflammatory states such as phimosis, accumulation of smegma, and balanitis are well documented.[7,22] **Phimosis has been reported to be present in 45-85% of patients with penile cancers.**[23] Similarly, **conditions such as infectious balanitis and genital lichen sclerosis (Balanitis Xerotica Obliterans- BXO) are noted to be present in up to 50% of penile cancer**

cases.[8,24] While the underlying pathogenetic mechanisms of chronic inflammatory conditions that lead to malignant changes in the epithelium of penile and preputial skin are not well understood, these associations remain common predispositions for cancer development. Similarly, poor hygiene, accumulation of smegma, tobacco use, and other infectious conditions appear to propagate the inflammatory and mutagenic environment necessary for malignant degeneration, particularly in the setting of the retained preputial skin. [25] In the psoriasis patient population, exposure to psoralen plus ultraviolet A treatment is associated with a substantial increase in penile cancer development. [26]

3. Anatomy

The penis is composed of three cylindrical chambers surrounded by an enveloping fascia and its overlying skin. Since **most cancers of the penis arise from the squamous epithelium of the epidermis and dermis**, it is most relevant to understand the natural pattern of infiltration into deeper tissues and metastatic progression to loco-regional sites. Beneath the penile shaft skin arises the superficial fascia (Dartos), followed by the deep fascia (Buck's). Within these layers are the superficial and deep dorsal veins and dorsal artery. It is also between these two layers that the mobility of the overlying skin of the penile shaft arises due to the loose connective tissue attachments of Dartos fascia to Buck's fascia. This remains in stark contrast to the skin of the glans penis, which remains fixed in place due to direct attachments of the epidermis and dermis to a thin layer of tunica albuginea. Within Buck's fascia are the two dorsal cavernosal bodies and ventral solitary spongiosum. Buck's fascia fuses with the tunica albuginea both distally at the corona of the glans, and proximally, deep to the bulbospongiosus and ischiocavernosus muscles in the perineum, enveloping the corpus spongiosus along its length. The erectile tissue of the corpora cavernosum and the cavernosal artery lie within the tunica albuginea. The fibrous septum of the tunica albuginea lies between the two compartments of the corpora cavernosa. This septum is fenestrated, resulting in free communication between the vascular spaces of both bodies.

The lymphatic drainage of the penis occurs principally to the inguinal lymph nodes in each groin and has no predictable laterality drainage patterns with cross-over occurring in 60-85% of cases.[27] The inguinal lymph nodes can be categorized as superficial or deep according to their location above or below the fascia lata. The superficial lymphatics coalesce near the sapheno-femoral vein junction, where they travel deep to the fascia lata and join the deep inguinal nodes. They continue to course superiorly along the medial aspect of the femoral vein, sending efferent vessels beneath the inguinal ligament through the femoral canal and draining into the node of Cloquet and pelvic lymph nodes.

4. Pathology

Precancerous lesions characterized using previous nomenclature such as **carcinoma in situ** (**CIS**), **Bowen's disease**, **and erythroplasia of Queyrat** have been more recently termed **penile intraepithelial neoplasia** (**PeIN**). These lesions are further subdivided based upon morphologic and microscopic characteristics including **differentiated and undifferentiated subtypes**. **Differentiated**

PeIN is more often associated with chronic inflammatory conditions, **and generally not associated with HPV positivity**.[28] Such conditions are seen more commonly in conjunction with keratinizing, pseudohyperplastic and papillary variants. **Undifferentiated PeIN can be further classified into basaloid, warty, and mixed wart-basaloid types**.[29] **Unlike the differentiated types, most of these are associated with HPV positivity**.[28]

The typical variegated lesion is flat to mildly raised, pearly white and/or red in color, with irregular borders. Basaloid lesions have a homogenous epithelium of small cells with scant basophilic cytoplasm. Warty lesions carry an epithelium composed of papillary fronds of atypical squamous cells. All of these precancerous subtypes of PeIN strongly correspond with the appearance of their invasive counterparts.[27]

Among invasive penile cancers, several additional subtypes have been characterized (**Table 1**). These can be more generally described based upon their appearance and pattern of growth/spread into the following groups (i) **superficial spreading** (ii) **vertical growth** (iii) **verruciform** (iv) **multicentric** and (v) **mixed**. The usual SCC subtype represents the most common form of penile cancer, occurring in up to two-thirds of reported cases. These are moderately differentiated tumors with a metastatic rate of 28-39% of reported cases.[30] Relative to the usual SCC cases, the other histologic subtypes can be characterized regarding their malignant potential. In general terms, **verrucous**, **pseudohyperplastic**, and **cuniculatum carcinomas have an excellent prognosis with no risk of metastatic spread to regional lymph nodes or association with disease-specific death**. **Warty** and **papillary carcinomas** are associated with a metastatic rate of approximately 20% and an overall low mortality rate. **Adenosquamous carcinomas** have a much higher metastatic potential (~50%) but are associated with a negligible mortality rate. **The subtypes with the worst prognosis are the sarcomatoid and basaloid carcinomas**, in which metastatic spread is seen in 50-100% of patients of whom the majority will ultimately succumb to their disease. While histologic subtypes serve as discriminatory features for prognostic comparison, **the most important pathologic predictors for metastatic spread and survival outcomes remain tumor grade, depth of invasion**, **and the presence of perineural invasion.**[31]

5. Clinical Diagnosis and Staging

Table 2: American Joint Committee on Cancer (AJCC) TNM Staging System for Penile Cancer (8th ed., 2018)	
NCCN Guidelines Version 2.2018 Staging Penile Cancer	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (Penile intraepithelial neoplasia [PeIN])
Ta	Noninvasive localized squamous cell carcinoma
T1	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)

T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumor invades into corpora cavemosum (including tunica albuginea) with or without urethral invasion
T4	Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)
Regional Lymph Nodes (N)	
Clinical Stage Definition	
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile ≥ 2 unilateral inguinal nodes or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
Pathologic Stage Definition	

pNX	Lymph node metastasis cannot be established
pN0	No lymph node metastasis
pN1	≤2 unilateral inguinal metastasis without extranodal extension
pN2	≥3 unilateral inguinal metastases or bilateral metastases
pN3	extranodal extension of lymph node metastases or pelvic lymph node metastases

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0is	Tis	N0	M0
Stage 0a	Ta	N0	M0
Stage I	T1a	N0	M0
Stage IIA	T1b T2	N0 N0	M0 M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-3	N1	M0
Stage IIIB	T1-3	N2	M0

Stage IV	T4 Any T Any T	Any N N3 Any N	M0 M0 M1

The assessment of a patient suspected of having penile cancer (PC) begins by obtaining a focused but detailed history including information pertaining to prior circumcision and, if performed, at what age (pre- versus post-pubertal), as well as a history of balanitis or other chronic penile inflammation. In a patient presenting with a penile lesion, it is important to inquire as to the history of prior penile trauma, history of sexually transmitted diseases (especially HPV), [32] lichen sclerosis (BXO), tobacco use, and history of phimosis.[33]

On physical examination, a careful inspection of the phallus and bilateral inguinal regions are critical. The penile lesion must be assessed, noting its diameter, character (fixed or mobile), location with regards to the phallus and relation to relevant anatomical structures (corpus spongiosum, corpus cavernosum, urethra), and morphological features (keratinization, papillary, nodular, erythematous, neovascularity, ulcerated). In the assessment of the inguinal regions, patients should be placed supine in a **slight frog-leg position**. Any palpable inguinal lymph nodes should be characterized as shotty versus grossly evident, mobile versus fixed, involvement of surrounding skin, and suspicion of an underlying infection (erythema, purulent drainage).

