Penile Cancer

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INTRODUCTION

Penile cancer accounts for less than 1% of adult male cancers in the Western world. The incidence in Europe and the United States is 0.1 to 0.9 per 100,000 and 0.7 to 0.9 per 100,000 men, respectively. This translates into an estimated 1470 cases of penile cancer in the United States in 2005, with 270 deaths attributable to the disease. However, in areas of Africa, Asia, and South America, penile carcinoma can account for up to 17% of malignant disease in men. Population-based cancer registries note an incidence of 3 per 100,000 people in rural India.

Penile carcinoma can occur at any age, including childhood, but its peak incidence is in the sixth and seventh decades of life. Incidence also varies among people of the same ethnic group but who live in or move to different geographic areas, although it is unclear whether this is secondary to social or environmental factors. Penile carcinoma is rare in ethnic groups that routinely practice circumcision. A 2004 review of the Surveillance, Epidemiology, and End Results program database that incorporated penile cancer cases from 1973 to 1998 found that factors predictive of decreased survival were higher stage of disease at diagnosis, age older than 65 years, African-American race, and disease within the lymph nodes. Cigarette smoking may also be a risk factor for the development of penile squamous cell carcinoma (SCC).

SCC is the most frequent variant of penile cancer, occurring in approximately 95% of cases. Penile carcinoma in situ (CIS) is restricted to the epithelium and does not invade the underlying dermis (known as erythroplasia of Queyrat or Bowen’s disease, depending upon location on the penis). A well-differentiated variant of SCC, verrucous carcinoma, is found in 3% to 5% of penile carcinomas. Most cases of verrucous carcinoma occur in patients younger than 50 years and appear to be more common in uncircumcised homosexual men. Sarcoma, melanoma, basal cell carcinoma, and lymphoma are all malignancies that can involve the penis.

Given the low prevalence of penile cancer, there is limited understanding of diagnosis, staging, and treatment. This manual reviews evaluation and management of the primary penile lesion as well as management of inguinal lymph nodes.

CLINICAL CORRELATES OF PENILE CANCER

In uncircumcised men, penile cancer has been correlated with smegma, a byproduct of bacterial action on desquamated cells within the preputial sac. Phimosis and poor hygiene allow smegma to collect under the foreskin. Although the exact carcinogenic mechanism is unclear, it is suspected that smegma leads to inflammation and recurrent infections, which may contribute to development of SCC of the penis. Phimosis is seen in approximately 75% of patients with penile carcinoma but the true incidence is probably higher, as the prepuce is often destroyed by the tumor in patients presenting with penile SCC. Neonatal circumcision appears to lower the risk of penile cancer by at least tenfold; however, the exact mechanism is unclear. Conversely, circumcision performed later in childhood or in adulthood does not appear to be protective against the development of SCC. This favors the argument that some exposure to smegma or a closed preputial sac is a key factor for cancer development.

SCC of the penis does not appear to be linked with sexually transmitted bacterial diseases; however, SCC is associated with sexually transmitted human papillomavirus (HPV). Genital HPV is detected in 15% to 71% of patients with penile carcinoma, and patients with a history of anogenital warts appear to have a 5 to 6 times greater risk for development of penile cancer over their lifetime. Several subtypes of HPV, including HPV 16, 18, 31, and 33, are present in a majority of invasive and in situ carcinomas, whereas HPV 6 and 11 may be more common in more well-differentiated verrucous carcinoma of the penis. Penile cancer has also been associated with HIV infection, but this correlation has been challenged because areas where HIV is endemic (e.g., Uganda) have not demonstrated an increased incidence of penile carcinoma.

