



Anita Philyaw. *Sometimes I Dream Ancient Memories* (detail), 2001. Acrylic on canvas, 18" × 24". Courtesy of Stella Jones Gallery, New Orleans, La.

*Penile cancer, a rare disease  
in the United States,  
poses diagnostic, staging,  
and treatment challenges.*

## Cancer of the Penis

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**Background:** *Cancer of the penis is an uncommon malignancy in developed countries, but the incidence is as high as 17% of all male cancers in some undeveloped countries. The surgical management of this disease has improved due to better knowledge of risk for metastasis and newer imaging technologies to assess the regional lymph nodes.*

**Methods:** *We review the literature on incidence, etiology, pathology, clinical presentation, staging, and management of penile cancer. We present our institutional experience with 160 patients who underwent extended ileoinguinal lymph node dissection, as well as with 7 patients who underwent a modified lymph node dissection.*

**Results:** *Better understanding of pathologic features allow for stratification of patients into low, intermediate, or high risk for lymph node involvement. Lymphatic mapping to this stratification improves selection of patients who might benefit from lymph node dissection after excision of the primary lesion. Our experience with lymph node dissection yielded a high incidence of positive lymph nodes when lymphadenopathy was present. The recent use of a modified lymph node dissection has minimized morbidity. Current chemotherapy agents are ineffective in this disease.*

**Conclusions:** *Pathologic features of the primary lesion and the incorporation of lymphatic mapping have improved the selection of patients who might benefit from lymph node dissection. The use of a modified lymph node dissection in selected patients has decreased morbidity. Effective chemotherapy agents are needed in the management of advanced penile cancer.*

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### Incidence

Penile cancer is an uncommon malignancy in developed countries. In the United States, 1,400 cases occur per year.<sup>1</sup> Higher incidence rates are seen in Africa and Asia (10% to 20%),<sup>2</sup> and in areas of Brazil, penile cancer accounts for 17% of all malignancies in men.<sup>3</sup> At the Instituto de Enfermedades Neoplásicas in Peru, 272 new cases of penile cancer were diagnosed between 1985-1997, making this disease the 23rd most

common malignancy and representing 1.3% of all malignancies in men.<sup>4</sup> In the Western world, the usual age at presentation is in the 6th decade.<sup>5</sup> Penile carcinoma is typically a disease of middle-aged to older men, most commonly affecting those between 50 and 70 years of age. Younger individuals are also affected; approximately 22% of patients are less than 40 years of age.

## Epidemiology

The most important etiologic factor of penile cancer is the presence of an intact foreskin. Penile cancer is rarely seen in Jewish individuals, who are circumcised at birth.<sup>6</sup> In the United States, the risk of this disease in uncircumcised men is 3-fold higher than that of circumcised men and approaches the rate seen in some underdeveloped nations.<sup>7</sup>

Maden et al<sup>7</sup> reported a study of 110 men with penile cancer and 355 control subjects. The risk of penile cancer was 3.2 times greater among uncircumcised men compared with men circumcised at birth and 3.0 times greater among those who had been circumcised after the neonatal period.

Schoen and colleagues<sup>8</sup> evaluated the relationship between newborn circumcision and invasive penile cancer among adult men who were members of a large health maintenance organization. Of 89 men with invasive penile cancer whose circumcision status was known, 2 (2.3%) had been circumcised as newborns and 87 were not circumcised. This study confirms the highly protective effect of newborn circumcision against invasive penile cancer.

The protective effect of circumcision is likely due to the lack of accumulation of smegma that forms from desquamated epithelial cells. To date, the precise carcinogenic substance in smegma is not known. The protective effect of circumcision is diminished when performed later in life as evidenced by the higher incidence of penile carcinoma among Muslim men compared with Jewish men. Poor hygiene also contributes to the development of penile carcinoma through accumulation of smegma and other irritants. In populations that practice good hygiene but are uncircumcised, the incidence of penile carcinoma approaches that of circumcised populations.

A history of phimosis (ie, narrowness of the opening of the prepuce) is found in approximately 25% of penile cancer patients. Phimosis is strongly associated with invasive carcinoma of the penis.<sup>9</sup> Precancerous lesions are found in an additional 15% to 20% of patients.<sup>10</sup>

An ongoing focus of research in the study of penile cancer is the association of human papilloma virus (HPV) with both benign and malignant lesions of the penis. Rubin et al<sup>11</sup> evaluated the prevalence of HPV DNA in different histological subtypes of penile carcinoma, dysplasia, and condyloma. HPV DNA was detected in 42% of cases of penile carcinoma, in 90% of cases of dysplasia, and in 100% of cases of condyloma.

Many studies have shown the presence of HPV types 16 and 18 in penile carcinoma.<sup>12-15</sup> In an examination of 30 specimens of penile cancer by polymerase chain reaction and in situ hybridization assays from 23 patients, the HPV-16 genome was found in 15 patients (65%), HPV-30 in 3 patients (13%), and HPV-6 or HPV-11 in 2 patients (9%).<sup>14</sup> Recently Bezerra et al<sup>15</sup> detected HPV DNA in 25 of 82 samples (30.5%). HPV-16 was the most frequent type detected (13 of 25, 52%).

The mechanism by which HPV leads to malignant transformation is likely mediated through two viral genes, E6 and E7, which are actively transcribed in HPV infected cells. The E6 and E7 proteins bind to and inactivate the host cell's tumor suppressor gene products p53 and pRb (retinoblastoma gene), both of which are known negative regulators of cellular proliferation, leading to uncontrolled growth.<sup>16</sup>

Based on a review of the epidemiology of invasive penile cancer identified by a MEDLINE search of scientific publications from 1966-2000, Dillner et al<sup>17</sup> evaluated the etiology of squamous cell carcinoma of the penis. In this study, strong risk factors (>10) identified by case-control studies included phimosis, chronic inflammatory conditions (eg, balanoposthitis and lichen sclerosus et atrophicus), and treatment with psoralen and ultraviolet A photochemotherapy (PUVA). A consistent association was found between penile cancer and smoking that was dose-dependent and not explained by confounding factors such as sexual history. Sexual history and self-reported history of condyloma were associated with a 3-5-fold increase in penile cancer risk. The authors also cite a case-control study showing that circumcision neonatally, but not after the neonatal period, was associated with a 3-fold decreased risk of penile cancer. Finally, in a large number of case series, HPV DNA was positive in invasive penile cancer in 40% to 50% of cases.

