Imaging Recommendations for Diagnosis, Staging, and Management of Penile Cancer

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Abstract

Penile cancer is more common in developing countries and presents unique challenges in treatment, given the psychological impact of surgical treatment options on patients. While clinical assessment of the lesions and nodal disease is critical, imaging does play a role in initial staging, response assessment, and surveillance. This article aims to delineate the guidelines for clinical and radiological evaluation of penile cancers and the approach to disease management.

Keywords
- guidelines
- imaging
- penile cancer
- recommendations

Introduction

Malignancy of the penis is a rare occurrence, more frequently afflicting men in the age group of 50 to 70 years.[1] Developing countries, such as those in South America, the Indian subcontinent and Africa, have the highest burden of cases as compared with the developed world, with high rates of occurrence of up to 6% of malignant neoplasms. These may correspond to lower rates of circumcision in these countries.[2] In penile malignancies, in addition to the diagnostic challenges, it is a unique battle to handle the psychological devastation to the patient, which must be dealt with at each phase, right from clinical and radiological diagnosis to curative or palliative treatment.[2,3]

Risk Factors and Etiopathogenesis

Majority of penile malignancies occur in the glans. Other sites of occurrence, in decreasing order of frequency, include the prepuce, coronal sulcus, and the shaft.[4] The aggressive nature of this malignancy can be attributed to invasive growth and the predisposition to early metastatic spread to lymph nodes.

There are multiple risk factors that contribute to the increased incidence of developing invasive disease,[4] which include phimosis, human papilloma virus (HPV), erythroplasia of Queyrat or Bowen's disease, immunocompromised status, obesity, smoking, poor genital hygiene, and ultraviolet-A phototherapy. Neonatal circumcision and HPV vaccination are known to be protective factors against malignancy.

Almost 95% of lesions in penile carcinoma arise from the glans epithelium that is nonkeratinized, or from the preputial inner layer[4]; the most common histology is squamous cell carcinoma. Extremely rare types of malignancies in the penis include melanoma, sarcoma, or metastases.

Various histologic subtypes of penile carcinoma are differentiated on the basis of the classification provided by the World Health Organization[5] (►**Table 1**). These differ with respect to their pathogenesis, histologic and molecular characteristics, and prognosis.[6]

Clinical Presentation

Penile malignancy may manifest as pain, bleeding, and discharge occurring from a visible or palpable mass. If these lesions remain below the phimotic foreskin, diagnosis may

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Table 1 The WHO classification of penile carcinomas, their relative frequency, and mean cancer-specific mortality[5,9]

Squamous-cell carcinomas	Relative frequency	Tumor-specific mortality
Non-HPV associated		
Squamous cell carcinoma, common type	70–75%	30%
Pseudohyperplastic carcinoma	<1%	0%
Pseudoglandular carcinoma	<1%	>50%
Verrucous carcinoma	2–3%	Low
Carcinoma cuniculatum	<1%	Low
Papillary carcinoma, NOS	5–8%	Low
Adenosquamous carcinoma	Rare	Low
Sarcomatoid carcinoma	1–4%	75%
HPV-associated		
Basaloid carcinoma	5–10%	>50%
Papillary basaloid carcinoma	Rare	
Warty carcinoma	5–10%	Low
Warty basaloid carcinoma	9–14%	30%
Clear-cell carcinoma	1–2%	20%

Abbreviations: HPV, human papilloma virus; NOS, not otherwise specified; WHO, World Health Organization.

be missed; this can be avoided by viewing discharge or bleeding from a nonretractile foreskin with a high index of suspicion.

Biopsy confirms the diagnosis of penile malignancy. Preferably an excisional biopsy is performed for gauging the T-stage of the disease. A negative surgical margin after an excision biopsy, with tumor free margin of 5 mm obtained in the intraoperative fresh frozen section, is considered oncologically adequate.[7]

Staging and Prognosis

Two systems of assessment are used in penile malignancy: the standard TNM system based on Tumor (T), Node (N), and Metastasis (M) given in ►**Table 2**[8] and the less frequently used Jackson classification system.

Probability of nodal infiltration depends on the T-stage of the penile lesion, histological subtype and grade, depth of the tumor, and presence of lymphovascular invasion. The extent of involvement of lymph node is a defining prognostic indicator.[9]

Imaging Considerations

Staging

Clinical examination is complemented by imaging for a comprehensive assessment of the T-stage of primary lesion, locoregional lymphadenopathy status, and distant organ metastases.