Patients with psoriasis treated with 8-methoxypsoralen...
and ultraviolet-A (PUVA) photochemotherapy are 286 times more likely to develop penile SCC compared with the general population.²⁰ Men who received more than 200 treatments with PUVA had a 30-fold increased risk of nongenital squamous skin cancer compared with those who did not receive PUVA.²¹ Men who receive PUVA who do not have genital psoriasis and men exposed to ultraviolet light in tanning booths should shield their genitals.²²

Balanitis xerotica obliterans (BXO) is a chronic inflammatory disorder of unknown etiology that occurs on the prepuce and/or glans. It often causes meatal stenosis, urethral strictures, and phimosis and has been associated with SCC of the penis.⁶ The exact mechanism of cancer formation is unclear, but it is thought that phimosis secondary to chronic inflammation associated with BXO may be more carcinogenic than BXO itself.²²

**PREMALIGNANT/PRECURSOR LESIONS**

Premalignant lesions such as cutaneous horn, balanitis, giant condyloma, and bowenoid papulosis have been associated with penile carcinoma. CIS of the penis is referred to as erythroplasia of Queyrat when it occurs on the glans and Bowen’s disease when it involves the skin of the penile shaft. Penile CIS is thought to be a precursor to penile SCC; 10% of patients with penile CIS develop invasive SCC, but this rarely results in regional metastatic disease.²³

There are no uniform guidelines regarding treatment of Bowen’s disease or erythroplasia of Queyrat. Surgical excision with negative margins is curative in most patients. For lesions on the foreskin, circumcision is effective.²¹ The typically indolent nature of penile CIS allows most local therapies to be successful. Laser therapy and cryotherapy with liquid nitrogen have also been effective in treating penile CIS.²⁵ Topical therapy with 5-fluorouracil and imiquimod cream either alone or in combination is successful in selected patients; however, treatment duration is unknown and may be as long as 16 weeks.²⁴,²⁶

**EVALUATION AND MANAGEMENT OF THE PRIMARY LESION**

**CLINICAL PRESENTATION**

The clinical presentation of penile SCC ranges from an area of induration to an ulcer or a warty exophytic mass.²⁵ Regardless of presentation, the affected areas will enlarge superficially and infiltrate deeper tissues. Erythema, induration, bleeding, and secondary infection are common.¹¹ Without treatment, the lesion advances until a persistent foul-smelling purulent discharge exudes from beneath a phimotic, nonretractive foreskin in uncircumcised men. Eventually, penile SCC progresses along the penile shaft and involves the corpora cavernosa.²³ Urinary fistulas and urinary retention may also be seen with invasion into the urethra.²⁷

In more than 90% of cases, penile SCC presents on the glans or foreskin. Primary involvement of the penile shaft occurs in only 2% of cases.²⁷ Patients may be asymptomatic, but most have pruritus, burning, or pain at presentation. Pain is usually minor in relation to the amount of local disease and does not usually cause the patient to seek medical attention. Weakness, malaise, and weight loss may also be seen in patients with advanced disease. Most patients delay seeking medical attention because of fear, embarrassment, ignorance, or personal neglect.⁶

Inguinal lymphadenopathy is present in 28% to 64% of patients with penile SCC.⁶,²⁷ Approximately 45% of those with lymphadenopathy at diagnosis have lymphatic metastasis.²⁸ In more than 50% of patients, swelling of regional inguinal lymph nodes is a result of secondary infection of the primary lesion. Approximately 20% of patients presenting with impalpable inguinal lymph nodes have nodal metastasis.²⁸,²⁹ Distant metastases—typically to lung and liver, less often to bone, brain, and skin—are rare and occur late in the disease process.¹²,³⁰

**CASE 1 PRESENTATION**

A 60-year-old uncircumcised man is referred to a urologist for evaluation of a 1-cm painless indurated lesion under the foreskin on the glans penis. The patient’s primary care physician treated the lesion with topical steroid therapy for 3 months with no success. Phimosis is evident on the foreskin, and the area around the lesion is raised, indurated, and erythematous. Results of routine serum testing are normal.

- **What is the best method to diagnose this suspicious penile lesion? How is penile carcinoma staged?**

**DIAGNOSIS AND STAGING**

The standard approach to diagnosing a suspicious penile lesion is by punch, incisional, or excisional biopsy. Biopsy of the primary lesion will confirm the diagnosis and the histologic grade of the tumor and allow extension into deeper tissues to be assessed.³¹ If
the primary lesion is concealed by phimotic foreskin, a dorsal slit or circumcision may be necessary to complete the biopsy. An adequate biopsy sample of the primary lesion is excision of a 1-cm elliptical wedge on the margin of the lesion so that it includes healthy tissue. In the case of small superficial lesions, biopsy may be both diagnostic and curative. Inguinal lymph nodes should be examined at the time of presentation to evaluate for the presence of adenopathy.