## Pathology

Malignancies of the penis are divided into primary malignancies (ie, those that originate from either the soft tissues, urethral mucosa, or covering epithelium) and secondary malignancies (ie, those that represent

metastatic disease and often affect the corpus cavernosum). The first step in the histological diagnosis of malignancy is the confirmation of the diagnosis and assessment of depth of invasion by microscopic examination of a biopsy specimen. A dorsal slit is often necessary to gain adequate exposure to the lesion.<sup>18</sup>

Secondary malignancies (metastatic tumors) should be suspected in patients with a known diagnosis of cancer and who also present with new-onset priapism (involvement of the corpora cavernosum) or an unusual penile lesion. Metastatic lesions are often multiple, palpable, painless nodules that may mimic syphilitic chancres. The primary malignancy is most often prostate, followed by bladder, rectosigmoid colon, and kidney, and it is spread most commonly by retrograde venous dissemination.<sup>19,21</sup>

Primary, nonsquamous malignancies comprise less than 5% of penile cancers. Sarcomas are the most frequent nonsquamous penile cancers, followed by melanomas, basal cell carcinomas, and lymphomas.<sup>18</sup> Kaposi's sarcoma, once isolated only in elderly men, has increased in frequency with the onset of AIDS. The lesion presents as a well-margined red nodule, often isolated to the glans, and represents the initial site of presentation in 3% of patients.<sup>22</sup>

Many penile lesions have been identified as pre-malignant to the development of invasive squamous cell carcinoma, including leukoplakia, balanitis xerotica obliterans (BXO), Bowen's disease, erythroplasia of Queyrat, and giant condyloma acuminatum. Leukoplakia represents a rare lesion more frequently arising in individuals with diabetes, most likely as a result of their susceptibility to chronic infections. Histologically, leukoplakia is characterized by hyperkeratosis, parakeratosis, and acanthosis. Grossly, plaques appear as one or more whitish patches that cannot be wiped away and are usually around or involving the meatus. If ulceration or fissuring is present, the lesion poses a high likelihood of malignant degeneration.<sup>23,24</sup>

BXO, the penile equivalent of lichen sclerosis et atrophicus, is typically limited to the glans and prepuce. BXO appears as a thin, scaly, dry lesion possibly with ulcerations or fissures and often causing pruritus and pain. Histologically, the epidermis is atrophic, with the dermis showing edema, fibrosis, and lymphocytic infiltrates of the reticular dermis.<sup>23,25</sup> The lesion is typically benign; 12 cases of squamous cell carcinoma associated with BXO have been reported in the past 30 years.<sup>26</sup>

Carcinoma in situ (CIS) reflects the full thickness alteration in the epithelium with loss of polarity, multiple atypical mitoses, and increased hyperchromatic

cells and multinucleated cells isolated strictly to the epithelium and with an intact basement membrane. Erythroplasia of Queyrat refers to CIS involving the glans penis, prepuce, or shaft, whereas Bowen's disease refers to CIS involving the remainder of the genitalia or perineal region.<sup>27</sup> A third, histologically identical lesion, bowenoid papulosis, has a clinically benign course and often presents in young men (mean age of 29.5) who are sexually active and circumcised. Bowenoid papulosis appears as multiple, pigmented red to brown papular lesions that can spontaneously regress in a number of cases yet poses no risk of malignant degeneration.<sup>28,29</sup>

Bowen's disease usually presents within the 5th to 6th decade as a solitary, thickened, gray-to-white plaque with crusting and oozing. Multiple biopsies are warranted to confirm that the dermal-epidermal border is sharply delineated by an intact basement membrane. Ulceration and erosion usually signify the development of invasive carcinoma. Bowen's disease has been reported to degenerate into invasive carcinoma in 5% to 10% of cases.<sup>24</sup> Conversely, erythroplasia of Queyrat has been noted to transform to invasive carcinoma more commonly, in approximately 10% to 33% of cases.<sup>23,27</sup> Erythroplasia of Queyrat usually presents as a red, velvety, well-margined lesion that is often nontender. As in Bowen's disease, the lesion presents more commonly in noncircumcised men (approximately 80% to 90% of cases), yet the increased likelihood of malignant degeneration may be secondary to its mucosal location.<sup>30</sup>

The majority of squamous cell carcinomas arise de novo. Jensen et al<sup>31</sup> presented a series of 511 patients with penile squamous cell carcinoma. Only 39 (7.6%) had a history of previous or concomitant penile lesions. Squamous cell carcinoma is diagnosed by the histological confirmation on biopsy of invasion through the basement membrane. At presentation, squamous cell carcinoma is found on the glans in 48% of cases, the prepuce in 21%, glans and prepuce in 9%, coronal sulcus in 6%, and shaft in <2%.<sup>32</sup> The histopathologic grading is based on the Broder's Classification System (I-IV).<sup>18</sup> In this system, grade I consists of cells well differentiated with keratinization, prominent intercellular bridges, and keratin pearls. Grade II to III includes greater nuclear atypia, increased mitotic activity, and decreased keratin pearls. Grade IV cells are deeply invasive and consist of marked nuclear pleomorphism, nuclear mitoses, necrosis, lymphatic and perineural invasion, and no keratin pearls.

Half of lesions presenting on the penile shaft are poorly differentiated, whereas only 10% of lesions on the prepuce are well differentiated.<sup>33</sup> Cubilla and

Table 1. — Jackson Classification for Carcinoma of the Penis

Stage	Description
I	Confined to glans of prepuce
II	Invasion into shaft or corpora
III	Operable inguinal lymph node metastasis
IV	Tumor invades adjacent structures; inoperable inguinal lymph node metastasis

From Jackson SM. The treatment of carcinoma of the penis. *Br J Surg.* 1966;53:33-35. Reprinted with permission from Blackwell Publishing.

group<sup>34</sup> associated the morphology of the primary lesion to disease progression. Superficially spreading squamous cell cancers occur most frequently and present with lymph nodes positive for metastatic disease in 42% of cases. Lesions with a deeper vertical growth present with positive lymph nodes in 82% of cases. Multicentric lesions have positive nodes in 33%, whereas verrucous lesions rarely present with metastasis to lymph nodes.<sup>34</sup> Differences between exophytic and ulcerative lesions have also been described. Patients with ulceration have a higher likelihood of node-positive disease.<sup>35</sup>

## Clinical Presentation

The clinical presentation of an invasive penile carcinoma is varied and may range from an area of induration or erythema to a nonhealing ulcer or a warty exophytic growth. Phimosis may obscure the tumor, thus possibly delaying diagnosis of the tumor until a bloody or foul-smelling discharge occurs.

