Diagnosis and Staging of Penile Cancer

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A comprehensive literature study was conducted to evaluate the levels of evidence (LEs) in publications on the diagnosis and staging of penile cancer. Recommendations from the available evidence were formulated and discussed by the full panel of the International Consultation on Penile Cancer in November 2008. The final grades of recommendation (GRs) were assigned according to the LEs of the relevant publications. The following consensus recommendations were accepted: physical examination of the primary penile lesion is mandatory, evaluating the morphologic and physical characteristics of the lesion (GR A). Evaluation of the primary lesion with ultrasonography is of limited value for local tumor staging (GR C); however, evaluation of the primary tumor with magnetic resonance (MRI) imaging during artificial erection induced by intracavernosal injection of prostaglandin might be more useful (GR B). Histologic or cytologic diagnosis of the primary lesion is mandatory (GR A). For accurate histologic grading and staging, a resected specimen is preferable to a biopsy specimen alone (GR B). Penile cancer should be staged according to the TNM system; however, the 1987/2002 TNM staging system requires revision using data from larger patient cohorts to validate the recently proposed modifications (GR B). The histopathology report should provide information on all prognostic parameters, including the tumor size, histologic type, grade, growth pattern, depth of invasion, tumor thickness, resection margins, and lymphovascular and perineural invasion (GR B). Physical examination of the inguinal and pelvic areas to assess the lymph nodes is mandatory (GR B). Ultrasound-guided fine needle aspiration cytology is indicated for both palpable and nonpalpable inguinal nodes. If the findings confirm lymph node metastasis (LNM), complete inguinal lymph node dissection is indicated (GR B). In patients with nonpalpable inguinal nodes, if the ultrasound-guided fine needle aspiration cytology findings are negative for tumor, dynamic sentinel node biopsy can be performed if the equipment and technical expertise are available (GR C). In patients at high risk of inguinal LNM according to the available guidelines and nomograms, surgical staging can be performed by complete, bilateral inguinal lymph node dissection, which might also be curative (GR B). In patients at intermediate risk of LNM, sentinel node biopsy or modified (limited) inguinal lymph node dissection might be performed (GR B). In patients with nonpalpable inguinal nodes, imaging with computed tomography (CT) or MRI is not indicated, because they are not useful in detecting small-volume LNM. Also, it is very unlikely that large-volume LNM (detectable by CT/MRI) would be present in the pelvic nodes (GR B). In patients with confirmed inguinal LNM, CT of the pelvis is indicated to detect iliac LNMs (GR B). Abdominal CT and chest radiography are advisable if the pelvic CT findings are positive (GR B). UROLOGY 76 (Suppl 2A): S15–S23, 2010.

Appropriate management and treatment outcomes in men with squamous cell carcinoma (SCC) of the penis depend critically on the correct diagnosis, grading, and staging of the malignancy. The relatively low incidence of penile SCC, the limited patient numbers in published reports, and the virtual absence of prospective, randomized clinical trials mean that numerous controversies are unresolved about the optimal methods for the diagnosis and staging of SCC.

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DIAGNOSIS AND LOCAL TUMOR STAGING

Clinical examination of the primary penile lesion should evaluate and document the number of lesions, tumor dimensions (size), sites involved (foreskin, glans, shaft), color, morphology (flat, papillary, nodular, ulcerating, fungating), relationship with other structures (corpus spongiosum, corpora cavernosa, urethra), and boundaries (edges).

Clinical staging of the primary tumor can be incorrect in ≤26% of patients. Understaging results from histologic infiltration not clinically evident and overstaging from edema and infection, giving a misconception of infiltration (LE 3).[1]

Staging with the aid of ultrasonography is unreliable, especially with regard to microscopic invasion by small tumors located at the glans.[2,3] However, for larger tumors, ultrasonography can be useful in delineating the

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anatomic relations to the tunica albuginea, corpus cavernosum, and urethra (LE 3).[2] One study concluded that lesions involving the glans alone were more often underestimated by clinical examination than those involving the shaft and that ultrasonography was more accurate than physical examination (LE 3).[4] Another study concluded that clinical examination is reliable for estimating the tumor size and determining corpus cavernosum infiltration, and ultrasonography is useful when infiltration of the corpora cannot be determined by physical palpation alone (LE 3).[5]