Results of biochemical testing are usually normal in patients with penile carcinoma. Patients with severe infection may demonstrate leukocytosis. In some patients with advanced disease, hypercalcemia may be seen. Severe local nodal invasion that causes ureteral obstruction may result in an elevation of serum creatinine.6

The most commonly used staging system in penile carcinoma is the 1987 TNM classification (Table 1),32 which incorporates the depth of invasion of the primary lesion and the extent of lymph node involvement. Survival for patients with invasive SCC is primarily related to lymph node involvement.33 Survival for those with T1 to T3, NO, MO tumors is as high as 93%, while patients with pelvic lymph node involvement have a 5-year survival less than 5%.34

Incisonal biopsies of the primary penile lesion may not correlate with the exact histologic grade (30%) and deepest point of penile invasion (91%) when compared with final penectomy specimens.35 Imaging may aid in staging patients more appropriately than biopsy and physical examination alone. Penile ultrasonography can accurately demonstrate invasion of the tunica or corpora cavernosa.36 This may be important when trying to preserve penile length in patients because physical examination often overestimates the extent of penile involvement.36,37 The nonspecific appearance of soft tissue on computed tomography (CT) makes this modality ineffective in evaluating primary penile lesions, but CT is very effective in detecting inguinal or pelvic lymphadenopathy. In those with advanced nodal involvement, CT is helpful in determining vascular invasion.6,38 Magnetic resonance imaging is more than 80% accurate in detecting depth of invasion of the primary lesion and can detect lymph node enlargement or vascular invasion of lymph nodes in patients with advanced disease.39 None of the aforementioned imaging modalities can detect microscopic lymph node metastasis in the absence of detectable lymphadenopathy.

**PREDICTING DISEASE-SPECIFIC SURVIVAL**

Several nomograms are available to predict disease-specific survival probabilities in urologic oncology and aid in selection of appropriate therapy in individual patients. A nomogram was recently developed to predict inguinal lymph node involvement in patients with SCC of the penis,39 using clinical and pathologic data from 265 patients treated for penile SCC at 11 centers over a 22-year period (1980–2002). The nomogram (Figure 1) has a concordance index of 0.876 (compared with 0.5 for flipping a coin), calibrates well, and includes various pathologic variables to evaluate the probability of lymph node metastasis. Using the same data, a similar nomogram was developed to evaluate cancer-specific survival in patients undergoing partial or total amputation of the penis.40 These nomograms also calibrate well and have a high concordance index (0.728 and 0.747, respectively).

**CASE 1 CONTINUED**

An incisional biopsy performed in the office under local anesthesia demonstrates a low-grade (grade 1) penile SCC that does not invade the deeper tissues. The lesion is not completely excised.

- **What are the options for management of this patient’s primary penile lesion?**

**MANAGEMENT OF THE PRIMARY LESION**

Penile SCC is largely a locoregional disease in which distant metastasis is rare, especially in Tis, Ta, T1, and lower-grade tumors. In selected cases in which the lesion is confined to the foreskin, circumcision alone is appropriate. The local recurrence rate of penile SCC treated with circumcision may approach 30%, and close follow-up is warranted.41 The standard of care for invasive carcinoma involving the glans, corpora cavernosa, or urethra is partial penectomy with a 2-cm surgical margin, with a goal of preserving sexual function and the ability to stand for urination. Total penectomy with perineal urethrostomy is reserved for patients with large lesions or proximal lesions in which a 2-cm surgical margin would leave the patient unable to stand and urinate.42 The local recurrence rate for tumors removed with partial penectomy and a 2-cm margin is approximately 6%. Local recurrence following partial penectomy is best managed with total penectomy and perineal urethrostomy.43 Local recurrence after total penectomy is very rare.44 Treatment of the primary lesion is often tailored to tumor size, grade, and depth of invasion (Figure 2).