All penile lesions, particularly those under a nonretractile foreskin, require a high index of suspicion for neoplasia. A penile lesion that does not resolve after 2 to 3 weeks of careful observation and skin care requires biopsy. If possible, biopsies should include enough tissue to determine the depth of invasion since this will ultimately affect therapy. In large lesions, the diagnosis is obtained by incisional biopsy.

In decreasing order of frequency, penile cancer develops in the glans (48%), prepuce (21%), glans and prepuce (9%), coronal sulcus (6%), and shaft (<2%). Careful palpation of the inguinal regions is important since palpable inguinal lymphadenopathy is present at diagnosis in 58% of patients (range 20% to 96%), and metastatic carcinoma will ultimately be diagnosed in 45% of these patients.<sup>32</sup> The remainder will have inflammatory lymphadenopathy that resolves following resection of the primary tumor and a 4- to 6-week course of oral antibiotics. In patients with nonpalpable inguinal lymph nodes at the time of resection of the pri-

mary tumor, 20% will ultimately be found to have metastatic disease in the superficial groin nodes. Late in the course of the disease, metastasis to retroperitoneal nodes, liver, lung, and brain can occur. Bulky unresectable nodes can erode into the femoral vessels leading to exsanguinating hemorrhage.<sup>36</sup>

The physical examination is key to the clinical evaluation of the patient with penile cancer. The assessment of the primary tumor should include the size, location, fixation, and involvement of the corporal bodies. The penile base and scrotum should be inspected to exclude neoplastic extension. Both groins should be palpated for inguinal lymphadenopathy.

## Staging

Two staging systems are used in penile carcinoma: the Jackson classification (Table 1)<sup>37</sup> and the TNM classification (Table 2).<sup>38</sup>

## Prognostic Factors

The grade of the primary tumor<sup>35,39,40</sup> and depth of invasion<sup>41-43</sup> are considered to be the most important indicators for metastatic spread. Recently, tumors of

Table 2. — TNM Classification for Carcinoma of the Penis

Stage	Description
<b>Tumor (T)</b>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures
<b>Node (N)</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single, superficial, inguinal lymph node
N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis in deep inguinal or pelvis lymph node(s) unilateral or bilateral
<b>Metastasis (M)</b>	
MX	Distant metastasis cannot be assessed
M0	No evidence of distant metastasis
M1	Distant metastasis

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the *AJCC Cancer Staging Manual*, 5th ed (1997) published by Lippincott-Raven Publishers, Philadelphia, Pa.

vertical growth<sup>41,44,45</sup> and with vascular or lymphatic invasion<sup>46,47</sup> are considered prognostic indicators for metastatic spread.

## Lymphatic Drainage of the Penis

The inguinal nodes are divided into two groups, superficial and deep. The superficial nodes are located beneath the subcutaneous fascia and above the fascia lata covering the muscles of the upper leg; 8 to 25 superficial nodes are present. The deep inguinal nodes are those around the fossa ovalis, the opening in the fascia lata where the saphenous vein drains into the femoral vein; 3 to 5 deep nodes are present. These nodes form the link to the second-line regional nodes, ie, the pelvic nodes. The deep nodes receive their afferents from the superficial ones and directly from the deeper structures of the penis. The most constant and usually largest node is found medial to the femoral vein and just underneath the inguinal ligament, the so-called node of Cloquet or Rosenmüller.<sup>48</sup> The skin of the penis and prepuce is drained primarily to the superficial inguinal nodes, especially the superomedial zone, where the sentinel node is located. The lymphatics of the glans may drain to the superficial inguinal nodes or feed directly to the deep inguinal nodes or even the external iliac group. The lymphatics of the corporal bodies may drain to the superficial or deep inguinal nodes or directly to the external iliac nodes. The simultaneous removal of first- and second-line nodes is traditionally called ilioinguinal lymph node dissection (IILND).

## Treatment of the Primary Lesion

Small tumors limited to the foreskin can be treated by circumcision with a 2-cm margin of clearance. Circumcision alone, especially with tumors in the proximal foreskin, may be associated with recurrence rates of 32%.<sup>49</sup> These high recurrence rates underscore the need for careful follow-up of patients treated by circumcision alone. Local recurrence, as high as 56%, most commonly occurs after organ-preserving procedures.<sup>50,51</sup>

Mohs micrographic surgery is used for the treatment of selected patients with small, superficial penile cancers.<sup>52</sup> The Mohs technique involves excision of the penile lesion and microscopic examination of the underside of each layer for systematic inspection of serial sections. Two techniques are used for the complete microscopic control of the excision of the cancer: (1) the fixed-tissue technique, in which the tissues are fixed with zinc chloride paste before the excision of

the successive layer and (2) the fresh-tissue technique, in which the tissues are excised in the fresh, unfixed state and evaluated by frozen section. A study by Mohs and colleagues<sup>52</sup> reported on 35 patients with squamous cell carcinomas of the penis who were treated by means of micrographic surgery. Eight patients recurred, with 6 developing uncontrolled metastases and 2 with tumor extension along the urethra. The 5-year cure rate and the overall local 5-year cure rate was 74%, and 94%, respectively.

Laser ablation using a neodymium:yttrium-aluminum garnet (Nd:YAG) or carbon dioxide (CO<sub>2</sub>) laser also has been used in selected patients with small superficial or superficially invasive penile cancers.<sup>53-55</sup> Since 1982 the Nd:YAG laser has been used at the Instituto de Enfermedades Neoplásicas in Lima, Peru, as a penis-conserving approach. Horenblas et al<sup>53</sup> reported on 110 patients with penile cancer, using penis-conserving treatment with an Nd:YAG laser in 51 patients (46%) and some form of amputation in 59 patients (54%). Overall, 16 (15%) of the 110 patients had local recurrence. The risk of local recurrence after penis-conserving therapy was significantly related to T category, with 10% local recurrences in stage T1 tumors in contrast to 32% and 100% in stages T2 and T3 tumors, respectively. All of the recurrences in patients with stage T1 tumors were localized, and all were successfully treated. Of 6 recurrences in the conservatively treated stage T2 disease group, 4 were strictly local. These were all moderately or well-differentiated tumors not exceeding 3.5 cm in diameter. Penile cancers that are more deeply infiltrative or poorly differentiated usually cannot be adequately controlled with laser therapy alone.<sup>53</sup>