Magnetic resonance imaging (MRI) with artificial erection, obtained by injecting 10 μg prostaglandin E_1 into the corpora cavernosa, showed that penile cancer is most often hypointense relative to the corpora on both T_1- and T_2-weighted images and enhances on gadolinium-contrasted images, although to a lesser extent than the corpora (LE 3).[6] It has been suggested that the combination of clinical examination and MRI provides the best correlation with the pathologic stage (LE 3).[7]

MRI staging errors can result from a lack of erection, motion artifact, previous radiotherapy to the penis, or associated infection (LE 3).[8] A recent study showed that MRI combined with pharmacologically induced penile erection performed better than clinical examination in staging penile cancer (LE 3).[9]

HISTOPATHOLOGIC EXAMINATION

All penile lesions that appear suspicious for malignancy or do not respond to a short trial of antibiotic therapy should undergo histologic evaluation, using one of the following methods[10,11]: incisional biopsy, tissue core biopsy, fine needle aspiration cytology (FNAC), brush biopsy, or excisional biopsy.

Incision biopsy is preferable, taking a wedge of tissue that includes the tumor and adjacent normal tissue. Small or superficial penile biopsies are difficult to classify with regard to histologic type, grade, invasion, and other pathologic parameters related to the prognosis.[12] The histologic type and grade can be misinterpreted in 30%, the depth of invasion has been undetermined in 91%, and vascular invasion can be missed in 88% of cases (LE 3).[12] It has been suggested that treatment decisions and prognosis should preferably be based on a resected specimen.[13] It is important that the surgical specimen has been properly pinned and orientated so the pathologist can identify the various true surgical margins.[11,14]

The pathology report should comment on all factors useful for therapy and prognosis (LE 3):[13,15-19] anatomic site, tumor size, histologic type or subtype, grade, growth pattern, front of invasion, depth of invasion, tumor thickness, resection margins, lymphovascular invasion, and perineural invasion.

GRADING

Grading of penile SCC is usually determined by the degree of cell anaplasia.[11] A common approach is to grade penile cancer as grade 1, well differentiated (no evidence of anaplasia); grade 2, moderately differentiated (<50% anaplasia); and grade 3, poorly differentiated (>50% anaplastic cells).[18] An alternative system grades penile SCC as grade 1, minimal deviation from normal or hyperplastic squamous epithelium, grade 3, any proportion of anaplastic cells, and grade 2, the remainder of tumors (LE 3).[13,20] A more sophisticated system with 4 grades has been proposed according to the degree of keratinization, cell atypia, mitotic activity, and the amount of inflammatory cell infiltrate (LE 3).[11,21] However, no study has compared the various methods used for grading penile cancer to determine which provides the best prognostication.[13]

A recent study identified heterogeneous tumors (>1 grade present in the same tumor) in 53% of cases, with most a combination of grade 2 and 3 (68%). Any proportion of grade 3 was associated with a significant risk of nodal metastasis, suggesting that any focus of grade 3 should be sufficient to grade the neoplasm as high grade (LE 3).[22]

A study of patients who underwent partial or total penectomy indicated that a 10-mm clearance is adequate for grade 1 and 2 lesions and 15 mm for grade 3 tumors. Considering that about 80% of tumors have minimal (<5 mm) microscopic extension beyond the visible proximal edge of the lesion, these findings indicate that local excision or partial penectomy might be adequate (LE 3).[23]

Another study of partial penectomy showed that the surgical margin was within 10 mm of the tumor edge in 48% and within <20 mm in 90% of cases. Only 6% of patients had tumor involvement of the surgical margin, indicating that a traditional 2-cm excision margin is unnecessary for treating penile SCC (LE 3).[24]

A study of surgically treated patients with recurrent penile SCC showed that in 24% of cases the recurrent tumor was a higher grade than the primary tumor. Recurrent tumors also had deeper invasion, more inguinal lymph node metastases (LNMs), and lower cancer-specific survival (LE 3).[25]