In noninfectious penile lesions, a **tissue biopsy** to rule out PC should be obtained and remains the gold standard. Various biopsy techniques can be employed including a punch, incisional, or excisional biopsy. Imaging techniques such as penile MRI (**Figure 1**) or ultrasound can be employed to help assess primary tumor stage and suitability for penile sparing surgical approaches.[34] **Once a tissue diagnosis of squamous cell carcinoma of the penis is made by a pathologist, clinical staging should be assigned using the 2018 AJCC TNM staging of PC** (**Table 2**).

MRI in patient with history of partial penectomy with local recurrence along the dorsal penile stump extending through the Dartos fascia along the dorsal penile stump and into the right dorsolateral Buck's fascia with possible extension into the right corpora cavernosa. Pathology from completion penectomy demonstrated a 2.2cm high grade squamous cell carcinoma invading the right corpus cavernosum (pT3).

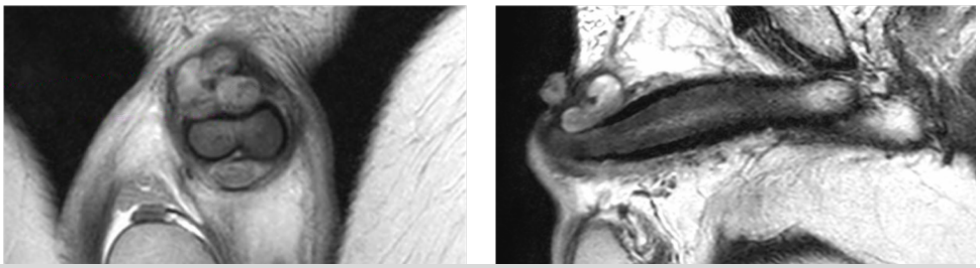

Figure 1

6. Management

6.1 Primary Penile Tumor

The suitability of various topical, ablative, surgical, and radiation therapeutic approaches for the management of primary penile tumors is ultimately determined by the **clinical stage** of the respective lesions as was recently illustrated in the 2021 National Comprehensive Cancer Network (NCCN) PC guidelines (**Figure 2** and **Figure 3**).[35] The American Urological Association (AUA)

update series by Pettaway et al. mirrors these approaches for managing the primary penile tumor.[36]

For **Tis and Ta primary penile tumors, topical therapy using 5% imiquimod or 5-fluorouracil as well as wide local excision encompassing circumcision for penile tumors situated on the penile foreskin are the preferred primary treatment approaches** .[37] **Other acceptable organ-sparing approaches for Tis or Ta include laser therapy (CO_2 or Nd-YAG) or complete glansectomy** .[38]

Patients presenting with **clinical stage T1 primary penile tumors are subdivided into lower and higher grade tumors** to guide treatment approaches offered.[39] Patients with **T1 low grade tumors are preferably offered penile preserving surgery consisting of a wide local excision +/- thick split thickness (STSG) or full thickness (FTSG) skin graft, with alternative options being laser ablative therapy or radiotherapy** . A high-volume center from the United Kingdom demonstrated a negative margin > 1 mm has a very low risk of local recurrence after organ-sparing treatment.[40] In contrast, **patients with T1 high grade tumors can be offered a range of therapeutic options including wide local excision +/- STSG or FTSG, glansectomy, partial penectomy, and total penectomy with perineal urethrostomy**.[41]

Total penectomy should only be considered if a functional penile stump cannot be preserved (typically greater than 2 cm) while insuring complete tumor eradication with negative surgical margins. Of note, the anticipated functional penile stump length should be measured in the standing and supine position given the risk of postoperative retraction resulting in a buried penile stump configuration, especially in obese patients or patients with a prominent prepubic fat pad, which can increase the risk of postoperative infection, annular skin strictures, hygiene complaints, and dissatisfaction.

A multi-center global study demonstrated that approximately one fifth of patients experienced postoperative complications within one month of total penectomy and perineal urethrostomy. The surgical revision rate for stenosis of perineal urethrostomy was approximately 10% at one year.[42] Alternative options for patients with T1 high-grade tumors include primary radiotherapy and radiation with systemic chemotherapy. Patients presenting with locally advanced primary penile tumors (T2 or greater) are preferably recommended partial or total penectomy with perineal urethrostomy, with an alternative option for T2 only tumors being radiotherapy +/- systemic chemotherapy. In experienced centers, penile-preserving surgery may be offered for highly selected patients with T2 tumors.[43]

There are several important clinical points that should be emphasized in the management of primary penile tumors. First, the suitability of patients for penile-sparing surgical approaches is primarily determined by the grade, stage of the primary tumor (typically T1 high-grade or less) and location of the tumor. **At no point should the adequacy of the surgical resection with negative margins be compromised even if this entails proceeding with a more extensive surgical resection (partial or total penectomy). It is imperative for surgeons caring for PC patients to have a detailed discussion with patients regarding the psychosocial and sexual implications of primary penile tumor resection and how this can impact present and future relationships. Patients should be**

provided with pre-operative counseling with the assistance of a psychosexual counselor or psychiatrist/psychologist whenever possible.