Radiation therapy has yielded local control rates similar to surgical resection.<sup>56</sup> Radiation therapy techniques include external-beam irradiation, iridium molds or wires, and interstitial brachytherapy. Using external-beam radiation therapy, Almgard and Edsmyr<sup>57</sup> achieved a control rate of only 50%. For T1-T2 penile carcinoma, an overall local control rate of 74% to 86% was achieved with <sup>192</sup>Ir interstitial implants and 80% with brachytherapy.<sup>58</sup>

Carcinomas of the penis involving the glans and the distal shaft are best managed by partial penectomy excising 1.5 to 2 cm of normal tissue proximal to the margin of the tumor. This should leave a 2.5- to 3-cm stump of penis to allow directable micturition in a standing posture, with some coital function as well. Recently, Agrawal et al<sup>59</sup> evaluated the possibility of reducing the margin of clearance at surgery for carcinoma of the penis without causing an increase in the incidence of local tumor recurrence in order to minimize the functional and cosmetic compromise associ-

ated with penectomy. Of 64 patients who underwent partial or total penectomy, 20 patients (31%) were grade I, 32 (50%) were grade II, and the remaining 12 (19%) were grade III. The maximum histological extent beyond the clinical lesion was 5 mm for grades I and II tumors and 10 mm for grade III tumors. The authors concluded that a 10-mm clearance is adequate for grade I and II lesions, and 15-mm clearance for grade III tumors, leaving a more acceptable penile stump length.

For bulky T3 or T4 proximal tumors involving the base of the penis, total penectomy with perineal urethrotomy is done. These proximal tumors are often advanced and associated with regional metastatic disease.

After 4 to 6 weeks of oral antibiotics following treatment of the primary lesion, the patient is reevaluated for the presence of palpable regional lymphadenopathy. The presence of palpable inguinal lymph nodes at the time of diagnosis may be due to inflammatory reaction or metastatic disease. Only 50% of patients presenting with palpable lymphadenopathy actually have metastatic disease, the remainder having lymph node enlargement secondary to inflammation. The development of new adenopathy during follow-up is more likely due to tumor in 70% of cases.<sup>3</sup>

Despite a negative physical examination, as many as 20% of patients undergoing prophylactic lymphadenectomy will have nodal metastasis.<sup>36,60</sup> In patients with minimal nodal metastases (ie, 1 positive node), the 5-year survival rate is 81% compared with 32% if more than 2 positive nodes are found.<sup>60</sup> Patients with clinically palpable lymphadenopathy and histologically proven inguinal node metastases treated by inguinal lymphadenectomy have a 5-year disease-free survival rate of 20% to 50%.<sup>60</sup>

The morbidity of inguinal lymphadenectomy may be considerable, with a 30% to 50% incidence of severe lymphedema and skin flap necrosis.<sup>3,61,62</sup>

A modification of the standard inguinal lymphadenectomy has been developed by Catalona<sup>63</sup> as another option for patients with clinically negative inguinal lymph nodes. The procedure differs from the standard lymphadenectomy in that the length of the skin incision is reduced, the subcutaneous tissue superficial to Scarpa's fascia is preserved, the dissection is reduced to exclude the regions lateral to the femoral artery and caudal to the fossa ovalis, the saphenous vein is preserved, and transposition of the sartorius muscles is eliminated (Fig 1). In patients with histologically negative inguinal nodes, pelvic lymphadenectomy is not performed. In patients with positive lymph nodes on frozen section, a bilateral iliac lymphadenectomy also is performed.

The technique has been associated with less morbidity than the standard lymphadenectomy, and the results are encouraging. Colberg and colleagues<sup>64</sup> reported on 9 patients who underwent modified inguinal lymphadenectomy. Three had histologically positive lymph nodes, and none of the patients with positive or negative nodes had evidence of recurrent disease. All patients were alive with a mean follow-up of 67.5 months (range 13 to 108 months). Early post-operative complications occurred in 2 patients with skin-flap necrosis, in 1 with prolonged lymphatic drainage, and in 1 with a delayed groin lymphocele and cellulitis. In another study, Parra<sup>65</sup> performed a modified inguinal lymphadenectomy on 12 patients. Five patients were identified with nodal metastasis. The sites of inguinal node involvement were localized within the boundaries of the dissection in all patients. No major complications occurred, and no permanent lymphedema or flap necrosis was encountered. Follow-up of 14 to 72 months demonstrated no disease. However, the reliability of this procedure in detecting histological metastases in patients with clinically negative groin nodes has been questioned.<sup>66</sup>

The timing of a lymph node dissection is important, particularly for patients who present with no clinical sign of metastatic disease. Proponents of an early or immediate lymphadenectomy note that patients

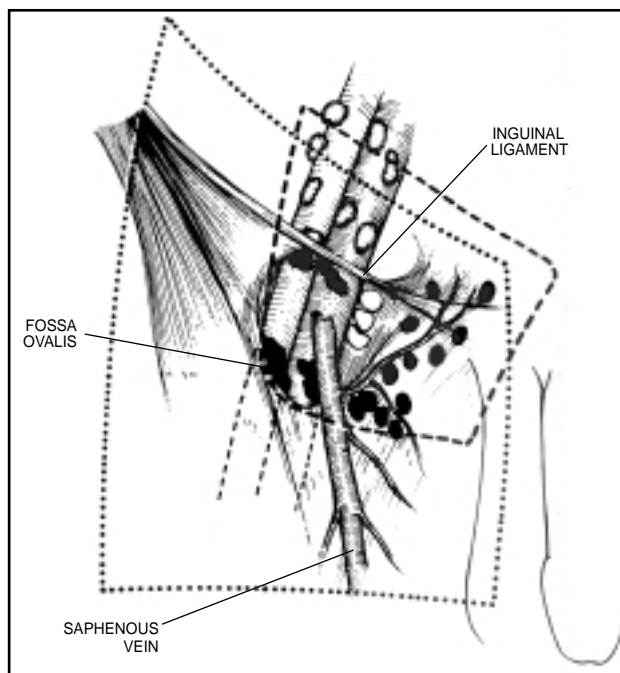


Fig 1. — Limits of dissection of modified inguinal lymphadenectomy (dashed line) with classical groin dissection (dotted line). Black: superficial inguinal nodes. White: deep inguinal nodes. Gray: external iliac nodes. From Catalona WJ. Modified inguinal lymphadenectomy for carcinoma of the penis with preservation of saphenous veins: technique and preliminary results. *J Urol.* 1988;140:306-310. Reprinted with permission. <http://www.com>

who do not undergo surgery but are observed often present at a stage where cure is no longer possible.<sup>67-70</sup> Horenblas and colleagues<sup>61</sup> proposed observation in patients with clinically negative nodes. Patients were followed every 2 months for 3 years, and almost all patients who developed lymph node metastases after treatment of the primary tumor were salvaged by lymph node dissection. Unreliable patients or others who cannot be followed adequately every 2 months are best served by prompt inguinal lymphadenectomy. Solsona et al<sup>40</sup> proposed three risk groups — low, intermediate, and high — for occult lymph node metastases in patients with penile carcinoma and clinically negative lymph nodes. Low-risk patients had stage T1/grade I tumors. None of these patients developed lymph node metastasis on follow-up. Intermediate risk group were patients with stage T1/grades II-III tumors or stages T2-3/grade I tumors. These patients had a 36.4% incidence of positive lymph nodes on follow-up. High risk group were patients with stages T2-3/grades II-III tumors with an 80% incidence of lymph node involvement on follow-up.