TNM STAGING SYSTEM

Historically, several staging systems have been used for carcinoma of the penis. The Jackson system was introduced in 1966, and the TNM classification was introduced in 1968 and revised in 1978, 1987, and 2002.[26-28]

Shortcomings have been observed in the various classifications, and a new clinical staging system was proposed in 1990, with better discrimination of survival rates according to the different stages (LE 3).[29] An alternative staging system using the grade of differentiation and the depth of invasion of the primary lesion was proposed in 1995 (Table 1) (LE 3).[30] A study comparing the 1978 clinical TNM staging system with this modified system concurred that the latter provided the best predictive distinction with regard to inguinal LNMs (LE 3).[31]

Table 1. Staging system using histologic grade plus invasion of primary lesion[30]

Stage	Definition	Lymphadenectomy	3-y Survival Rate (%)
1	Grade 1, superficial, no extension into subcutaneous tissue	No	100
2 A	Grade 1-2, locally invasive, without involvement of corpus spongiosum or cavernosum	No	100
2 B	Grade 3, or invasion into corpus spongiosum or cavernosum	No	17
		Immediate	92
		Delayed	33
3	Palpable inguinal nodes persisting after 6 wks of antibiotics	Immediate	75
		No or delayed	33
4	Inoperable inguinal nodes, iliac node involvement, distant metastases		

Table 2. Comparison of current TNM staging system and proposed modification[27,28]

Stage	Current Category (TNM 2002)	Proposed Modification of T Category
Tx	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T0	No evidence of primary tumor	No evidence of primary tumor
Tis	Carcinoma in situ	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma	Noninvasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum	Tumor invades corpus spongiosum
T3	Tumor invades urethra or prostate	Tumor invades corpus cavernosum
T4	Tumor invades other adjacent structures	Tumor invades adjacent structures (including prostate)
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in a single superficial inguinal lymph node	Unilateral inguinal metastasis, mobile
N2	Metastasis in multiple or bilateral superficial lymph nodes	Bilateral inguinal metastasis, mobile
N3	Metastasis in deep inguinal or pelvic lymph nodes, unilateral or bilateral	Fixed inguinal metastasis, or pelvic lymph node metastasis

A recent study of patients whose tumors were classified using the current TNM staging system noted that men with Stage T3 tumors had better survival than those with T1 and T2 disease, suggesting that the system should be revised (LE 3).[32] Accurate clinical staging can be difficult, because several categories are defined by anatomic structures that cannot readily be identified by physical examination or imaging.[27] The T3 category is defined by invasion of the urethra or prostate (Table 2). However, histologic invasion of the anterior urethra occurs in 25% of cases and is not necessarily associated with a poor outcome. Invasion of the prostate by penile cancer (T3) is extremely unusual in the absence of regional extension (T4) or systemic metastases.[13,27,28,33,34] The prognosis of patients with tumor invasion of the corpus spongiosum is better than that for those with invasion of the corpus cavernosum (LE 3).[28,30,35,36] The probable explanation is that the capacity of a tumor to break through the relatively thick tunica albuginea covering the corpora cavernosa reflects more invasive properties.[28]

The presence and extent of regional LNMs are the most important determinants of survival in patients with penile SCC.[37] In the 1987 TNM staging system, the division between the N1 and N2 groups was determined by the number of involved nodes (1 vs ≥2) and/or bilateral inguinal involvement. Several studies have reported that an increased number of tumor-positive lymph nodes is associated with decreased survival (LE 3).[3,38] One study found that only ≥4 positive inguinal nodes had a significantly negative effect on survival (LE 3).[39] Another study defined >3 positive inguinal nodes as an adverse prognostic factor (LE 3).[40] Several studies have reported that the survival of patients with bilateral node involvement was significantly worse than that of patients with unilateral involvement (LE 3).[3,38,39,41]