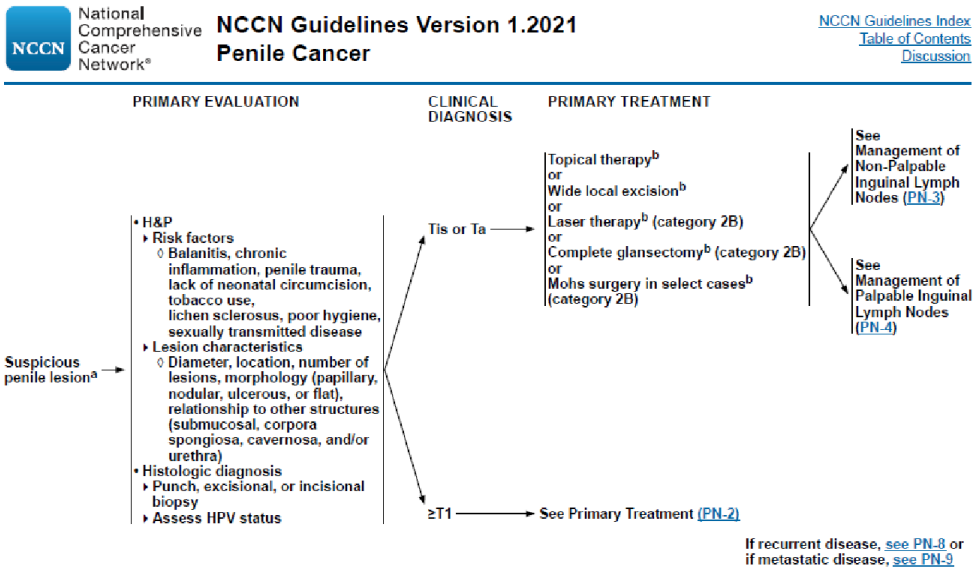

Figure 2

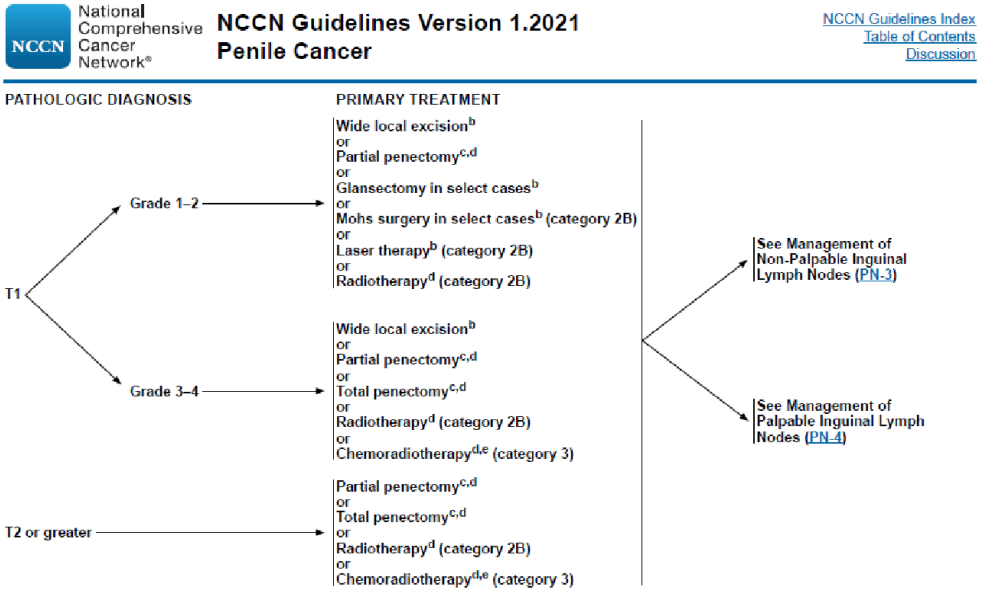

Figure 3

6.2 Inguinal Lymph Nodes

A careful physical and radiographic examination of the inguinal lymph nodes are essential and can be classified as **(i) non-palpable (ii) palpable (non-bulky defined as < 4 cm in diameter and non-fixed) and (iii) palpable (≥ 4 cm and/or fixed).**

6.2.1 Non-Palpable Nodes

In patients with low clinical stage (Tis, Ta, T1) and grade tumors and no inguinal adenopathy, most patients will undergo post-resection surveillance of bilateral inguinal regions by

physical examination (typically every 6-12 months), with the selective use of imaging (CT, MRI, or ultrasound) in those patients where the inguinal region cannot be well assessed secondary to prior therapy and/or obesity.[44,45] An alternative treatment option is to proceed with a **dynamic sentinel node biopsy (DSNB)** provided there is adequate expertise with this treatment.[46,47] With further refinement of technique of DNSB using a hybrid fluorescent-radioactive tracer, false negative rate was reduced to 1.4%.[48]

In patients with **clinical stage T1 high-grade or higher stage tumors, patients can harbor occult inguinal lymph node metastasis in up to 50-80% of cases**. In a previous study by Slaton et al., **high-risk criteria for inguinal lymph node metastases included (i) clinical stage T2 or greater (ii) greater than 50% poorly differentiated (grade) tumor, and (iii) the presence of lymphovascular invasion**.[49] Among those high-risk PC patients without palpable inguinal adenopathy, proceeding with a bilateral superficial inguinal lymph node dissection (ILND) with deep ILND if any positive lymph nodes are identified on the superficial ILND is the most common and acceptable treatment approach. **A threshold of 15 or more lymph nodes removed has been found as an optimal yield after ILND**.[50] It is reasonable in this high-risk PC patient cohort to proceed with a bilateral DSNB. Regardless of modality chosen, inguinal lymph node dissection should be performed in a timely fashion given that delaying lymphatic staging for greater than 3 months may be associated with worse outcomes.[51]

6.2.2 Palpable (Non-Bulky) Nodes

Among PC patients with palpable inguinal adenopathy, a distinction is made between patients exhibiting palpable, non-bulky inguinal lymph nodes (< 4 cm) and those with bulky (≥ 4 cm) and/or fixed inguinal lymph nodes. **Patients with non-bulky inguinal lymph nodes should undergo a diagnostic fine needle aspiration (FNA) or may proceed directly to ILND if there is high clinical suspicion for inguinal lymph node metastases. If the FNA is negative or non-diagnostic, it is recommended to proceed with an excisional lymph node biopsy**. If the lymph node biopsy is negative, patients should undergo surveillance with regular physical examination and selective imaging studies every 6-12 months. In patients with a positive excisional lymph node biopsy, proceeding with an ILND in the same setting or shortly thereafter is strongly recommended.

6.2.3 Palpable (Bulky) Nodes

For patients with bulky and/or fixed palpable inguinal adenopathy, it is important to establish a definitive diagnosis of inguinal metastases which can be obtained by FNA and if needed, excisional lymph node biopsy. Once a tissue diagnosis of bulky inguinal lymph node metastases secondary to PC is made, the treatment approach as recommended by the NCCN is presented in **Figure 4**.[35] There has been a major paradigm shift for this subset of patients with the integration of a **multimodal approach consisting of neoadjuvant systemic chemotherapy (+/- radiotherapy) followed by consolidative surgery (superficial/deep ILND) in those patients with tumor regression or stability following neoadjuvant therapy** .[52] PET-CT imaging may help establish the suspected burden of metastatic disease prior to initiating neoadjuvant systemic chemotherapy and in

select patients with palpable inguinal lymph nodes prior to proceeding with definitive therapy. **In select patients with bulky inguinal lymph node metastases, upfront ILND can be considered in patients who are highly symptomatic (pain, skin infection/breakdown, bleeding) provided they are felt to be completely resectable. An ipsilateral pelvic lymph node dissection should be considered in patients with 2 or more positive inguinal lymph nodes on the superficial/deep ILND**.[49,53] Consideration of adjuvant systemic chemotherapy should be offered to those patients with viable cancer following ILND in this clinical setting and in those patients exhibiting extranodal extension on pathological review of the ILND specimen.

A pelvic lymph node dissection (PLND) either in the same clinical setting or in a delayed fashion should be considered in patients with two or more positive inguinal lymph nodes with metastases, presence of inguinal lymph node metastasis 3 cm or greater in maximal diameter, and the presence of inguinal extranodal extension.[54,55] Furthermore, bilateral rather than unilateral pelvic lymph node dissection should be contemplated if 4 or more inguinal lymph nodes harbor metastatic disease.[56]

To address some of the controversies regarding the management of PC, the International Rare Cancer Initiative has opened the International Penile Advanced Cancer Trial (InPACT) (NCT02305654), This is multinational collaboration plans to recruit 200 patients with clinically-palpable lymph nodes over a 5-year period. Patients will be randomized into either upfront ILND, neoadjuvant chemotherapy followed by ILND, or neoadjuvant chemoradiotherapy followed by ILND. Additionally, the study will examine whether prophylactic PLND will improve outcomes in patients at risk of recurrence. Those at high risk will be divided into a prophylactic PLND arm versus a surveillance arm. Results from InPACT should provide valuable prospective data on the optimal timing of systemic therapies and the integration and sequencing of systemic therapy with consolidative surgery.