In patients with unilateral nodal recurrence during the follow-up, bilateral lymph node dissection should be done. In these cases, the probability of occult contralateral involvement is 60% to 79% of cases due to crossover lymphatics at the base of the penis.<sup>71,72</sup>

Metastasis to the pelvic nodes in the absence of inguinal node metastasis is a rare event and has not been observed in many modern series.<sup>67,73</sup> In the setting of negative superficial and deep inguinal lymphadenectomies and a negative pelvic computed tomography scan, pelvic lymphadenectomy is not required.

## Institutional Experience

At the Instituto de Enfermedades Neoplásicas in Lima, Peru, 160 patients with the diagnosis of squamous cell carcinoma of the penis underwent bilateral IILND 6 weeks after excision of the primary penile lesion between June 1953 and July 2001. Surgical technique of the IILND involved one parallel incision 2 cm below the inguinal ligament extending below the pubic tubercle for an inguinal approach. The incision is deepened to the level of Scarpa's fascia. The superior and inferior skin flaps are raised and the lymph node dissection is begun superiorly 4 to 5 cm above the inguinal ligament. The medial and lateral dissection extends to the lymph nodes along the adductor longus and sartorius muscles. The inferior dissection extends across the apex of the femoral triangle at the level of the fascia lata. The greater saphenous vein is identified and divided. All tissues are dissected off the

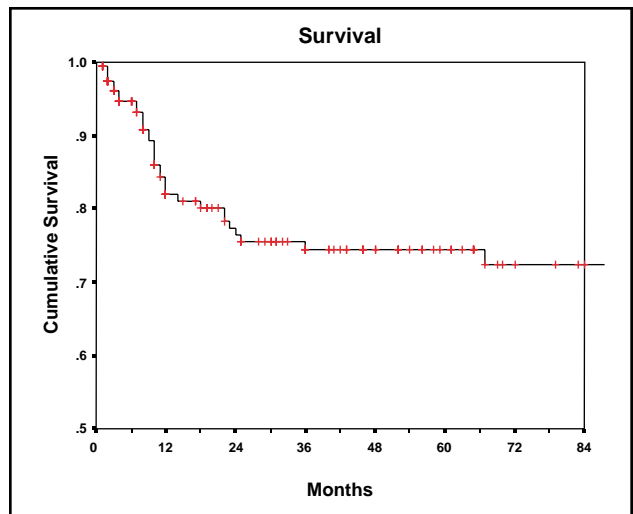


Fig 2. — Overall survival of patients with squamous cell carcinoma of the penis undergoing bilateral IILND.

anterior and lateral aspects of the femoral vessels. The dissection proceeds superiorly and medially, freeing the entire package until its only attachments are deep to the inguinal ligament, and the lymph nodes are removed en bloc. A pelvis lymph node dissection is performed simultaneously through incision of the inguinal ligament. The external femoral artery and vein are identified, and all lymphatic tissue is freed from these structures. At the end of lymphadenectomy, the sartorius muscle is rotated over the femoral vessels, and it is anchored to the inguinal ligament.

Mean patient age was 54 years (range 21 to 78 years). Mean time from the appearance of lesion to treatment was 13 months (range 1 to 96 months). Phimosis was present in 42 (26%) of 160 patients. Penile cancer developed in the glans and prepuce in 76 patients (47.5%), in the glans in 36 (22.5%), in the glans, prepuce, and shaft of the penis in 34 (21%), in the prepuce in 10 (6%), and in the shaft in 4 (2%). Pathology was reviewed and patients were stratified retrospectively according to the 1997 TNM classification<sup>38</sup> and Broder's grading system.<sup>74</sup> Among these 160 patients, 100 tumors were classified as well differentiated, 45 as moderately differentiated, and 7 as poorly differentiated. The remaining 8 tumors could not be classified according to grade.

Lymph node metastasis was present in 6 (9%) of 68 patients without palpable adenopathy and in 66 (72%) of 91 patients with palpable adenopathy. Overall survival is shown in Fig 2. The 5-year survival rate for pN0, pN1, pN2, and pN3 disease was 92%, 100%, 68%, and 31%, respectively. With standard lymphadenectomy in 153 patients, flap necrosis occurred in 98 (64%), lower extremity lymphedema in 57 (37%), and lower extremity cellulitis in 9 (5%).

Since July 2000, we have performed 7 modified inguinal lymphadenectomies, with frozen section study of the lymph nodes as described by Catalona.<sup>63</sup> None of these 7 patients had lymph node metastases. Flap necrosis developed in 1 patient, lymphedema in 3 patients, and delayed cellulitis in 2 patients.

## Lymphoscintigraphy and Sentinel Node Biopsy

Sentinel node biopsy, which has been extensively validated in breast cancer and melanoma, is being used increasingly in the evaluation of penile cancer. The concept of the sentinel node, the first lymph node to contain metastatic cancer within a tumor's lymphatic basin, was introduced by Cabanas<sup>75</sup> in 1977. In an effort to more accurately stage and avoid extensive lymph node dissections in the majority of patients with penile cancer, Cabanas studied 100 cases of local T2 or greater disease using lymphangiograms, anatomic dissections, and/or microscopic evaluations. Anatomically, the sentinel lymph node was discovered to be part of the lymphatic system around the superficial inferior epigastric vein, and theoretically, skip metastases beyond this node were supposedly rare. In the study, 46 sentinel node biopsies were performed, with 15 nodes being positive for metastatic disease and thus warranting a formal inguinal node dissection. No further involvement of other inguinal nodes was present in 12 of these 15 cases. Lymphatic channels draining into the iliac nodes without first draining into the sentinel lymph node were not seen, and inguinal-femoral lymph nodes were not involved with metastatic disease in the absence of sentinel lymph node positive disease. Based on these findings, Cabanas recommended bilateral sentinel node

biopsy followed by inguino-femoral dissection only when biopsy of the sentinel node was positive. When the sentinel node was negative for metastatic disease, no further surgical treatment was recommended.<sup>75</sup>

The reliability of this approach was limited by its relatively poor localization technique, and therefore it failed to gain widespread acceptance. Further refinements of the technique, including the use of radiolabeled colloids in conjunction with gamma imaging or gamma probe-guided detection of the sentinel node at surgery, has resurrected the issue.<sup>76</sup> By combining pre-operative lymphatic mapping with intraoperative gamma probe detection, use of this nuclear medicine procedure to identify sentinel nodes is increasing.