The current TNM classification makes a distinction between superficial and deep inguinal nodes, although clinically, and even histopathologically, it is difficult or impossible to distinguish between them. In the current classification, a single tumor-positive superficial node is classified as N1, and a tumor-positive deep inguinal node is classified as N3 (Table 2). In contrast to the 1978 TNM version, the presence of a fixed inguinal node is not categorized as a separate entity. Fixed inguinal nodes are generally considered inoperable and confer an ominous prognosis; thus, it seems contradictory that a fixed, but single and unilateral, tumor-positive node would be classified as N1.[27,28]

Extracapsular nodal extension of malignancy has been reported to negatively influence survival in patients with penile cancer.[39,40,42] Because the assessment of the mobility of lymph nodes is subjective and because the size of the metastatic inguinal lymph node is associated with poor prognostic factors, such as extranodal extension and

pelvic LNMs, a clinical N category using the lymph node size, instead of mobility, has been proposed.[43]

INGUINAL NODES—CLINICAL STAGING

At the initial presentation, clinically palpable inguinal lymph nodes are present in 28%-64% of patients with penile SCC. In 47%-85% of these patients, lymphadenopathy is caused by metastatic invasion, and inflammatory reactions account for the remainder. Approximately 25% of patients with palpable inguinal metastases will have bilateral and 75% will have unilateral palpable nodes.[3,44-46]

The characteristics that should be assessed regarding palpable nodes include the number, localization (unilateral or bilateral), dimensions, mobility or fixation, relationship to other structures (skin, Cooper's ligaments), and edema of the penis, scrotum, and/or legs.

Physical examination to predict pathologically involved lymph nodes is not reliable, with a false-negative rate of 11%-62%. Noninvasive imaging (ultrasonography, CT, and MRI) and minimally invasive methods, such as FNAC and sentinel node biopsy (SNB), have also been associated with false-negative findings (LE 3).[1,47,48] However, patients with clinically palpable lymph nodes should undergo imaging with abdominopelvic CT to define the extent of disease, because massive pelvic adenopathy could be an indication for neoadjuvant chemotherapy.[49]

INGUINAL NODES—SURGICAL STAGING

In patients with no clinically palpable nodes (cN0), 12%-20% will harbor occult metastases.[11,50,51] Several studies have shown the sensitivity of clinical node staging to be 40%-60%, with a false-negative rate of around 10%-20%.[30,52]

In patients with nonpalpable inguinal lymph nodes, surgical staging can be performed by complete inguinal lymph node dissection (ILND). Evidence has shown that early ILND in men with impalpable positive nodes significantly improves cancer-specific survival (LE 3).[30,50] However, the therapeutic benefits of early ILND in all patients (in which 80%-90% of procedures might be unnecessary) have to be weighed against the risk of postoperative complications in 24%-87% of patients and a mortality rate of about 3%.[45,46,53] Selective biopsy of palpable inguinal nodes ("inguinal pick" procedure) is not sufficiently sensitive; therefore, a negative result does not guarantee the absence of regional metastases (LE 3).[54]

The risk of nodal metastasis is influenced by both tumor stage and grade.[35] This observation led to the recommendation for risk stratification, in which ILND is performed in high-grade, high-stage tumors, and surveillance is used for low-grade, low-stage tumors. However, the problem lies with the intermediate group, in which management remains controversial.[35]

Surgical staging of the inguinal lymph nodes has been recommended for patients with Stage pT1, grade 2 penile SCC (LE 3).[55] Evidence has shown that the metastatic potential of Stage T1, grade 2 tumors is greater than expected.[47,56] One study showed inguinal metastases in 7.7% of low-risk (pT1, grade 1-2), 28.6% of intermediate-risk (pT2-4, grade 1-2), and 75% of high-risk (any T, grade 3) tumors.[57] Another study showed nodal metastasis in 6.3% of Stage T1, grade 1 tumors, 12.2% of Stage T1, grade 2, and 44.6% of Stage T1, grade 3 tumors (LE 3). Consequently, these investigators have recommended ILND for Stage pT1, grade 2 and all grade 3 tumors.[27]