ILND is a technically demanding surgical procedure which has traditionally been associated with a high complication rate. These complications include skin necrosis, wound infection, tissue breakdown, significant lower extremity and penoscrotal lymphedema, as well as deep venous thrombosis . Methods to minimize complications include meticulous surgical technique preserving thick skin flaps with robust vascular supply, careful and rigorous ligation of lymphatic channels, preservation of the saphenous vein, and a sartorius myocutaneous rotational flap whenever a deep ILND is performed to provide tissue coverage over the femoral vessels. Reliable coverage of femoral vessels may not be possible due to thinning of skin flaps if a large tumor involving superficial tissues is resected. Moreover, adjuvant chemoradiation after radical ILND is recommended in cases with palpable bulky inguinal lymph nodes or enlarged pelvic nodes, confirmed pN2-3 disease of initially palpable non-bulky inguinal nodes, and local recurrence in inguinal region.[35] Extra tissue coverage over femoral vessels at the time of ILND can enable safer adjuvant radiotherapy administration to the inguinal area if needed.

The sartorius flap involves transposition of the sartorius muscle over the exposed vessels. The medial border of the sartorius muscle forms the lateral border of radical inguinal lymph node

dissection.[57] It is mobilized from its insertion at the anterior superior iliac spine (ASIS) and rolled over to cover the dissected femoral vessels. The muscle insertion is then sutured to the inguinal ligament superiorly medial to ASIS, and its margins are sutured to the muscles of the thigh adjacent to the femoral vessels. In aggressive inguinal dissections with more extensive tissue defects, a more complex primary closure may be necessary, such as rectus abdominis myocutaneous flap.[58] **Surgeons are encouraged to leave suction drains following ILND to minimize the risk of lymphocele and seroma formation which can be a nidus for subsequent wound infection or wound breakdown. These drains are typically removed when they exhibit minimal output (less than 100-150 cc over a 24-hour period)**. Although patients have traditionally been restricted to bed rest for the first 24-48 hours postoperatively, this is not universally recommended. For PC patients undergoing a sartorius myocutaneous flap, however, a short period of bed rest is typically recommended. For all patients, pneumatic compression stockings and deep venous thrombosis anticoagulation should be employed.

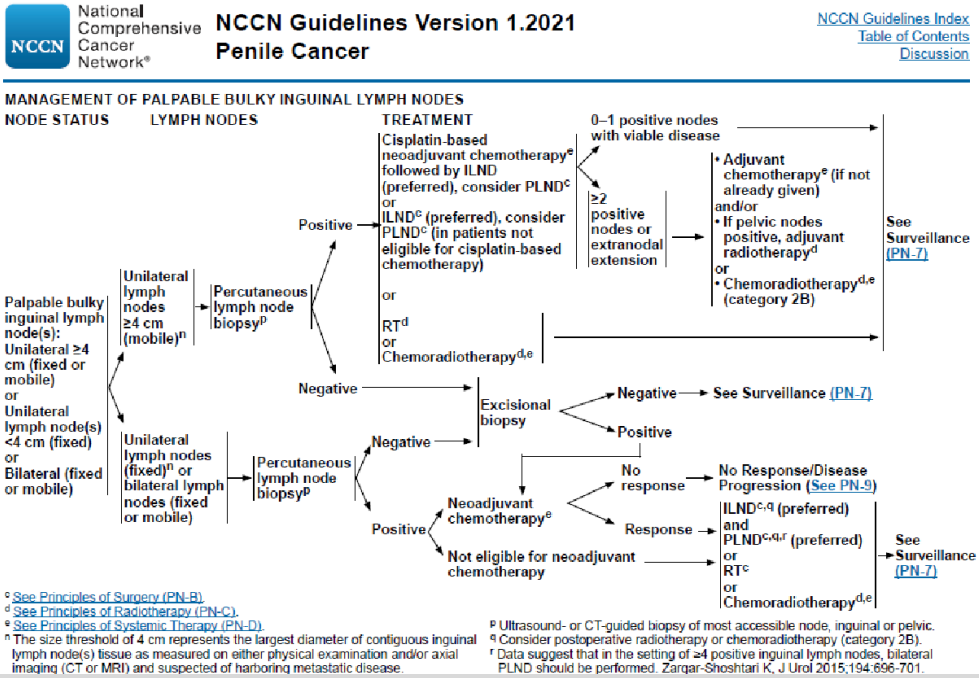

Figure 4: Management of Bulky/Unresectable Inguinal Lymph Nodes

7. Surveillance Strategy for PC Patients

There is a paucity of peer-reviewed scientific literature detailing surveillance strategies following treatment of PC. The NCCN guidelines regarding surveillance are presented in **Figure 5**. **Patients undergoing penile-sparing surgical approaches should be followed more stringently for the first 2 years (every 3 months) versus those undergoing partial/total penectomy (every 6 months for the first 2 years)**.[35]

The most suitable strategy for surveillance of the inguinal nodes should be based on the pathological status of the inguinal lymph nodes. A multicenter retrospective study that evaluated recurrence

patterns following ILND demonstrated that post-ILND recurrence was significantly associated with pN2 and pN3 (ORs of 1.9 and 7.2, respectively).[59] For patients with bulky pathological lymph nodes (N2/3), regular physical examination (every 3-6 months) for the first 2 years is recommended with abdomino-pelvic imaging (CT or MRI) every 3 months for the first year and then every 6 months for the second year. Chest imaging (x-ray or CT non-contrast) every 6 months for the first 2 years is recommended. In patients with negative clinical nodes (Nx), negative pathological nodes (N0), or non-bulky pathological nodes (N1), regular physical examination (every 3-6 months) for the first 2 years then every 6-12 months for years 3 through 5 is recommended. Selective imaging using chest imaging (chest x-ray or CT non-contrast) or abdomino-pelvic imaging (ultrasound, CT, or MRI) is reasonable in those in whom assessment of the inguinal region is difficult (obesity, prior surgery and/or therapy).

Recent work demonstrated that median time to PC recurrence was 10 months for distant recurrences, 12 for inguinal, 10.5 for pelvic, and 44.5 for local. Greater than 95% of distant, inguinal, and pelvic recurrences occurred within 48 months of ILND, versus 127 months for local recurrences. Post-ILND recurrence was associated with pN2 (OR 1.99, 95% CI 1.0-4.1), and pN3 (OR 7.2, 95% CI 4.0-13.7). Patients who had local recurrence had similar OS to those without (HR 1.5, 95% CI 0.6-3.8), and worse OS was identified in patients with inguinal (HR 4.5, 95% CI 2.8-7.1), pelvic (HR 2.6, 95% CI 1.5-4.5), or distant (HR 4.0, 95% CI 2.7-5.8) recurrences. Patients with lung recurrences had worse OS than other sites (HR 2.2, 95% CI 1.1-4.3). [60] Therefore, patients with higher stage disease should be considered for more stringent surveillance within the first 5 years following local treatment.