Horenblas et al<sup>72</sup> reported on a series of 55 patients with stage T2 or greater node-negative disease who underwent lymphoscintigraphy with technetium-99m nanocolloid injected intradermally around the tumor. Sentinel nodes were found intraoperatively using patent blue dye injected intradermally around the tumor and a gamma detection probe (Fig 3). Regional node dissections were limited to patients with tumor-positive sentinel nodes. A total of 108 sentinel nodes were removed, and 11 patients underwent a regional node dissection secondary to a sentinel node positive for metastatic disease. At a median follow-up of 22 months, 1 patient had nodal metastasis despite prior excision of a tumor-free sentinel node. More recently, Valdes Olmos and colleagues<sup>77</sup> reported on a series of 74 patients with T2 or greater disease clinically negative lymph nodes who underwent gamma mapping. The sentinel node visualization rate was 97%, and lymphatic inguinal drainage was bilateral in 81% of cases. Bilateral lymph node drainage was asynchronous in 62%, with half initially draining to the left inguinal nodes and half to the right. In total, 173 sentinel nodes were visualized, with 161 removed at surgery. Twenty-two percent of patients had positive sentinel nodes and underwent a standard regional node dissection. Mean follow-up was 28 months. Two patients with negative sentinel nodes on initial evaluation developed nodal metastasis in the mapped lymphatic basin at follow-up. Both studies concluded that lymphoscintigraphy offers a valid, well-tolerated method for lymphatic mapping and sentinel node identification. However, further study in prospective clinical trials is needed before this technique can be accepted as standard practice.

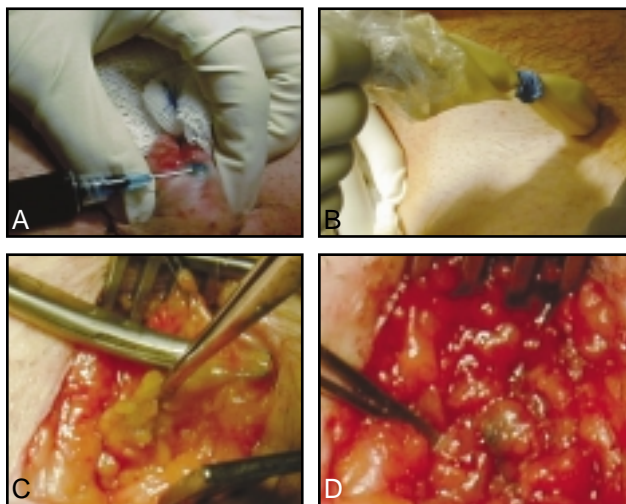


Fig 3. — Images of the sentinel node biopsy demonstrating (A) injection of dye and radiopharmaceutical around primary lesion, (B) localization of the node using the gamma probe, (C) small groin incision to access the sentinel node, and (D) excision of sentinel node.

## Chemotherapy for Penile Cancer

The experience with cytotoxic drugs in penile and urethral carcinomas is limited to small series, with inconclusive results. Some response has been observed with

cisplatin, bleomycin, and methotrexate, as well as with combinations of these agents.<sup>78</sup> Shamma et al<sup>79</sup> used cisplatin and 5-fluorouracil to treat 8 patients with advanced squamous cell carcinoma of the penis (Jackson stages III and IV). Two patients achieved a partial response, 1 requiring a further operation and 1 requiring surgery with radiotherapy to achieve a complete response. These 2 patients were disease-free at 32 and 57 months. Nonresponders had a survival range of 2 to 28 months after chemotherapy.<sup>79</sup> Kattan and associates<sup>80</sup> treated 14 patients with cisplatin-based chemotherapy combined with other chemotherapeutic agents. Thirteen patients were evaluable for response. Objective responses were achieved in 2 patients (15%), with 1 complete and 1 partial. There were 2 patients with long-term evidence of no disease among 12 patients with stage IV disease. These 2 patients received complementary irradiation in association with the chemotherapy. In this study, methotrexate-based regimens seemed to be most effective.<sup>80</sup> Pizzocaro et al<sup>81</sup> evaluated neoadjuvant chemotherapy with combined vincristine, bleomycin, and methotrexate in 16 patients with fixed inguinal nodes. Nine (56%) of the 16 patients underwent successful surgical resection, and 5 (31%) achieved 5-year disease-free survival. The Southwest Oncology Group<sup>82</sup> evaluated combination chemotherapy with cisplatin, bleomycin, and methotrexate in patients with metastatic disease. Of 40 patients evaluable for response, 5 complete responses and 8 partial responses occurred for a 32.5% response rate. The therapy was associated with excessive toxicity, with 5 treatment-related deaths. Six of the remaining patients evaluable for toxicity had 1 or more life-threatening toxic episodes.

## Conclusions

Penile cancer, though a rare disease, poses many diagnostic, staging, and treatment challenges. Accurate treatment and staging of the primary lesion is important to aid in predicting the status of the regional lymph nodes. Modifying the groin lymph node dissection has lessened morbidity from this procedure, and sentinel node localization offers the possibility of less extensive surgery for some patients.