Imaging of the Primary Tumor

Infiltration of the corpora can be assessed by ultrasound (USG). Penile Doppler USG appears to have a higher staging accuracy than magnetic resonance imaging (MRI) for corporal infiltration. Penile Doppler may prove to be of higher value in organ preserving surgery.[10]

However, MRI is a more preferred modality for T-staging. Proper positioning by elevation of the scrotum and penis is a prerequisite for MRI of the penis. Present guidelines issued by the European Association of Urology (EAU) state that injection of the corpora with prostaglandin E1 causing penile erection prior to MRI study may improve local staging; however, due to the disadvantage of priapism which is sometimes associated with this method, prostaglandin E1 is not commonly used.[9,11,12]

For local staging, T2-weighted and gadolinium-enhanced postcontrast T1-weighted sequences are essential. Postcontrast T1-weighted images can confirm early onset recurrence and presence of small masses and can serve as problem-solving sequences when noncontrast MRI findings are equivocal. If multifocal lesions are seen in the corpora cavernosa and corpus spongiosum on T1- and T2-weighted sequences, penile metastases may be suspected. Adjacent organ involvement such as prostate invasion by the penile mass can be evaluated.[11]

Imaging of Lymph Nodes

Management of penile malignancies differs depending on the size of the nodes, which are primarily assessed by palpation. However, there can be over-staging as palpable inguinal lymph nodes may be reactive.

The characterization of lymph nodes on imaging is best done with USG. The superficial USG transducer (7.5 MHz) can detect enlarged nodes which are abnormal. Highly specific findings for metastases include the loss of the lymph node hilum and decreased longitudinal/transverse diameter ratio.[13] A longitudinal/transverse diameter ratio of more than 2 is considered normal for inguinal lymph nodes. Inguinal

Table 2 TNM classification of tumors of the penis (primary carcinomas)[8]

T	Primary tumor
Tx	Tumor cannot be assessed
T0	Absence of tumor
Tis	Carcinoma in situ
Ta	Superficial verrucous cancer
T1	Tumor invades subepithelial connective tissue
T2	Invasion of the corpus spongiosum or cavernosum
T3	Invasion of the urethra or prostate
T4	Invasion of other adjacent structures
N	**Regional lymph nodes**
Nx	Cannot be assessed
N0	Absence of regional lymph node metastases
N1	Single superficial inguinal lymph node metastasis
N2	Bilateral or multiple superficial inguinal lymph node metastases
N3	Unilateral or bilateral deep inguinal or pelvic metastasis or metastases
M	**Distant metastases**
Mx	Cannot be assessed
M0	Absence of metastases
M1	Distant metastasis or metastases

lymph nodes with short-axis diameter greater than 20 mm or eccentric cortical hypertrophy of 2mm may be considered as indeterminate.[14] Indeterminate nodes can be targeted for fine-needle aspiration cytology (FNAC) or biopsy under USG guidance for confirmation of metastases.

MRI enables both local tumor staging and lymph node assessment. Lymphotropic nanoparticle–enhanced MRI is a novel imaging technique that has been shown to accurately differentiate benign from metastatic lymph nodes and rule out metastatic disease, with significant sensitivity and specificity rates of 100 and 97% respectively, according to a study by Tabatabaei et al.[15] Provided that similar specificity and sensitivity rates are obtained with larger sample studies, usage of lymphotropic nanoparticles in MRI has the potential to be an all-inclusive staging technique obviating the need for multiple modalities for staging.[9,11,15,16]

Nonpalpable Inguinal Lymphadenopathy

Even if the lymph nodes are not clinically palpable, the chance of micrometastatic disease is still approximately 25%.[9,16] In this scenario, there is no utility of imaging studies in staging clinically normal inguinal regions. Definite detection of micrometastases with computed tomography (CT) or MRI is not possible.[16] Positron emission tomography/CT (PET/CT) also cannot detect metastatic inguinal nodes, when short-axis diameter of a node is less than 10 mm.[17,18] Imaging is useful in obese patients where palpation of the nodes may not be reliable.

Pathological risk factors dictate further course of treatment of patients with nonpalpable inguinal lymphadenopathy. Grade and local staging with lymphovascular invasion can predict lymphatic metastasis.[17,19]

Palpable Inguinal Lymphadenopathy

Palpable inguinal lymph nodes can suggest lymph node metastases. Additional imaging does not change management. Patients having an intermediate to high risk (pT1b, T2-T4) of lymphatic spread are required to undergo invasive lymph node staging in this case.[9,11,20,21]

Pelvic lymph nodes can be assessed by CT or imaging by PET/CT with fluorine-18-fluorodeoxy-D-glucose, which shows significant sensitivity (88–100%) and specificity (98–100%) for confirming metastases in palpable inguinal lymphadenopathy.[17,19,22]

Imaging of Distant Metastases

Lung, liver, and retroperitoneum are frequent sites of metastases in penile malignancy. Distant metastases occur infrequently (less than 3% of cases) and herald poor prognosis. Current EAU guidelines recommend that patients with metastatic inguinal lymphadenopathy undergo evaluation for systemic metastases.[9,20]

CT has a miniscule role in primary tumor local invasion assessment, but it is the mainstay of evaluation of distant spread.