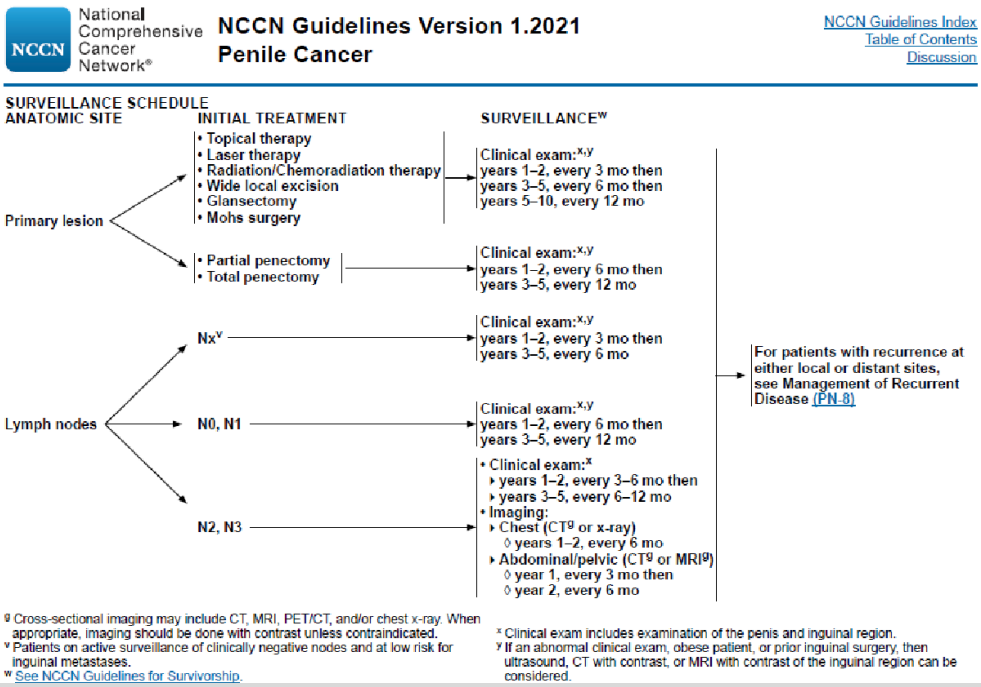

Figure 5: 2020 NCCN Guidelines: Surveillance Recommendations

8. Management of Local Recurrences

Although relatively infrequent, the management of local recurrences can be quite challenging as there is a paucity of peer-reviewed literature available on this subject. The management of a primary penile tumor site recurrence is determined by whether corporal invasion is present or not. **In patients with primary recurrence in the absence of corporal invasion, repeat penile sparing surgery or topical therapy, partial penectomy, and total penectomy are all acceptable treatment choices depending on the anatomical site and size of the recurrence. In patients with primary tumor recurrences exhibiting corporal invasion, patients should undergo either partial or total penectomy** . Decisions between partial and radical nephrectomy are made based on the anticipated length of the final penile stump and careful counseling of patients regarding their priorities and preferences.

For patients with a local recurrence in the inguinal region post-ILND and in the absence of distant metastatic disease, a range of treatment options alone or in combination are feasible including surgical resection, external beam radiotherapy, and/or systemic chemotherapy.[61]

9. Metastatic Disease

For PC patients presenting with advanced/metastatic disease, or those who develop distant metastases, the prognosis is very poor. **Treatment options for PC patients with bulky adenopathy, fixed nodes, and inguinal tumor recurrence requires a multi-modality approach utilizing chemotherapy with consolidative surgery (preferably), radiotherapy or chemoradiation** , as outlined in the NCCN PC 2022 and in an AUA Update Series.[35,62]

It is important to accurately assess the presence of pelvic nodal metastases in patients with inguinal node metastases as it portends worse treatment related outcome and prognosis.[63] Patients with pathological node positive PC who experienced an inguinal recurrence after therapeutic lymphadenectomy have poor outcomes with limited salvage options. Graafland et al. determined the clinicopathological features predictive of such recurrences and found that **patients with 3 or more unilateral metastatic inguinal nodes, extranodal extension, and/or pelvic nodal involvement represent a high-risk group with poor survival outcomes and multi-modality treatment is recommended** .[63,64]

Stage IV PC patients most commonly present with bulky inguinal or pelvic metastases and the most common sites of distant metastases are distant nodes, lung, bone, and uncommonly other organs including liver and brain.[62] In select cases of retroperitoneal disease, post-chemotherapy retroperitoneal lymph node dissection has been reported to be associated with durable disease survival.[65] **Use of PET-CT scanning is a reliable tool to detect pelvic lymph node involvement and distant metastases in such advanced PC patients**.[65,66] Multimodal treatment utilizing a combination of systemic chemotherapy, radiotherapy or consolidative surgery is recommended for optimal outcomes in advanced and metastatic PC patients, as discussed below. [12]

9.1 Chemotherapy

There is a lack of randomized studies comparing different chemotherapy regimens due to the rarity of

this disease, but evidence suggests that **cisplatin-based combination-chemotherapy regimens are effective as first-line agents for patients with advanced/metastatic PC**. The efficacy of a bleomycin, methotrexate and cisplatin regimen (BMP) was studied in advanced PC patients but is not recommended due to associated high rates of severe adverse events.[13]

The combination of **paclitaxel, ifosfamide, and cisplatin (TIP)** has shown promising response rates with acceptable safety profile. In a study of thirty men with advanced PC, 50% had an objective response and 73% were able to undergo surgery after completion of neoadjuvant chemotherapy.[52] Bermejo et al. also reported responses in four out of five patients treated with this regimen, who then underwent surgical consolidation following completion of chemotherapy.[67] **TIP is currently the preferred chemotherapy regimen for neoadjuvant, adjuvant and first-line systemic therapy of PC.** Cisplatin and 5-Fluorouracil (5-FU) have also been studied in advanced PC patients. In a small series reported in 1990 by Hussein et al., five patients with advanced PC were treated with cisplatin and 5-FU and achieved partial responses.[68] In another small retrospective study of eight patients, 2 out of 8 (25%) patients demonstrated a response and underwent further treatments including surgery and radiation as shown in **Table 3**.[69] **Therefore, Cisplatin and 5-FU remains as an alternative to TIP for adjuvant and first-line systemic therapy of PC.**

Patients who achieve an objective response to chemotherapy should be considered for consolidative surgery consisting of bilateral superficial and deep ILND +/- PLND. Overall, pooled findings suggest that approximately 50% of the patients with bulky regional lymph node metastases from penile cancer respond to platinum-based neoadjuvant chemotherapy and approximately 16% of patients achieve a pathological complete response.[70]

There is no standard second-line chemotherapy regimen for metastatic PC patients who progress after first-line chemotherapy. Currently, the NCCN panel recommends participation in **clinical trial** for second-line systemic therapy of PC. The other preferred option for this setting is **Pembrolizumab**, a PD-L1 inhibitor, after progression on previously approved line of therapy if the tumor is microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) or mutational tumor burden-high (TMB), TMB≥10 mut/Mb. A Phase 2 multicenter prospective study demonstrated that 200 mg IV Pembrolizumab once every 3 weeks achieved objective responses in 34% of patients with MSI-H/dMMR progressed solid tumors,[71] and in 29% of patients in MSI-H progressed solid tumors.[72] The current NCCN guidelines state that Paclitaxel and Cetuximab are recommended as alternative options to participation in clinical trials and treatment with Pembrolizumab, especially if the cancer respond to prior treatment with a similar class of agent.