**Limited Tumor Excision**

Patients often refuse radical therapies for penile SCC, and over the last 2 decades, there have been changes in how primary penile lesions are managed.
to avoid disfiguring surgery. The need for 2 cm surgical margins has been questioned. A prospective histologic analysis concluded that microscopic tumor spread correlated with tumor grade. Grades 1 and 2 tumors showed maximal histologic spread of 5 mm, and grade 3 tumors showed maximal histologic spread of 10 mm.\textsuperscript{45} Another review confirmed maximal microscopic margins of 10 mm in pathologic specimens from tumors of grade T1 or greater.\textsuperscript{46} A 2005 study evaluated 51 patients with penile SCC treated with partial penectomy, wide local excision, and glans excision over a 26-month period and found that margins less than 2 cm did not compromise oncologic control.\textsuperscript{47} Two patients (4\%) developed local tumor recurrence that was successfully treated with partial penectomy. Both patients had grade 3 lesions, but 1 lesion was a T1 tumor and the other was a T3 lesion. The authors concluded that there were no histopathologic factors to distinguish patients at higher risk for recurrence.\textsuperscript{47} These data suggest that 2-cm margins may not be required to excise lower-grade lesions with negative intraoperative frozen section margins. It should be noted that these data have not yet been evaluated in a prospective study, and close follow-up of patients is required.

Limited Excision and Reconstruction

Reconstruction of the distal penis following glansectomy for cancer limited to the glans has been successful using scrotal or preputial flaps.\textsuperscript{48,49} In a recent study, 7 patients with invasive penile SCC (4 with T1 and 3 with T2 lesions) underwent wide local excision followed by resurfacing with skin grafts (either split-thickness or full-thickness) or shaft skin advancement.\textsuperscript{50} There was 1 recurrence over a 1- to 5-year follow-up, which was treated successfully with wide local excision. Limitations to phallus-sparing approaches include proximal lesions, deep tumor invasion, and poor health status of patients who could not tolerate salvage therapy in the event of a recurrence.

Mohs Micrographic Surgery

Mohs micrographic surgery involves excising the neoplasm layer by layer while microscopically examining frozen sections of tissue to ensure that normal tissue and function are preserved.\textsuperscript{51} This technique is most successful in penile CIS and very small lesions. Lesions larger than 3 cm or those with corpora cavernosa invasion have unacceptable recurrence rates, and the use of Mohs micrographic surgery should be discouraged in these patients.\textsuperscript{52} Recurrence following Mohs micrographic surgery should be treated with wide local excision or amputation.\textsuperscript{53}

**Table I. TNM Classification and Staging of Penile Carcinoma**

<table>
<thead>
<tr>
<th>Classification</th>
<th>T: Primary Tumor</th>
<th>N: Regional lymph nodes</th>
<th>M: Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td>Primary tumor cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>No evidence of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No regional lymph node metastasis</td>
<td>N0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N1</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive verrucous carcinoma</td>
<td>N2</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue</td>
<td>N3</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades corpus spongiosum or cavernosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades urethra or prostate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades other adjacent structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td><strong>T</strong></td>
<td><strong>N</strong></td>
<td><strong>M</strong></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ta</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>N0, N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N0, N1, N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>