In accordance with the National Comprehensive Cancer Network (NCCN) guidelines, in patients with T1a and nonpalpable inguinal lymphadenopathy, evaluation of the chest, abdomen, and pelvis for distant metastases with CT is not recommended. Patients with T1b or greater invasion levels or with palpable inguinal lymphadenopathy warrant CT of the chest, abdomen, and pelvis. Pelvic CT can detect nodes not amenable to palpation such as retroperitoneal and pelvic nodes. PET/CT can also be performed, though results may be ambiguous when there are micrometastases to inguinal lymph nodes.[9,11,20,23]

The use of CT is not only confined to staging and treatment response but also finds use in the early postoperative phase, especially during occurrence of complications like collections and abscesses. These complications can also be addressed by CT-guided drainage procedures.

Follow-Up Imaging

The objective of surveillance is to diagnose recurrence. Long-term survival is not significantly reduced by local recurrence, if detected early and appropriately treated.

Once the inguinal lymph nodes are affected, it signifies worse prognosis and negatively impacts long-term survival. Most regional or local nodal recurrences are known to occur within 2 years of primary treatment.[9,24]

An additional benefit of regular follow-up is detection and management of treatment-related complications.

Regular follow-up visits are recommended by EAU as well as NCCN guidelines. The timeline is once in 3 months

for the first 2 years, every 6 months during years 3 to 5, and annually thereafter.[9,23] Disease stage and grade, though, have not been strictly considered while putting forth these recommendations. As recurrence may occur even after 5 years, indefinite follow-up may be the recommendation.[23,25]

In case of suspicion of recurrence in local or inguinal postoperative bed, according to NCCN guidelines, image-guided biopsy may be performed.[23]

A chest CT is suggested at 6 months interval during the first 2 years after diagnosis. In addition, an abdominopelvic CT is recommended once in 3 months during the first year and then, once in 6 months for a period of 2 years for N2 or N3 disease. This is done to detect early recurrence, so that local therapies, including lymphadenectomy, chemotherapy and radiation therapy can be administered. Patients with metastatic disease will require regular follow-up for treatment response assessment.

In cases where initial treatment was organ sparing or in obese patients, MRI can be done to detect local recurrence, necessitating a partial or total penectomy.[23,26]

CT or MRI for the purpose of detection of regional recurrence is not routinely used. In suspicious cases, USG and guided FNAC may be used for detection of regional recurrence.[27]

Treatment

The most important principle of penile cancer surgery is organ preservation while pursuing an essential degree of radicality.

Radical circumcision is done for lesions confined to the preputial inner layer. Glans sparing techniques in pTis, pTa tumors of the glans include local chemotherapy, immunotherapy, laser ablation, radiation therapy, or surgery. Chemotherapy and topical immunotherapy (imiquimod, 5-fluorouracil) are treatment modalities for carcinoma in situ (pTis). Laser (CO2, neodymium-doped yttrium aluminum garnet) ablation, glans resurfacing, and radiation therapy are other treatment options, especially considered for recurrent or persistent lesions.

Localized treatment is followed up with posttreatment biopsy from primary tumor site to rule out residual disease. Local excision or partial or complete amputation of the glans is the mainstay for treatment of pT1 and pT2 tumors of the glans.

Measures such as glans amputation with plastic reconstruction are employed for tumors invading the corpus spongiosum or the corpora cavernosa.

Partial amputation of the penis or radical penectomy is performed in large tumors (pT4).

In T2 and higher stages, superficial and deep inguinal lymph node dissection is also indicated.

As squamous cell carcinomas are sensitive to radiation, lesions up to 4 cm in size can be subjected to local radiation therapy.

After radical lymphadenectomy, four to six cycles of adjuvant chemotherapy improve tumor-specific survival.

For the management of patients who are not candidates for curative intent, palliative radiotherapy or chemotherapy is considered.[3,28,29]

Summary of Recommendations

1. Early detection of penile cancer is mainly by clinical examination. Imaging plays a role in staging that should be performed accurately.
2. Inguinal lymph node assessment is a very important factor for prognostication, disease management, and surveillance.
3. Newer imaging techniques that can detect micrometastases in inguinal nodes can be promising additions for comprehensive staging of penile cancer.

Conclusion

Penile carcinoma can be easily staged with present-day imaging modalities, and suitably treated with good outcomes in early cases. With better imaging techniques, there is scope for increasing focus on organ-preserving techniques. This will help in reducing the psychological implications associated with the diagnosis and contribute to quality of life. Patient education on follow-up self-examination will go a long way in the early treatment of recurrences and prolonged survival.

Conflict of Interest
None declared.

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