Durable treatment responses to check-point inhibitors have been recently reported in a small case series of select patients with metastatic PC who progressed after initial chemotherapy. High tumor mutational burden and positive PD-L1 expression appeared to be predictive for treatment response to Pembroizumab.[73,] Likewise, complete response to Cemiplimab, a PD-1 inhibitor was noted in a patient who had metastatic PC progressed after radiotherapy and cisplatin-based chemotherapy.[74]

Emerging treatment paradigms for metastatic PC are incorporating targeted and immunotherapy

agents both as combination therapies and in sequence. Currently, there are several ongoing clinical trials exploring the efficacy of immunotherapy with anti-PD-1/PD-L1 therapies in penile cancer. (NCT03391479, NCT03686332, NCT03866382).[75] In retrospective single cohort series, PD-L1 expression was detected in up to 40-62% of primary PC cases and the concordance of PD-L1 expression between matched primary and metastatic samples was reported high (78%).[76] Furthermore, a recent next generation sequencing study that included 78 metastatic penile squamous cell carcinoma patients demonstrated that more than a quarter of the patients harbored genomic alterations in tyrosine kinase, DNA repair and mTOR pathways (ERBB2 (4%), FGFR3 (4%), ATM (7%), BRCA2 (7%), NF1 (7%) and PTEN (4%)), all of which could be potentially targetable by existing available therapies.[77]

9.2 Radiation

Although, squamous cell carcinoma is considered a radiosensitive malignancy, the role of radiotherapy in advanced PC is debated. Radiation monotherapy to regional lymph node metastases in patients with penile cancer is less effective than it is for the treatment of the primary lesion. However, radiation can be considered pre-operatively in patients with advanced PC for mobile lymph nodes ≥ 4 cm. Ravi et al. demonstrated the benefit of radiation when used as neoadjuvant, adjuvant, or palliative therapy in 120 patients with lymph node metastases and 9 with distant metastases.[78] Radiation improved local control, allowed for surgical resectability for some men, and offered palliation for unresectable inguinal or bone metastases.

A systematic review by the European Association of Urology did not find benefit for radiation treatment **after** removal of the nodes.[79] In contrast, a recent Danish national penile cancer database study demonstrated that in patients with pT1-T4, N3, M0 penile cancer who underwent ILND, adjuvant chemoradiation (external beam therapy of involved regions and cisplatin-based chemotherapy) provided comparable survival outcomes, a median overall survival of 84 months, to historical cohorts, suggesting adjuvant chemoradiation remains an alternative to PLND.[80] Similarly, a UK study recently reported that 5-year cancer specific survival in pN3 PC was 51% in patients treated with adjuvant radiotherapy with a weekly low-dose chemo-sensitization following ILND, highlighting more promising outcomes with radiotherapy in contemporary era.[81] Due to paucity and low quality of existing data, the role of radiation remains controversial and the ongoing International Penile Advanced Cancer Trial (InPACT, NCT02305654) is expected to shed more light on the value and sequencing of radiotherapy in advanced PC. Moreover, there is emerging data indicating that a subgroup of penile cancer patients might benefit from perioperative radiotherapy and that HPV status is predictive of response to treatment. In a propensity-matching analysis of a multicenter penile cancer cohort treated with ILND, HPV+ cases were found to have longer overall survival after peri-operative radiotherapy than HPV- cases.[82]

Table 3. Combination Chemotherapy Regimens for Penile Cancer

Agent/Regimen	References	N	Number of Responders
Paclitaxel, Ifosfamide, Cisplatin (TIP) (Paclitaxel 175 mg/m2 on day 1, Ifosfamide 1200 mg/ m2, Cisplatin 25 mg/ m2 on days 1-3 every 3 weeks)	Pagliaro et al.[52]	30	13/30 (50%)
Paclitaxel, Ifosfamide, Cisplatin (TIP) (Paclitaxel 175 mg/m2 on days 1-5, Ifosfamide 1200 mg/m2 on days 1-3, Cisplatin 20 mg/m2 on days 1-3)	Barmejo er al.[66]	5	4/5 (20%)
Cisplatin, 5-Fluorouracil (Cisplatin 100 mg/m2 on day 1, 5-FU 1,000 mg/m2/day on days 1-5 every 3-4 weeks)	Shammas et al.[13]	8	2/8 (25%)
Cisplatin, 5-Fluorouracil (Cisplatin 100 mg/m2 cisplatin on day 1, 5-FU 960 mg/m2/day for 5 days every 3-4 weeks)	Hussein et al.[12]	5	5/5 (100%)

Videos

Loop Perineal Urethrostomy following Total Penectomy

Open radical ILND with Sartorius transposition

Da Vinci Robot Assisted Video Endoscopic Inguinal Lymphadenectomy: Video Demonstration of The Technique

Perineal Urethrostomy with Z-Plasty Flap

Perineal Urethrostomy

Presentations

Penile Neoplasms Presentation 1

References

1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30.

2 Hernandez BY, Barnholtz-Sloan J, German RR, Giuliano A, Goodman MT, King JB, et al. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998-2003. Cancer. 2008 Nov 15;113(10 Suppl):2883-91.

3 ☆ Guimaraes GC, Cunha IW, Soares FA, Lopes A, Torres J, Chaux A, et al. Penile squamous cell carcinoma clinicopathological features, nodal metastasis and outcome in 333 cases. Journal of urology. 2009 Aug;182(2):528-34; discussion 34.

4 Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. Medical Microbiology and Immunology. 2004 Feb;193(1):35-44.

5 Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. Aids. 2006 Aug 1;20(12):1645-54.

6 ☆ Sarkar FH, Miles BJ, Plieth DH, Crissman JD. Detection of human papillomavirus in squamous neoplasm of the penis. Journal of urology. 1992 Feb;147(2):389-92.

7 Bleeker MC, Heideman DA, Snijders PJ, Horenblas S, Dillner J, Meijer CJ. Penile cancer: epidemiology, pathogenesis and prevention. World journal of urology. 2009 Apr;27(2):141-50.

8 Schoen EJ, Oehrli M, Colby C, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics. 2000 Mar;105(3):E36.

9 Solsona E, Algaba F, Horenblas S, Pizzocaro G, Windahl T, European Association of U. EAU Guidelines on Penile Cancer. European urology. 2004 Jul;46(1):1-8.

10 Schoen EJ. Neonatal circumcision and penile cancer. Evidence that circumcision is protective is overwhelming. Bmj. 1996 Jul 6;313(7048):46; author reply 7.

11 Schoen EJ. The relationship between circumcision and cancer of the penis. CA: a cancer journal for clinicians. 1991 Sep-Oct;41(5):306-9.

12 Pettaway CA, Pagliaro L, Theodore C et al. Treatment of visceral, unresectable, or bulky/unresectable regional metastases of penile cancer. Urology 76.2, 2010: S58-S65.

13 ☆ Haas GP, Blumenstein BA, Gagliano RG, et al. Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: a Southwest Oncology Group study. Journal of urology 1999;161:1823-1825.

14 Rubin MA, Kleter B, Zhou M et al. Am J Pathol 2001; 159: 1211.

15 Backes DM, Kurman RJ, Pimenta JM et al. Cancer Causes Control 2009; 20: 449.

16 ☆ Bethune G, Campbell J, Rocker A et al. Urology 2012; 79: 1092.

17 Miralles-Guri C, Bruni L, Cubilla AL et al. J Clin Pathol 2009; 62: 870.

18 ☆ Tang et al. J Urol. 2015 Feb;193(2):519-25.