A recent study of patients who underwent ILND according to these risk stratification guidelines found that those with palpable nodes had pathologically confirmed metastases in 72%, and 18% of those with impalpable nodes had lymph node disease. The investigators concluded that the current risk stratification guidelines are limited in predicting micrometastatic disease, with the result that 82% of patients undergo unnecessary ILND.[32]

Regarding the question of whether bilateral or unilateral ILND should be performed in patients at high risk of nodal metastases, a prospective study showed that spread to the right side, left side, and both sides occurred in 24%, 30%, and 46% of patients, respectively. Therefore, it was proposed that bilateral ILND should be the standard.[58]

To improve the accuracy of predicting inguinal LNM, a nomogram has been developed that incorporates 8 clinical and pathologic variables (ie, tumor thickness, microscopic growth pattern, histologic grade, presence of vascular or lymphatic embolization, infiltration of the corpora cavernosa, corpus spongiosum, or urethra, and clinical stage of inguinal lymph nodes).[45,46,53] Another study proposed a prognostic index using the histologic grade, tumor invasion, and perineural invasion to predict the risk of inguinal LNM and the necessity for ILND.[59]

SENTINEL NODE BIOPSY

The sentinel lymph node (SLN) concept postulates that a specific lymph node center is the first filter in the lymphatic pathway and the most likely node to harbor metastatic carcinoma.[60] Focused analysis of the SLN could reveal cancer that might otherwise go undetected by conventional histopathologic methods. Several early studies suggested that rate of false-negative results from SNB was unacceptably high, but these studies had involved small sample sizes and had not used lymphoscintigraphy and blue dye to localize the SLN.[61-65]

A modified bilateral ILND has been proposed, in which the saphenous vein is preserved, together with reduction of the lateral, distal, and proximal margins of dissection (LE 3).[66] However, it has been suggested that modified bilateral ILND is not reliable (LE 3).[67] It has also been suggested that even extended SLN dissection is associated with a significant false-negative rate (LE 3).[63] However, a comparison of bilateral ILND with SNB

found similar rates of nodal metastases, with SNB associated with considerably lower postoperative morbidity.[68]

DYNAMIC SNB

Dynamic SNB (DSNB) is performed by intradermal injection of technetium-99m nanocolloid around the primary tumor, preoperative lymphoscintigraphy, and intraoperative identification of the SLN with the aid of intradermally administered patent blue dye and a gamma ray detection probe. Histopathologic examination of SLNs includes serial sectioning and immunohistochemical staining.[69]

The pitfalls of lymphoscintigraphy in SCC of the penis include inguinal skin contamination during injection, intracavernous administration, and delayed lymph node filling (LE 3).[70] Using an isolated gamma probe technique for SLN detection has a low sensitivity and high false-negative rate of 16%-43% (LE 3).[65,69,71,72] It has been noted that in patients with clinically impalpable nodes, it has the same false-negative rate as clinical examination.[32]

Some studies of DSNB have reported high reliability and negative predictive values, with false-negative rates of 0%-9% and low complication rates (LE 3).[73-75] The group at The Netherlands Cancer Institute has been performing DSNB in clinically node-negative patients with penile carcinoma since 1994. Over time, several modifications were made to reduce the false-negative rate and increase the sensitivity. Comparing patients treated from 1994 to 2001 with those treated from 2001 to 2004 showed that the false-negative rate decreased from 19.2% to 4.8%, and the complication rate decreased from 10.2% to 5.7% (LE 3).[76]

DSNB is not useful in men with clinically palpable inguinal nodes (LE 3).[77] It has been suggested that extensive metastatic involvement of a SLN can lead to blocked inflow and rerouting of lymph to a "neosentinel node" that might not yet contain tumor cells, causing a false-negative result. A study of patients with unilateral palpable and cytologically proven inguinal LNM evaluated with conventional lymphoscintigraphy and single photon emission CT before DSNB confirmed the concept of tumor blockage and rerouting in 76% of the groins with palpable metastases (LE 3).[78]

The low false-negative rate reported by the group at The Netherlands Cancer Institute resulted from the following refinements[79-81]:

- Inguinal ultrasonography with FNAC to detect subtle architectural changes in nonpalpable positive nodes
- Direct palpation of the inguinal area or visualization of nodes stained with blue dye to identify nodes that were not detected by gamma emission
- Surgical exploration of the groins with low or no signal
- Routine serial sectioning and immunohistochemical examination of the involved lymph nodes.

