

CANCER OF THE PENIS

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Abstract

Objectives: To review the outcomes of modification of groin lymph nodes dissection on morbidity from surgical treatment of a patient with penile cancer and to find out accurate treatment plan according to stages of the primary lesion from current literatures.

Methods: We searched the pubmed database for English Language published in the past for years using incidence, etiology, pathology, clinical presentation, staging and management of penile cancer.

Result: From retrieved literatures 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. The recent use of a modified lymph node dissection has minimized morbidity. Current chemotherapy agents are ineffective in this disease.

Conclusion: 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 selection patients has decreased morbidity. Effective chemotherapy agents are needed in the management of advanced penile cancer.

Key words: Penile cancer, Modified inguinal lymphadenopathy staging of penile cancer, lymphadenopathy, pathology of penile cancer.

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Introduction:

Penile cancer is an uncommon malignancy but sometimes devastating for the patient. It is typically a disease of middle aged to older men, most commonly affecting those between 50 to 70 years of age. But the cancer is not unusual in younger men. Although rare in the developed countries, penile cancer constitutes a substantial health cancer in many African, South American and Asian Countries.

As it is an uncommon disease so progress in the diagnosis and treatment has occurred slowly. So, there is a scope of new diagnostic and therapeutic techniques as well as attempts to identify patients who may be benefited from less invasive treatment.

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Incidence

The incidence of penile cancer in less than 1 man in 1,00,000 and accounts for ten than 1% of cancers in men in the united stages. It accounts for upto 10% in cancers in some parts of Asia, African and South American.

Etiology

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. In the United State, the risk of this disease in uncircumcised men is 3-fold higher than that of circumcised men as approaches the rate seen in some underdeveloped nations.

Maden et al 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 period¹.

Schoen and colleagues evaluated the relationship between newborn circumcision and invasive penile cancer among adult men who were members of a large health maintenance organization². 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.

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. Precancerous lesions are found in an additional 15% to 20% of patients.

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 penis. Rubin et al evaluated the prevalence of HPV DNA in different histological subtypes of penile carcinoma, dysplasia, and condyloma³. 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. 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%). Recently Bezerra et al detected HPV DNA in 25 of 82 samples (30.5%). HPV-16 was the most frequent type detected (13 of 25, 52%)⁴. Researchers believe that infection with HPV is an important risk factor for penile cancer.

Dillner et al evaluated the etiology of squamous cell carcinoma of the penis⁵. 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-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.

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.

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

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. 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.

The majority of squamous cell carcinomas arise de novo. Jensen et al presented a series of 511 patients with penile squamous cell carcinoma⁶. 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%. The histopathologic grading is based on the Broder's Classification System. 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. Cubilla and group associated the morphology of the primary lesion to disease progression⁷. 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. Differences between exophytic and ulcerative lesions have also been described. Patients with ulceration have a higher likelihood of node-positive disease.

Clinical Presentation

The initial evaluation of any suspected penile lesion relies on clinical examination of both the primary tumor and inguinal lymph nodes. 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. 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 primary 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.

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

A staging system is a standardized way to summarize information about how far a cancer has spread. Two staging systems are used in penile carcinoma: The Jackson classification (Table-I)⁸ and the TNM classification (Table-II)⁹. From a historical point of view, Jackson's staging system represents the original penile cancer staging system. In the current TNM system the primary tumor is staged according to histological features and the precise anatomic structure invaded.

Table-I
Jackson's classification for Ca-penis

Stage-I	: Tumor confirmed to glans, prepares
Stage-II	: Tumor extending on to shaft of penis.
Stage-III	: Tumor with inguinal metastases that are operable.
Stage-IV	: Tumor involving adjacent structures tumor associated with inoperable inguinal metastasis or distant metasis.

Table-II
TNM classification of tumors of the penis.

Tx:	Primary tumor
To:	Cannot be assessed
Tis:	No evidence of primary tumor
Ta:	Noninvasive verrucous carcinoma
T1:	Invades subepithelial connective tissue
T2:	Invades corpus spongiosum or cavernosum
T3:	Invades urethra or prostate
T4:	Invades other adjacent structures.
N-	Regional lymph nodes.
Nx:	Cannot be assessed
No:	No regional lymph node metastasis
N1:	Metastasis in single superficial inguinal node
N2:	Metastasis in multiple or bilateral superficial inguinal nodes.
N3:	Metastasis in deep inguinal or pelvic node
M-	Distant metastasis
Mx:	Cannot be assessed
Mo:	No distant metastasis
M1:	Distant metastasis is present.