## References

- Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. *CA Cancer J Clin*. 1999;49:8-31, 1.
- Narayana AS, Olney LE, Loening SA, et al. Carcinoma of the penis: analysis of 219 cases. *Cancer*. 1982;49:2185-2191.
- Ornellas AA, Seixas AL, Marota A, et al. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. *J Urol*. 1994;151:1244-1249.
- Liria MP, Alarcon A, Cavero M, et al. Epidemiología Descriptiva de Neoplasias Malignas. Instituto de Enfermedades Neoplásicas "Dr Eduardo Cáceres Graziani." Departamento de Epidemiología y Estadística; 2000:98.
- Hoppmann HJ, Fraley EE. Squamous cell carcinoma of the penis. *J Urol*. 1978;120:393-398.
- Licklider S. Jewish penile carcinoma. *J Urol*. 1961;86:98.
- Maden C, Sherman KJ, Beckmann AM, et al. History of circumcision, medical conditions and sexual activity and the risk of penile cancer. *J Natl Cancer Inst*. 1993;85:19-24.
- Schoen EJ, Oehrli M, Colby C, et al. The highly protective effect of newborn circumcision against invasive penile cancer. *Pediatrics*. 2000;105:E36.
- Tsen HF, Morgenstern H, Mack T, et al. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes Control*. 2001;12:267-277.
- Maiche AG. Epidemiological aspects of cancer of the penis in Finland. *Eur J Cancer Prev*. 1992;1:153-158.
- Rubin MA, Kleter B, Zhou M, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *Am J Pathol*. 2001;159:1211-1218.
- Huben RP. Biology of penile cancer. In: Raghavan D, Scher HI, Leibel SA, et al, eds. *Principles and Practice of Genitourinary Oncology*. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:921.
- Guerrero I, Pow-Sang M, Pow-Sang JE, et al. Improved DNA extraction from paraffin-embedded tissue for human papillomavirus detection in penile cancer by polymerase chain reaction. *Urologia Panamericana*. 2000;12:20-21.
- Varma VA, Sanchez-Lanier M, Unger ER, et al. Association of human papillomavirus with penile carcinoma: a study using polymerase chain reaction and in situ hybridization. *Hum Pathol*. 1991;22:908-913.
- Bezerra AL, Lopes A, Santiago GH, et al. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer*. 2001;91:2315-2321.
- Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16, and 18 E6 proteins with p53. *Science*. 1990;248:76-79.
- Dillner J, von Krogh G, Horenblas S, et al. Etiology of squamous cell carcinoma of the penis. *Scand J Urol Nephrol Suppl*. 2000;205:189-193.
- Lucia MS, Miller GJ. Histopathology of malignant lesions of the penis. *Urol Clin North Am*. 1992;19:227-46.
- Belvider WD, Cohen JA. Secondary penile malignancies: the spectrum of presentation. *J Surg Oncol*. 1992;51:134-137.
- Morga Egea JP, Ferrero Doria R, Guzman Martinez-Valls PL, et al. Metastasis priapism. Report of 4 new cases and review of the literature [Spanish]. *Arch Esp Urol*. 2000;53:447-452.
- Muro Bidaurre I, Aspiazu Arnaiz P, Recarte Barriola JA, et al. Metastatic carcinoma of the penis: clinical assessment, treatment, and review of the literature [Spanish]. *Arch Esp Urol*. 1999;52:994-998.
- Hermida Gutierrez JF, Gomez Vegas A, Sillmi Moyano A, et al. Kaposi's sarcoma of the penis: our experience and review of the literature [Spanish]. *Arch Esp Urol*. 1995;48:153-158.
- Mikhail GR. Cancers, precancers, and pseudocancers in the male genitalia. A review of clinical appearances, histopathology, and management. *J Dermatol Surg Oncol*. 1980;6:1027-35.
- Schellhammer PF, Jordan GH, Robey EL, et al. Premalignant lesions and nonsquamous malignancy of the penis and carcinoma of the scrotum. *Urol Clin North Am*. 1992;19:131-142.
- Grossman HB. Premalignant and early carcinomas of the penis and scrotum. *Urol Clin North Am*. 1992;19:221-226.
- Campus GV, Alia F, Bosincu L. Squamous cell carcinoma and lichen sclerosus et atrophicus of the prepuce. *Plast Reconstr Surg*. 1992;89:962-964.
- Graham JH, Helwig EB. Erythroplasia of Queyrat. A clinicopathologic and histochemical study. *Cancer*. 1973;32:1396-1414.
- Wade TR, Kopf AW, Acherman AB. Bowenoid papulosis of the genitalia. *Arch Dermatol*. 1979;115:306-308.
- Gross G, Hagedorn M, Ikenberg H, et al. Bowenoid papulosis. Presence of human papillomavirus (HPV) structural antigens and of HPV 16-related DNA sequences. *Arch Dermatol*. 1985;121:858-863.
- McAninch JW, Moore CA. Precancerous penile lesions in young men. *J Urol*. 1970;104:287-290.
- Jensen MO. Cancer of the penis in Denmark 1942 to 1962 (511 cases). *Dan Med Bull*. 1977;24:66-72.