Data coming from breast cancer studies have suggested that before routinely adopting DSNB, surgeons should complete ≥20 procedures, followed by full lymphatic clearance, with a false-negative rate of <5%. Considering the rarity of penile carcinoma, it will be extremely difficult to fulfill these requirements outside of a few high-volume referral centers.[45,46,65]

The clear advantage of DSNB compared with standard ILND is the reduced morbidity (8% vs 88%). A recent review indicated that when patients have only micrometastases (≤2 mm) in the SLN, all other inguinal nodes are clear of tumor, and the patient can be spared additional nodal dissection (LE 3).[82]

The potential disadvantages of DSNB include (a) the relatively high false-negative rate, (b) the requirement for considerable expertise and collaboration between specialists in surgery, pathology, and nuclear medicine, (c) the time required to learn and gain experience with the procedure, (d) the high cost, and (e) the necessity for quality control.[83]

Ideally, a randomized study of DSNB against standard management according to the European Association of Urology guidelines with disease-free survival as the primary endpoint should be conducted, preferably in a multi-institutional setting.[83,84] If DSNB is not feasible, superficial or modified ILND with intraoperative frozen section analysis represents an alternative for defining the presence of microscopic metastases, with relatively low morbidity.[85,86]

INGUINAL NODES—IMAGING

The high-resolution ultrasound features of early LNM include increased size, abnormal shape, short/long axis ratio <2, eccentric cortical hypertrophy, absence of an echogenic hilum, hypoechogenicity (necrosis), and abnormal peripheral vascularity using power Doppler.[87,88]

However, micrometastatic nodes cannot be reliably identified by ultrasonography alone. The major role for ultrasonography is identifying nodes infiltrated with tumor that have been bypassed by both nanocolloid and blue dye during DSNB.[88]

The diagnostic yield of ultrasonography can be improved by the addition of FNAC; however, only metastases >2 mm in size can be detected.[89,90] Ultrasonography with FNAC is only helpful if positive, because false-negative rates of ≤29% have been reported (LE 3).[1,44,91] If the FNAC findings are negative in the presence of clinical suspicion, repeat aspiration has been recommended.[44]

A prospective study showed that the combination of DSNB and groin ultrasonography, with or without FNAC, accurately identified those with occult LNM (LE 3).[88] If the ultrasound and FNAC findings confirm bilateral disease, SNB might not be necessary, and the patient can proceed to bilateral ILND (LE 3).[90] This could reduce the number of DSNB investigations needed by 10%. FNAC permits early ILND if the findings are pos-

itive, without the need for prolonged antibiotic treatment (LE 3).[92]

CT or MRI is recommended in the presence of palpable inguinal lymph nodes to assess their size, extent, and location, the possibility of major blood vessel involvement and the presence of pelvic and retroperitoneal lymph nodes and distant metastases.[44,93] In patients with nonpalpable nodes, the capacity of CT and MRI to detect LNM is limited.[5,44,94]

Positron emission tomography (PET) imaging using 18F-fluorodeoxyglucose has a high sensitivity and specificity for detecting metastases and disease recurrence in a variety of malignancies.[88,95] PET in isolation provides limited anatomic detail, and combined PET/CT correlates the functional and morphologic information.