Leijte et al have proposed some changes for better prognostic differentiation, but these changes have yet to be widely implemented¹⁰.

Prognostic Factors

The grade of the primary tumor and depth of invasion are considered to be the most important indicators for metastatic spread. Recently, tumor of vertical growth and with vascular or lymphatic invasion are considered prognostic indicators for metastatic spread^{11,12}.

Surgical Treatment

The aim of treatment of penile cancer is to optimize loco-regional and systemic disease eradication with preservation of penile function and minimal disfiguring.

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%. These high recurrence rates under score 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. A pathological assessment of surgical margins is essential in apply these procedure and to reduce the rate of local recurrence¹³.

Mohs micrographic surgery is used for the treatment of selected patients with small, superficial penile cancers¹⁴. 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 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 5year cure rate was 74%, and 94%, respectively.

The use of laser as an organ sparing therapy for penile carcinoma was first reported by Hofstetter et al in 1978¹⁵. Laser ablation using a neodymium: yttrium-aluminum garnet (Nd:YAG) or carbon dioxide (CO₂) laser also has been used in selected patients with small superficial or superficially invasive penile cancers.

Radiation therapy is indicated usually for T₁-T₂ tumors that are less than 4cm. Radiation therapy has yielded local control rates similar to surgical resection. Radiation therapy techniques include external-beam irradiation, iridium molds or wires, and interstitial brachytherapy. Using external-beam radiation therapy, Almgard and Edsmyr achieved a control rate of only 50%. For T1-T2 penile carcinoma, an overall local control rate of 74% to 86% was achieved with Ir interstitial implants and 80% with brachytherapy.

Carcinomas of the penis involving the glans and distal shaft are best managed by partial penectomy margin of the tumor. This should leave a 2.5 to 3cm stump of penis to allow directable micturition in a standing posture, with some coital function as well. Recently, 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 associated 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 10mm clearance is adequate for grade I and II lesions, and 15mm clearance for grade III tumors, leaving a more acceptable penile stump length^{16,17,18}.

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.

The morbidity of inguinal lymphadenectomy may be considerable, with a 30% to 50% incidence of severe lymphedema and skin flap necrosis.

A modification of the standard inguinal lymphadenectomy has been developed by Catalonia as another option for patients with clinically negative inguinal lymph nodes¹⁹. 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. 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 reported on 9 patients who underwent modified inguinal lymphadenectomy²⁰. 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 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.

The timing of lymph node dissection is important, particularly for patients who present with no clinical sign of metastatic disease. Proponent of an early or immediate lymphadenectomy note that patients who do not undergo surgery but are observed often present at a stage where cure is no longer possible. Horenblas and colleagues 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 proposed three risk groups – low, intermediate and high – for occult lymph node metastases in patients with penile carcinoma and clinically negative lymph nodes²¹. 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/grade 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.

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. In the setting of negative superficial and deep inguinal lymphadenectomies and a negative pelvic computed tomography scan, pelvic lymphadenectomy is not required.

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 in 1977²². 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.

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. By combining preoperative lymphatic mapping with intraoperative gamma probe detection, use of this nuclear medicine procedure to identify sentinel nodes is increasing.

Horenblas et al 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 tumor²³. Sentinel nodes were found intraoperatively using patent blue dye injected intradermally around the tumor and a gamma detection probe. 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 tumor-free sentinel node. More recently, Valdes Olmos and colleagues 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 technique can be accepted as standard practice.

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. Shammas et al used cisplatin and 5 fluorouracil to treat 8 patients with advanced squamous cell carcinoma of the penis (Jackson stages III and IV)²⁴. 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. Kattan and associates treated 14 patients with cisplatin based chemotherapy combined with other chemotherapeutic agents²⁵. 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 regimes seemed to be most effective. Pizzocaro et al evaluated neoadjuvant chemotherapy with combined vincristine, bleomycin, and methotrexate in 16 patients with fixed inguinal nodes²⁶. Nine (56%) of the 16 patients underwent successful

surgical resection, and 5 (31%) achieved 5 year disease free survival. The Southwest Oncology Group 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 had lessened morbidity from this procedure, and sentinel node localization offers the possibility of less extensive surgery for some patients.

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