Laser Therapy

Laser treatment of penile cancer relies mainly on ablation of the tumor by vaporization or coagulation. The most common lasers used for penile SCC are the CO\textsubscript{2} laser and Nd:YAG (neodymium:yttrium-aluminum-garnet) laser.\textsuperscript{55} The depth of penetration of the CO\textsubscript{2} laser is 0.1 mm, whereas the depth of penetration of the Nd:YAG laser is up to 6 mm.\textsuperscript{54} Recurrence rates after use of the CO\textsubscript{2} laser have been as high as 50\%, presumably due to the laser’s limited tissue penetration.\textsuperscript{55,56} The CO\textsubscript{2} laser ablates lesions in a bloodless field with
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minimal tissue coagulation, allowing for immediate microscopic examination of tissue margins. Recurrence rates following use of the Nd:YAG laser have been comparable with partial penectomy. In a study of 29 men with CIS and T1 lesions treated with Nd:YAG laser followed by tumor base biopsies, 2 recurrences (6.9%) were noted with a mean follow-up of 46.7 months. In a study of 67 women treated with a combination of the CO2 laser to ablate the lesion followed by the Nd:YAG laser to ensure deep margin ablation, there were 13 (19%) local recurrences over a mean follow-up of 42 months, with no deaths. Laser therapy may have a role in selected patients with smaller, low-grade lesions if combined with frozen section biopsies. However, local recurrence is possible, and close follow-up is mandatory.

Radiotherapy

In Europe, external beam radiotherapy is a popular treatment for penile SCC. SCC is typically radioresistant, and high doses (> 60 Gy) of radiotherapy are required for proper sterilization of the tumor. However, the high dose of radiation can lead to urethral fistulas, strictures, penile necrosis, and penile pain in 6% to 45% of patients. Secondly, radionecrosis or postradiation ulcers cannot be distinguished from recurrent cancer, which may lead to repeated biopsies. In addition, biopsies from this irradiated tissue may be difficult to interpret by pathologists and can also lead to further penile necrosis at the biopsy site. Local control rates using radiotherapy can be as high as 80% for small lesions (≤ T2), but recurrence rates may approach 66% for larger lesions (> 3 cm) or T2 to T3 lesions.

Brachytherapy has been the treatment of choice for penile SCC in France for more than 20 years. Local control rates with iridium 192 implants range from 70% to 95%. Side effects of brachytherapy are similar to those seen with external beam radiotherapy. There are no prospective trials comparing external beam radiotherapy with brachytherapy for treatment of penile SCC. Proponents of radiotherapy argue that there are psychosexual advantages of phallus preservation; yet, most acknowledge that surgical amputation provides superior local control than radiation. However, there does not appear to be a survival advantage for one modality over the other, and most recurrences following radiation can be successfully treated with surgical excision.
**LYMPH NODE MANAGEMENT**

**CASE 2 PRESENTATION**

A 64-year-old uncircumcised man presents for a second opinion regarding treatment for a 2-cm indurated penile lesion. The lesion was excised by the patient’s primary urologist, and pathologic findings confirmed a T1, grade 3 lesion. At the time of his first visit, the patient had palpable tender inguinal adenopathy on the left side, which resolved following 2 weeks of antibiotics. A CT scan failed to demonstrate lymphadenopathy. The patient refused the first urologist’s recommendation of inguinal lymphadenectomy.

- **What is your recommendation for inguinal lymph node management?**

  The presence and extent of inguinal lymph node involvement is the most significant predictor of survival in men with SCC of the penis. Patients with no inguinal lymph node metastasis have survival rates more than double those of patients with untreated lymph node metastasis. Metastasis to pelvic lymph nodes is associated with very low 5-year survival. Unlike other genitourinary cancers in which systemic therapies are given once metastasis occurs, inguinal lymph node dissection in penile SCC is diagnostic and can be curative in a majority of cases. However, inguinal lymph node dissection is associated with relatively high surgical morbidity rates and may not be required in every patient. The availability of minimally invasive techniques for lymph node sampling appears to have decreased morbidity by facilitating selection of patients who can safely avoid full inguinal node dissection.