19 Zargar et al. Clin Genitourin Cancer. 2015 Dec 23.

20 McCance DJ, Kalache A, Ashdown K, Andrade L, Menezes F, Smith P, et al. Human papillomavirus types 16 and 18 in carcinomas of the penis from Brazil. International journal of cancer Journal international du cancer. 1986 Jan 15;37(1):55-9.

21 Castellasgue X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. The New England journal of medicine. 2002 Apr 11;346(15):1105-12.

22 Velazquez EF, Bock A, Soskin A, Codas R, Arbo M, Cubilla AL. Preputial variability and preferential association of long phimotic foreskins with penile cancer: an anatomic comparative study of types of foreskin in a general population and cancer patients. The American journal of surgical pathology. 2003 Jul;27(7):994-8.

23 Tsen HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). Cancer causes & control : CCC. 2001 Apr;12(3):267-77.

24 Perceau G, Derancourt C, Clavel C, Durlach A, Pluot M, Lardennois B, et al. Lichen sclerosus is frequently present in penile squamous cell carcinomas but is not always associated with oncogenic human papillomavirus. The British journal of dermatology. 2003 May;148(5):934-8.

25 Maden C, Sherman KJ, Beckmann AM, Hislop TG, Teh CZ, Ashley RL, et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. Journal of the National Cancer Institute. 1993 Jan 6;85(1):19-24.

26 Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. The New England journal of medicine. 1990 Apr 19;322(16):1093-7.

27 ☆ Horenblas, S, van Tinteren, H . Squamous cell carcinoma of the penis. Prognostic factors of survival: analysis of tumor, nodes, and metastasis classification system. Journal of urology, 1994; 151: 1239.

28 Chaux et al, Am J Surg Pathol 2010;34:385-92.

29 Chaux et al, Hum Pathol 2012;43:1020-7.

30 Chaux A, Caballero C, Soares F, Guimaraes GC, Cunha IW, Reuter V, et al. The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. The American journal of surgical pathology. 2009 Jul;33(7):1049-57.

31 Chaux A, Torres J, Pfannl R, Barreto J, Rodriguez I, Velazquez EF, et al. Histologic grade in penile squamous cell carcinoma: visual estimation versus digital measurement of proportions of grades, adverse prognosis with any proportion of grade 3 and correlation of a Gleason-like system with nodal metastasis. The American journal of surgical pathology. 2009 Jul;33(7):1042-8.

32 Novara G, Galfano A, De Marco V, Artibani W, Ficarra V. Prognostic factors in squamous cell carcinoma of the penis. Nature clinical practice urology. 2007 Mar;4(3):140-6.

33 Dillner J, von Krogh G, Horenblas S, Meijer CJ. Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl 2000:189-193.

34 Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. International journal of cancer 2005;116:606-616.

35 National Comprehensive Cancer Network. Penile Cancer (Version 1.2021). 2021; Available from: https://www.nccn.org/professionals/ physician_gls/pdf/penile.pdf.

36 ☆ Pettaway CA, Davis JW. Contemporary management of penile carcinoma. Part I: overview of epidemiology, diagnosis, staging and management of the primary tumor. AUA Update Series. 2012;15:149.

37 ☆ Feldman AS, McDougal WS. Long-term outcome of excisional organ sparing surgery for carcinoma of the penis. Journal of urology 2011;186:1303-1307.

38 Pietrzak P, Corbishley C, Watkin N. Organ-sparing surgery for invasive penile cancer: early follow-up data. BJU international 2004;94:1253-1257.

39 Paner GP, Stadler WM, Hansel DE, et al. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. European Urology 2018; 74 (4): 560-569

40 Sri D1, Sujenthiran A1, Lam W1, Minter J1, Tinwell BE1, Corbishley CM1, Yap T1, Sharma DM1, Ayres BE1, Watkin NW1. A study into the association between local recurrence rates and surgical resection margins in organ-sparing surgery for penile squamous cell cancer. BJU Int. 2018 Oct;122(4):576-582. doi: 10.1111/bju.14222. Epub 2018 Apr 27.

41 Hatzichristou DG, Apostolidis A, Tzortzis V, et al. Glansectomy: an alternative surgical treatment for Buschke-Lowenstein tumors of the penis. Urology 2001;57:966-969.

42 de Vries HM, Chipollini J, Slongo J, Boyd F, Korkes F, Albersen M, Roussel E, Zhu Y, Ye DW, Master V, Le TL, Johnstone PA, Muneer A, Brouwer OR, Spiess PE. Outcomes of perineal urethrostomy for penile cancer: A 20-year international multicenter experience. Urol Oncol. 2021 Aug;39(8):500.e9-500.e13. doi: 10.1016/j.urolonc.2021.04.023. Epub 2021 Jun 13. PMID: 34134926.

43 Baumgarten A, Chipollini J, Yan S, et al. Penile Sparing Surgery for Penile Cancer: A Multicenter International Retrospective Cohort. Journal of Urology 2018; 199 (5): 1233-1237

44 Mueller-Lisse UG, Scher B, Scherr MK, Seitz M. Functional imaging in penile cancer: PET/computed tomography, MRI, and sentinel lymph node biopsy. Current opinion in urology 2008;18:105-110.

45 ☆ Tabatabaei S, Harisinghani M, McDougal WS. Regional lymph node staging using lymphotropic nanoparticle enhanced magnetic resonance imaging with ferumoxtran-10 in patients with penile cancer. Journal of urology 2005;174:923-927.

46 Leijte JAP, Kroon BK, Valdes Olmos RA, et al. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. Eur Urol 2007;52:170-177.

47 Valdes Olmos RA, Tanis PJ, Hoefnagel CA, et al. Penile lymphoscintigraphy for sentinel node identification. European journal of nuclear medicine 2001;28: 581-585.

48 Dell'Oglio P et al. Will Dynamic Sentinel Lymph Node Biopsy Become the New International Standard for Evaluating High-risk Penile Cancer in Patients with Clinically Negative Lymph Nodes? Eur Urol, 78:865-872, 2020. https://doi.org/10.1016/j.eururo.2020.09.039

49 ☆ Slaton JW, Morgenstern N, Levy DA, et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. Journal of urology 2001;165:1138-1142.

50 Chipollini J1, Azizi M2, Lo Vullo S3, Mariani L3, Zhu Y4, Ye DW4, Ornellas AA5, Watkin N6, Ager M6, Hakenberg O7, Heidenreich A8, Raggi D3, Catanzaro M3, Ornellas P5, Salvioni R3, Cheriyan SK2, Necchi A3, Spiess PE2. Identifying an optimal lymph node yield for penile squamous cell carcinoma: prognostic impact of surgical dissection. BJU Int. 2020 Jan;125(1):82-88. doi: 10.1111/bju.14883. Epub 2019 Aug 26.

51 Chipollini J, Tang DH, et al. Delay to Inguinal Lymph Node Dissection Greater than 3 Months Predicts Poorer Recurrence-Free Survival for Patients with Penile Cancer. Journal of Urology 2017; 198 (6)L 1346-1352

52 Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. Journal of clinical oncology 2010;28:3851-3857.

53 ☆ Lont AP, Kroon BK, Gallee MPW, et al. Pelvic lymph node dissection for penile carcinoma: extent of inguinal lymph node involvement as an indicator for pelvic lymph node involvement and survival. Journal of urology 2007;177:947-952.