In studies of PET/CT in patients with penile cancer, the inability to detect micrometastases (<2 mm) limited its use as a staging modality (LE 3).[44,96,97] The radiation dose from PET/CT is high compared with that from DSNB, and the availability of PET systems remains limited.[88] Because MRI is highly accurate for staging of both primary penile cancer and LNM, it might be the most useful single modality in the staging of penile cancer.[95]

Lymphotropic nanoparticle-enhanced MRI is effective because malignant lymph nodes do not take up ferumoxtran-10 (ultrasmall superparamagnetic iron oxide particles). Because the interpretation is determined by nodal function, and not structure, it is possible to detect subcentimeter metastases with high sensitivity and specificity (LE 3).[88,98]

An early study evaluated gallium-67 citrate radionuclide scanning of metastatic inguinal lymph nodes and concluded that additional study is needed (LE 3).[99]

A recent study of a novel fluorescence assay using 5-aminolevulinic acid in patients with clinical lymphadenopathy recommended additional evaluation in a larger cohort of patients (LE 3).[100]

PELVIC (ILIAC) NODES—IMAGING AND SURGICAL STAGING

In one study, the 5-year survival rate for patients with pelvic LNM was 0%.[39] However, patients with microscopic pelvic LNM might benefit from early pelvic lymph node dissection (LE 3).[15]

The prognostic factors for pelvic LNM include the number of positive inguinal nodes, involvement of Cloquet's node, the lymph node ratio (number of positive lymph nodes/total number removed), extranodal extension, p53 expression, >3 enlarged inguinal nodes on preoperative CT imaging, and lymph node size ≥3.5 cm (LE 3).[101,102]

In a single-institution study of 100 consecutive patients, pelvic lymph node dissection was positive in only 17% of men, underlining the need for stronger prognostic indicators to improve case selection (LE 3).[32]

DISTANT METASTASES

Distant metastases are uncommon in patients who present with penile cancer (<3%-5% of cases), and these are generally accompanied by regional LNMs.[98,103] Generally, hematogenous metastases occur late in the disease course and are associated with a dismal prognosis.[44]

In patients who died of disseminated penile cancer, the following metastatic sites were involved (in order of frequency): lymph nodes, liver, lungs, heart, kidneys, adrenal glands, bone, skin, thyroid, brain, pancreas, spleen, and pleura.[104,105] Hypercalcemia of malignancy has also been reported.[106]

RECOMMENDATIONS

Physical examination of the primary tumor is mandatory to evaluate the morphologic and physical characteristics of the lesion (GR A).

Evaluation of the penile lesion with ultrasonography is of limited value for local tumor staging (GR C).

Evaluation of the primary lesion with MRI during artificial erection induced by intracavernosal injection of prostaglandin can be useful for tumor staging (GR B).

Histologic or cytologic diagnosis of the primary lesion is mandatory (GR A).

For accurate histologic grading and pathologic staging, a resected specimen is preferable and not a specimen from biopsy alone (GR B).

Penile cancer should be staged according to the TNM system; however, the 1987/2002 TNM staging system requires revision that includes data from larger patient cohorts to validate the recently proposed modifications (GR B).

The histopathology report should provide information on all prognostic parameters, including the tumor size, histologic type, grade, growth pattern, depth of invasion, tumor thickness, resection margins, and lymphovascular and perineural invasion (GR B).

Physical examination of the inguinal and pelvic areas to assess the lymph nodes is mandatory (GR B).

Ultrasound-guided FNAC is indicated for both palpable and nonpalpable inguinal nodes. If the findings of FNAC confirm LNM, complete ILND is indicated (GR B).

In patients with nonpalpable inguinal nodes, if ultrasound-guided FNAC findings are tumor negative, DSNB can be performed if the equipment and technical expertise are available (GR C).

In patients at high risk of inguinal lymph node metastases according to the available guidelines and nomograms, surgical staging can be performed by complete, bilateral ILND, which might also be curative (GR B).

In patients at intermediate risk of inguinal lymph node metastases, SNB or modified (limited) ILND can be performed (GR B).

In patients with nonpalpable inguinal nodes, imaging with CT or MRI is not indicated, because it is not useful in detecting small-volume LNMs, and it is very unlikely

for large-volume LNMs (detectable by CT/MRI) to be present in the pelvic nodes (GR B).

In patients with confirmed inguinal lymph node metastases, CT of the pelvis is indicated to detect iliac node metastases (GR B).

Finally, abdominal CT and chest radiography are advisable if the pelvic CT findings are positive (GR B).

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