**LYMPHATIC DRAINAGE OF THE PENIS**

The inguinal nodes are divided into superficial and deep nodes, with superficial nodes situated below Scarpa’s fascia and above the fascia lata covering the muscles of the thigh. The deep nodes are situated around the fossa ovalis (the opening in the fascia lata where the saphenous vein drains into the femoral vein) and connect to the deep pelvic nodes around the iliac crest.
vessels. Superficial and deep nodes cannot be distinguished by physical examination.\textsuperscript{23} Lymphoscintigraphy studies confirm that bilateral lymphatic drainage of the penis is the rule.\textsuperscript{65}

**PROPHYLACTIC INGUINAL LYMPH NODE DISSECTION**

Fifty percent of palpable nodes present at the time of diagnosis are reactive/inflammatory and will resolve with antibiotic therapy. However, the majority of palpable lymph nodes after antibiotic treatment harbor malignancy, and these patients should undergo inguinal lymph node dissection. Lymphadenectomy is curative in 80% of patients who present with 1 or 2 invaded lymph nodes.\textsuperscript{25,66} Lymphadenectomy cure rates decrease as the extent of lymph node involvement increases, but cure is still possible even with involved pelvic nodes.\textsuperscript{25} There has been debate regarding the need for and timing of inguinal lymphadenectomy in patients with clinically negative lymph nodes at diagnosis. Up to 29% of patients with clinically negative nodes will have occult metastasis detected on lymphadenectomy.\textsuperscript{67} If inguinal lymph node dissection were performed on all patients with penile cancer and clinically negative lymph nodes, 70% of these men could experience significant morbidity without benefit. The question remains whether or not prophylactic inguinal lymph node dissection is beneficial compared with treating lymph node metastasis as it develops.

Four contemporary series demonstrate that prophylactic inguinal lymphadenectomy provides a significant survival advantage compared with treating metastasis as it develops.\textsuperscript{44,68,69} A most recent series by Kroon et al\textsuperscript{70} confirmed these results; 3-year survival in patients with occult metastasis was 84% in the early lymphadenectomy group versus 35% for those who underwent observation followed by therapeutic lymphadenectomy. In addition, many patients who underwent observation with subsequent lymphadenectomy had extranodal extension of the cancer at the time of lymphadenectomy. As in the previous series, delayed therapeutic resection was much less successful in curing patients with disease recurrence. Although these studies provide a strong argument for prophylactic lymph node dissection, the data are retrospective and no prospective randomized trials have been completed.

Anatomic structures surrounding the inguinal lymph nodes include the femoral artery and vein, inguinal ligament, adductor muscle, and sartorius muscle. Compared with pelvic or retroperitoneal lymphadenectomy where complications are limited, an ilio-inguinal lymph node dissection can cause substantial morbidity, including phlebitis, wound infection, disabling lymphedema of the scrotum and legs, deep venous thrombosis, and lymphocele. Modern surgical techniques, such as myocutaneous flap coverage, saphenous vein preservation, and dermal sparing, have reduced surgical morbidity.\textsuperscript{71} Surgical complications have also been reduced in cases of prophylactic dissections and microscopic metastasis compared with gross nodal involvement,\textsuperscript{72} possibly as a result of preserving local blood supply and fewer radical excisions of lymphatic channels. A contemporary series of 40 inguinal lymph node dissections revealed a 10% rate of lymphedema and 2.5% flap necrosis rate, with only 2.5% of patients requiring percutaneous drainage of a lymphocele.\textsuperscript{72}

**ALTERNATIVES TO INGUINAL LYMPH NODE DISSECTION**

Alternatives to full inguinal lymph node dissection include techniques that can identify patients who are truly lymph node negative, thus avoiding the morbidity of full lymph node dissection.

**Assessment of Pathologic Indicators**

Table 2 outlines patients who can be categorized as low risk or high risk for occult lymph node metastasis based on pathologic findings from biopsy.\textsuperscript{23,67} Studies suggest that lymph node dissection can be safely avoided in patients with Tcis, Ta, and low-grade T1 tumors if close follow-up is maintained. Only 2 cases of lymph node metastasis have been reported in patients with CIS (Tcis), and there has never been a case of metastasis noted in patients with verrucous carcinoma (Ta). T1 cancers are associated with occult metastasis in 4% to 14% of patients.\textsuperscript{73,74} Studies have demonstrated that tumor grade is the largest predictor of occult metastasis in T1 tumors. Low-grade T1 tumors (grades 1 and 2) have an approximately 4% to 6% chance of harboring metastasis compared with a 81% risk in high-grade (grade 3) T1 tumors.\textsuperscript{75,76}