32. Sufrin G, Huber R. Benign and malignant lesions of the penis. In: Gillenwater JY, Howards SS, Duckett JW, eds. *Adult and Pediatric Urology*. 2nd ed. St Louis, Mo: Mosby-Year Book; 1991;1643.
33. Ro JY, Amin MB, Ayala AG. Pathology of penis and scrotum. In: Bostwick DG, Eble JN, eds. *Urologic Surgical Pathology*. 3rd ed. St. Louis, Mo: Mosby; 1996.
34. Cubilla AL. Carcinoma of the penis. *Mod Pathol*. 1995;8:116-118.
35. Cubilla AL, Barreto J, Caballero C, et al. Pathologic features of epidermoid carcinoma of the penis. A prospective study of 66 cases. *Am J Surg Pathol*. 1993;17:753-763.
36. Burgers JK, Badalament RA, Drago JR. Penile cancer. Clinical presentation, diagnosis, and staging. *Urol Clin North Am*. 1992;19:247-256.
37. Jackson SM. The treatment of carcinoma of the penis. *Br J Surg*. 1966;53:33-35.
38. Fleming ID, ed. *AJCC Cancer Staging Manual*. 5th ed. American Joint Committee on Cancer. Philadelphia, Pa: Lippincott-Raven; 1997.
39. Hall MC, Sanders JS, Vuitch E, et al. Deoxyribonucleic acid flow cytometry and traditional pathologic variables in invasive penile carcinoma: assessment of prognostic significance. *Urology*. 1998;52:111-116.
40. Solsona E, Iborra I, Rubio J, et al. Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. *J Urol*. 2001;165:1506-1509.
41. Lummen G, Sperling H, Pietsch M, et al. Treatment and follow-up of patients with squamous epithelial carcinoma of the penis [German] *Urologe A*. 1997;36:157-161.
42. Heyns CE, van Vollenhoven P, Steenkamp JW, et al. Cancer of the penis: a review of 50 patients. *S Afr J Surg*. 1997;35:120-124.
43. Chiu TY, Huang HS, Lai MK, et al. Penile cancer in Taiwan: 20 years' experience at National Taiwan University Hospital. *J Formos Med Assoc*. 1998;97:673-678.
44. Villavicencio H, Rubio-Briones J, Regalado R, et al. Grade, local stage and growth pattern as prognostic factors in carcinoma of the penis. *Eur Urol*. 1997;32:442-447.
45. Banon Perez VJ, Nicolas Torralba JA, Valdelvira Nadal P, et al. Squamous carcinoma of the penis [Spanish]. *Arch Esp Urol*. 2000;53:693-699.
46. 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. *J Urol*. 2001;165:1138-1142.
47. Lopes A, Hidalgo GS, Kowalski LP, et al. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. *J Urol*. 1996;156:1637-1642.
48. Dewire D, Lepor H. Anatomic considerations of the penis and its lymphatic drainage. *Urol Clin North Am*. 1992;19:211-219.
49. McDougal WS, Kirchner FK Jr, Edwards RH, et al. Treatment of carcinoma of the penis: the case for primary lymphadenectomy. *J Urol*. 1986;136:38-41.
50. Brkovic D, Kalble T, Dorsam J, et al. Surgical treatment of invasive penile cancer: the Heidelberg experience from 1968 to 1994. *Eur Urol*. 1997;31:339-342.
51. Ficarra V, D'Amico A, Cavalleri S, et al. Surgical treatment of penile carcinoma: our experience from 1976 to 1997. *Urol Int*. 1999;62:234-237.
52. Mohs FE, Snow SN, Larson PO, et al. Mohs micrographic surgery for penile tumors. *Urol Clin North Am*. 1992;19:291-304.
53. Horenblas S, van Tinteren H, Delemarre JF, et al. Squamous cell carcinoma of the penis. II. Treatment of the primary tumor. *J Urol*. 1992;147:1533-1538.
54. Malloy TR, Wein AJ, Carpinello VL. Carcinoma of the penis treated with neodymium YAG laser. *Urology*. 1988;31:26-29.
55. Gerber GS. Carcinoma in situ of the penis. *J Urol*. 1994;151:829-833.
56. McLean M, Akl AM, Warde P, et al. The results of primary radiation therapy in the management of squamous cell carcinoma of the penis. *Int J Radiat Oncol Biol Phys*. 1993;25:623-628.
57. Almgard LE, Edsmyr F. Radiotherapy in treatment of patients with carcinoma of the penis. *Scand J Urol Nephrol*. 1973;7:1-5.
58. Elwell CM, William GJ. Radiation Therapy for Penile Cancer. In: Vogelzang NJ, Scardino PT, Coffey DS, et al, eds. *Comprehensive Textbook of Genitourinary Oncology*. 2nd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:1065-1069.
59. Agrawal A, Pai D, Ananthakrishnan N, et al. The histological extent of the local spread of carcinoma of the penis and its therapeutic implications. *BJU Int*. 2000;85:299-301.
60. Lynch FL Jr, Schellhammer PE. Tumors of the penis. In: Walsh PC, Vaughn ED Jr, Wein AJ, eds. *Campbell's Urology*. 7th ed, vol 3. Philadelphia, Pa: WB Saunders; 1998:2453-2485.
61. Horenblas S, van Tinteren H, Delemarre JF, et al. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. *J Urol*. 1993;149:492-497.
62. Horenblas S, van Tinteren H. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. *J Urol*. 1994;151:1239-1243.
63. Catalona WJ. Modified inguinal lymphadenectomy for carcinoma of the penis with preservation of saphenous veins: technique and preliminary results. *J Urol*. 1988;140:306-310.
64. Colberg JW, Andriole GL, Catalona WJ. Long-term follow-up of men undergoing modified inguinal lymphadenectomy for carcinoma of the penis. *Br J Urol*. 1997;79:54-57.
65. Parra RO. Accurate staging of carcinoma of the penis in men with nonpalpable inguinal lymph nodes by modified inguinal lymphadenectomy. *J Urol*. 1996;155:560-563.
66. Lopes A, Rossi BM, Fonseca FP, et al. Unreliability of modified inguinal lymphadenectomy for clinical staging of penile carcinoma. *Cancer*. 1996;77:2099-2102.
67. Fraley EE, Zhang G, Manivel C, et al. The role of ilioinguinal lymphadenectomy and significance of histological differentiation in treatment of carcinoma of the penis. *J Urol*. 1989;142:1478-1482.
68. Ornellas AA, Seixas AL, de Moraes JR. Analyses of 200 lymphadenectomies in patients with penile carcinoma. *J Urol*. 1991;146:330-332.
69. McDougal WS. Carcinoma of the penis: improved survival by early regional lymphadenectomy based on the histological grade and depth of invasion of the primary lesion. *J Urol*. 1995;154:1364-1366.
70. Johnson DE, Lo RK. Management of regional lymph nodes in penile carcinoma. Five-year results following therapeutic groin dissections. *Urology*. 1984;24:308-311.
71. Ekstrom T. Cancer of the penis: a clinical study of 229 cases. *Acta Chir Scand*. 1958;115:25-29.
72. Horenblas S, Jansen L, Meinhardt W, et al. Detection of occult metastasis in squamous cell carcinoma of the penis using a dynamic sentinel node procedure. *J Urol*. 2000;163:100-104.
73. Srinivas V, Morse MJ, Herr HW, et al. Penile cancer: relation of extent of nodal metastasis to survival. *J Urol*. 1987;137:880-882.
74. Broders A. Squamous cell epithelium of the skin. *Ann Surg*. 1928;141-149.
75. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer*. 1977;39:456-466.
76. Schlag PM. The "sentinel node" concept: more questions raised than answers provided? *Oncologist*. 1998;3:VI-VII.
77. Valdes Olmos RA, Tanis PJ, Hoefnagel CA, et al. Penile lymphoscintigraphy for sentinel node identification. *Eur J Nucl Med*. 2001;28:581-585.
78. Eisenberger MA. Chemotherapy for carcinomas of the penis and urethra. *Urol Clin North Am*. 1992;19:333-338.
79. Shamma S, Ous S, Fossa SD. Cisplatin and 5-fluorouracil in advanced cancer of the penis. *J Urol*. 1992;147:630-632.
80. Kattan J, Culine S, Droz JP, et al. Penile cancer chemotherapy: twelve years' experience at Institut Gustave-Roussy. *Urology*. 1993;42:559-562.
81. Pizzocaro G, Piva L, Nicolai N. Treatment of lymphatic metastasis of squamous cell carcinoma of the penis: experience at the National Tumor Institute of Milan. *Arch Ital Urol Androl*. 1996;68:169-172.
82. 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. *J Urol*. 1999;161:1823-1825.