54 ☆ Djajadiningrat RS, van Werkhoven E, Horenblas S. Prophylactic pelvic lymph node dissection in patients with penile cancer. Journal of urology, 2015;193:1976-1980.

55 ☆ Lughezzani G, Catanzaro M, Torelli T, et al. The relationship between characteristics of inguinal lymph nodes and pelvic lymph node involvement in penile squamous cell carcinoma: a single institution experience. Journal of urology, 2014;191:977-982.

56 ☆ Zargar-Shoshtari K, Djajadiningrat R, Sharma P, et al. Establishing criteria for bilateral pelvic lymph node dissection in the management of penile cancer: Lessons learned from an International Multicenter Collaboration. Journal of urology, 2015;194:696701.

57 Bartlett EK, Meise C, Bansal N, et al. Sartorius transposition during inguinal lymphadenectomy for melanoma. J Surg Res. 2013 Sep;184(1):209-15.

58 Bare RL, Assimos DG, McCullough DL, et al. Inguinal lymphadenectomy and primary groin reconstruction using rectus abdominis muscle flaps in patients with penile cancer. Urology. 1994 Oct;44(4):557-61.

59 ☆ Chakiryan NH, et al. Real-World Survival Outcomes Associated With First-Line Immunotherapy, Targeted Therapy, and Combination Therapy for Metastatic Clear Cell Renal Cell Carcinoma. J Urol, In Press, 2021 May. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8150693/

60 ☆ Chakiryan NH, Dahmen A, Bandini M, Pederzoli F, Marandino L, Albersen M, Roussel E, Zhu Y, Ye DW, Ornellas AA, Catanzaro M, Hakenberg OW, Heidenreich A, Haidl F, Watkin N, Ager M, Chahoud J, Briganti A, Salvioni R, Montorsi F, Necchi A, Spiess PE. Patterns of Recurrence following Inguinal Lymph Node Dissection for Penile Cancer: Optimizing Surveillance Strategies. J Urol. 2021 Oct;206(4):960-969. doi: 10.1097/JU.0000000000001790. Epub 2021 May 25. PMID: 34032492.

61 Pagliaro LC, Crook J. Multimodality therapy in penile cancer: when and which treatments? World J Urol 2009;27:221-225.

62 ☆ Pettaway CA, Pagilaro L. Penile squamous carcinoma. Part II: Contemporary management of the inguinal region. AUA Update Series 2012; 31:158.

63 ☆ Graafland NM, van Boven HH, van Werkhoven E et al. Prognostic Significance of Extranodal Extension in Patients With Pathological Node Positive Penile Carcinoma, Journal of Urology 2010; 184: 1347-1353.

64 ☆ Graafland NM, Moonen LM, van Boven HH, et al. Inguinal recurrence following therapeutic lymphadenectomy for node positive penile carcinoma: outcome and implications for management. Journal of urology 2011;185:888-893.

65 Tang DH, Chipollini J, Spiess PES. Postchemotherapy lymph node dissection for isolated retroperitoneal nodal recurrences for penile cancer: Is cure possible in highly selected cases? Urologic Oncology 2016; 36 (1): 1-3

66 Graafland NM, Niels M., Valdes Olmos RA, et al. Scanning with 18F-FDG-PET/CT for detection of pelvic nodal involvement in inguinal node-positive penile carcinoma. European urology 56.2, 2009: 339-345.

67 ☆ Bermejo,C, Busby,JE, Spiess PE, et al. Neoadjuvant Chemotherapy Followed by Aggressive Surgical Consolidation for Metastatic Penile Squamous Cell Carcinoma, Journal of urology, 2007; 177: 4, 1335-1338

68 Hussein, AM, Benedetto, P, Sridhar, KS, et al. Chemotherapy with cisplatin and 5-fluorouracil for penile and urethral squamous cell carcinomas. Cancer, 65, 1990

69 ☆ Shammas,FV, Ous, S, Fossa SD et al. Cisplatin and 5-fluorouracil in advanced cancer of the penis. Journal of urology, 1992: 147, 630

70 ☆ Azizi M, Aydin AM, Hajiran A, et al. Systematic Review and Meta-Analysis-Is there a Benefit in Using Neoadjuvant Systemic Chemotherapy for Locally Advanced Penile Squamous Cell Carcinoma?. J Urol. 2020;203(6):1147-1155. doi:10.1097/JU.0000000000000746

71 Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10.

72 Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020 Oct;21(10):1353-1365.

73 Chahoud J, et al, Case Report: Two Cases of Chemotherapy Refractory Metastatic Penile Squamous Cell Carcinoma With Extreme Durable Response to Pembrolizumab. Front Oncol, 10:615298, 2020. https://doi.org/10.3389/fonc.2020.615298

74 Denis C, Sakalihasan S, Frères P, et al. Cemiplimab for Cisplatin Resistant Metastatic Penile Cancer. Case Rep Oncol. 2021 Jun 21;14(2):972-976.

75 Aydin AM, Chahoud J, Adashek JJ, Azizi M, Magliocco A, Ross JS, Necchi A, Spiess PE. Understanding genomics and the immune environment of penile cancer to improve therapy. Nat Rev Urol. 2020 Oct;17(10):555-570. doi: 10.1038/s41585-020-0359-z. Epub 2020 Aug 18. PMID: 32812000.

76 Chahoud J, Skelton WP 4th, Spiess PE, Walko C, Dhillon J, Gage KL, Johnstone PAS, Jain RK. Case Report: Two Cases of Chemotherapy Refractory Metastatic Penile Squamous Cell Carcinoma With Extreme Durable Response to Pembrolizumab. Front Oncol. 2020 Dec 23;10:615298. doi: 10.3389/fonc.2020.615298. PMID: 33425770; PMCID: PMC7793656.

77 ☆ Jacob JM, Ferry EK, Gay LM, et al. Comparative Genomic Profiling of Refractory and Metastatic Penile and Nonpenile Cutaneous Squamous Cell Carcinoma: Implications for Selection of Systemic Therapy. J Urol. 2019 Mar;201(3):541-548. doi: 10.1016/j.juro.2018.09.056. PMID: 30291913.

78 Ravi, R, Chaturvedi, HK, Sastry DV. Role of radiation therapy in the treatment of carcinoma of the penis. BJU international, 1994, 74: 646

79 Robinson R, Marconi L, MacPepple, et al. Risks and Benefits of Adjuvant Radiotherapy After Inguinal Lymphadenectomy in Node-positive Penile Cancer: A Systematic Review by the European Association of Urology Penile Cancer Guidelines Panel. European Urology 2018; 74 (1): 76-83

80 Maibom SL, Jakobsen JK, Aagaard M, et al. DaPeCa-4: outcome in penile cancer patients with N3 disease due to extra nodal extension treated with surgery and chemo-irradiation. Scand J Urol. 2020 Aug;54(4):334-338.

81 Ager M, Njoku K, Serra M, et al. Long-term multicentre experience of adjuvant radiotherapy for pN3 squamous cell carcinoma of the penis. BJU Int. 2021 Oct;128(4):451-459.

82 Bandini M, Ross JS, Zhu Y, et al. Association Between Human Papillomavirus Infection and Outcome of Perioperative Nodal Radiotherapy for Penile Carcinoma. Eur Urol Oncol. 2021 Oct;4(5):802-810. doi: 10.1016/j.euo.2020.10.011. Epub 2020 Nov 14. PMID: 33199252.