Tumor invasion into the corpora cavernosa (T2) is associated with an approximately 60% chance of inguinal

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**Table 2.** Categorizing Patients at Low and High Risk for Occult Metastasis

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tcis, Ta</td>
<td>Grade 3 pathology</td>
</tr>
<tr>
<td>T1 grade 1 and 2</td>
<td>T2–T3</td>
</tr>
<tr>
<td>No vascular invasion</td>
<td>Vascular invasion</td>
</tr>
</tbody>
</table>

metastasis. Vascular invasion has been shown to correlate with the presence of inguinal metastasis. In an analysis of patients with penile SCC, nodal metastasis was seen in 71% of patients with T2 or greater tumors with vascular invasion compared with 11% of patients without vascular invasion. Lymph node evaluation is warranted for high-risk patients, such as those with high-grade T1 lesions or with vascular invasion and greater than T2 lesions.

Fine-Needle Aspiration

Multiple diagnostic techniques for evaluation of inguinal lymph nodes have been proposed. Fine-needle aspiration (FNA) requires lymphangiography for nodal localization and multiple nodes must be sampled, but experience with this approach is limited. Sensitivity is approximately 71% in clinically negative nodes. The low sensitivity and technical challenges of FNA limit its use in patients with clinically negative lymph nodes. However, FNA can be used to examine large palpable nodes in which a positive aspiration can confirm metastasis and guide treatment.

Sentinel Lymph Node Biopsy

The sentinel node is the first lymph node that receives direct drainage from the primary tumor. Lymphangiographic studies completed in the 1970s confirmed that the penis may have a sentinel node, although anatomic studies demonstrated that the sentinel node was in fact multiple nodes located around the superficial epigastric vein. Multiple tracers and techniques have been used to advance lymphatic mapping and improve the technique of sentinel node biopsy. A dual-tracer technique utilizing preoperative blue dye injection and gamma ray detection of lymph nodes was able to identify a sentinel node in 98% of patients with clinically negative lymph nodes. The sensitivity of this technique was approximately 80%; therefore, the authors recommended very close follow-up. Seven percent of patients had complications from the procedure, including wound infections and seromas, but all complications resolved without long-term sequelae. It should be noted that positive results with any of the above techniques should be followed with inguinal lymph node dissections.

Penile Lymphangiography

Penile lymphangiography has shown that direct pelvic lymph node metastasis without inguinal lymph node involvement is rare. Therefore, superficial inguinal or modified inguinal lymph node dissections have been proposed as accurate inguinal lymph node staging techniques with minimal morbidity. Superficial node dissection involves removal of nodes superficial to the fascia lata. If positive nodes are found on frozen section analysis, complete ilio-inguinal lymphadenectomy should be performed. Two studies have shown that no positive nodes were found deep in the fascia lata unless superficial nodes were positive. Modified inguinal lymph node dissection was first proposed in 1998 and is now defined as preservation of the saphenous vein and reduction of external and inferior boundaries. There is no transposition of the sartorius muscle, and the skin incision is much smaller than with radical lymphadenectomy. The diagnostic sensitivity is high, and although the procedure is not without morbidity, morbidity occurs less often as compared with radical lymphadenectomy. Sanchez-Ortiz and Pettaway explained 3 additional benefits of modified or superficial inguinal lymph node dissections: (1) more tissue is available, making pathologic testing more reliable as compared with biopsy of 1 node or a group of nodes, (2) the approach removes all first-level nodes, thereby avoiding improper identification of a sentinel node, and (3) there is an easy learning curve for any surgeon experienced in inguinal surgery.

CASE 2 CONTINUED

The patient undergoes bilateral modified inguinal lymph node dissections. Pathology on the right side is consistent with SCC metastasis, and formal lymph node dissection on the right side demonstrates involvement of 3 nodes microscopically with vascular invasion.

- Is contralateral inguinal dissection indicated? What about pelvic node dissection?

EXTENT OF LYMPHADENECTOMY

In patients with clinically positive nodes, bilateral radical lymphadenectomy should be performed after a 2- to 4-week course of antibiotics. This will reduce the incidence of wound infections and wound complications. Bilateral lymphadenectomy is advocated in patients with unilateral palpable lymphadenopathy due to bilateral lymph node drainage evident on penile lymphangiography. In patients who present with unilateral lymphadenopathy following treatment of a penile lesion, it should be assumed that clinically undetectable inguinal metastasis would enlarge at the same rate and thus adenopathy would be uniformly present. Currently, formal inguinal lymph node dissection and pelvic lymph node dissection on the involved side and a diagnostic modified or superficial dissection on the contralateral side are recommended, followed by formal dissection if superficial nodes are positive.
The average 5-year survival of patients with pelvic lymph node metastasis is approximately 10%,25 Pelvic lymph node dissection can be curative (as high as 66%) in patients with focal involvement.85 Patients with inguinal metastasis have a 20% to 30% chance of pelvic lymph node involvement.29,86 Those with only 1 involved lymph node and no involvement of the highest lymph node dissected in the chain have a low chance of pelvic lymph node involvement.29 Current standard of care is pelvic lymph node dissection in patients with 2 positive inguinal nodes or extracapsular invasion; however, some authorities advocate pelvic node dissection in all patients with positive inguinal nodes.84 While the full therapeutic value of pelvic lymph node dissection is debatable, it can confirm cancer stage and may identify candidates for adjuvant chemotherapy or radiation.

CASE 3 PRESENTATION

A 64-year-old man presents with penile SCC following total penectomy for a large indurated penile mass extending from the glans down the shaft of the penis. CT demonstrates multiple, large matted nodes in the inguinal region and enlarged pelvic lymph nodes, which appear to be unresectable at this time. FNA of 1 inguinal node is positive for SCC.

- Are there any chemotherapeutic regimens to which this tumor may respond?

MULTIMODAL THERAPY

Following definitive surgical therapy, penile cancer recurs in patients with poor prognostic features (> 2 lymph nodes involved, bilateral inguinal metastasis, extranodal extension, pelvic node metastasis).32,67 Use of chemotherapy in penile cancer is limited, but the most studied regimens include combinations of methotrexate, bleomycin, cisplatin, and cisplatin with 5-fluorouracil.87 This regimen has the potential for systemic toxicity and possibly death. Partial response occurs in approximately two thirds of patients with metastatic disease, and complete response is seen in fewer than 15% of patients.67,88 Systemic chemotherapy may be used in patients with fixed nodal metastasis, bulky adenopathy, or disease extension to contiguous structures to decrease tumor burden before surgical excision is contemplated.89 Additional clinical trials are needed to clarify the benefit of adjuvant chemotherapy in patients with inguinal metastasis and of neoadjuvant therapy in patients with widespread unresectable disease.

Radiotherapy appears to have no role as primary treatment in patients with lymph node metastasis, with a 5-year survival of at least half that of surgery.25 There are no solid data supporting adjuvant radiotherapy in metastatic groins that have been treated with surgical excision. In a study of 9 patients who underwent adjuvant radiotherapy following surgical resection, only 1 patient had recurrence, but the study did not stratify patients by the extent of nodal involvement.80 Pelvic radiation may aid in local control in patients with widespread nodal metastasis or pelvic fixation.23 Multinstitutional randomized studies are needed to define the role of adjuvant and neoadjuvant radiation either alone or in combination with surgery or chemotherapy.

CONCLUSION

Penile cancer is a relatively rare malignancy in the Western world, and the limited incidence has made clear etiology and risk factors difficult to ascertain. Penile cancer is a locoregional disease best managed with surgery. New data have demonstrated that phallic preservation with ablative therapies (eg, laser, creams, Mohs surgery) or limited surgical excision (partial penectomy) is safe in selected patients. Management of patients with clinically negative nodes remains controversial, but current data suggest a survival benefit with prophylactic lymphadenectomy in patients with invasive disease or high-risk features. Chemotherapy and radiotherapy may have a role in patients with widespread metastatic disease, but the exact benefit of their use alone or in combination with each other or with surgery is yet to be determined.

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