CHAPTER

57 Penile Cancer

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INCIDENCE

Penile cancer occurs in approximately 1 in 100,000 North American and European men (accounting for 0.4% to 0.6% of all male cancers), but it represents as much as 10% of male malignancies in parts of Asia, Africa, and South America.

BIOLOGIC CHARACTERISTICS

Human papillomavirus (HPV) types 16 and 18 are detected in 40% to 45% of penile cancers. Moderate or poor differentiation, invasion of the corpora, and the presence of tumor emboli in lymphovascular channels predict regional spread.

STAGING EVALUATION

Circumcision is recommended for full evaluation of the primary tumor. Magnetic resonance imaging (MRI) may supplement palpation in the determination of invasion of the corpora. Computed tomography (CT) for staging lacks sufficient sensitivity for evaluation of lymph nodes. For adverse pathology (grade, invasion of corpora, or lymphovascular spaces), surgical staging of lymph nodes is recommended and can be done by either bilateral superficial inguinal lymph node dissection or sentinel lymph node biopsy.

PRIMARY THERAPY

Penile conservation is recommended for Tis, Ta to T1, and G1 to G2 lesions and can be considered for those with G3 T1 or T2 category lesions (tumor < 4 cm) and for selected T3 tumors. Laser surgery for Tis and T1 tumors yields satisfactory local control and cosmesis.

Interstitial brachytherapy for T1 to T2 category tumors allows penile preservation in 70% to 85% of patients. The most common sequelae of treatment are meatal stenosis (12% to 45%) and soft-tissue ulceration (8% to 25%).

For external beam radiation therapy (EBRT), penile preservation rates are 50% to 65%.

ADJUVANT THERAPY

Adjuvant EBRT is recommended after lymph node dissection for patients with multiple positive groin nodes or extracapsular disease.

LOCALLY ADVANCED DISEASE

Locally advanced penile cancer is a highly lethal malignancy that requires a multimodality approach. This may begin with total or partial penectomy and lymph node dissection for cases that are surgically resectable. For unresectable presentations, combined chemoradiotherapy can be used as either a preoperative approach or continued to a definitive dose. Neoadjuvant chemotherapy may render the disease operable (response rate 50%).

PALLIATION

Unresectable nodes are rarely controlled by radiation therapy (RT), but palliation may be possible. A combined approach with systemic chemotherapy is warranted if the patient's general condition permits.

The penis is divided into three portions: the root, the body (or shaft), and the glans. The root is embedded in the superficial perineum. The shaft consists of the erectile bodies composed of the corpora cavernosa, the corpus spongiosum, and the overlying skin. The glans comprises the distal part of the corpus spongiosum and is covered by a skinfold known as the prepuce. The coronal sulcus delimits the glans from the shaft.

Early-stage, well-differentiated cancers of the penis can be effectively managed with local therapy, and attention should be paid to preservation of penile function and morphology. Traditional primary surgical management is effective but is associated with considerable psychosexual morbidity. Even partial penectomy can have a profound effect on sexual health and self-image.[1] Suicide or attempted suicide after partial penectomy has been reported.[2,3] In recent years, emphasis is increasingly in favor of penile-sparing approaches and surgical options have been developed in this regard, including procedures such as glans-sparing penectomy. EBRT and interstitial RT are also organ-sparing alternatives that preserve penile morphology and function without compromising disease control or survival in selected patients. Referral is encouraged to centers specialized in management of this rare cancer. Quality of life and sexual health after treatment requires more study. Sexuality and expectations should be discussed with the patient and partner when deciding on primary management. Advanced or poorly differentiated tumors require a multimodality approach. A recent study of 12 European Cancer registries and the Surveillance, Epidemiology, and End Results (SEER) program in the United States showed no improvement in 5-year survival for penile cancer patients since 1990.[4]

ETIOLOGY AND EPIDEMIOLOGY

Carcinoma of the penis is rare, with an estimated incidence of 1 case per 100,000 men in North America and Europe, where it accounts for 0.4% to 0.6% of cancers. Higher incidences are seen in parts of Asia, Africa, and South America, where it represents up to 10% of malignancies in male patients.[5] The peak incidence is in the sixth decade in developed countries but earlier where the incidence is higher.

Case-control studies have identified important risk factors (odds ratio [OR] > 10) to be phimosis, chronic inflammatory conditions such as lichen sclerosis, treatment with psoralens and ultraviolet A photochemotherapy (PUVA), tobacco products (dose-dependent association), and a history of genital

condylomata (threefold to fivefold increase in risk). Neonatal circumcision is associated with a threefold decrease in risk of penile carcinoma. However, circumcised men with a history of HPV infection remain at increased risk.[6] Oncogenic HPV, especially type 16, has been identified in about 50% of invasive penile cancers.[7] Penile trauma may be another risk factor for penile cancer. There is a threefold increase in development of carcinoma in the scarred penile shaft after penile tears or injury.[8]

PREVENTION AND EARLY DETECTION

Infant circumcision is highly effective in prevention of this disease, but it is not recommended on these grounds alone. The emphasis is instead on education, promotion of good hygiene for the normally retractile foreskin, and surgical correction of phimosis. Men should be aware of the association between certain HPV subtypes, venereal warts,[6] and cancer, as well as the premalignant nature of conditions such as lichen sclerosis, which may precede the diagnosis of cancer by many years. In a recent report from Scandinavia, patients delay an average of 6 months before seeking medical attention.[9]

Genital condyloma or warts and genital HPV infection refer to a sexually transmitted disease caused by HPV. Although not reportable, the number of new infections is estimated at 500,000 to 1 million annually. The prevalence of HPV in U.S. males is more than 50%, being 60% in uncircumcised and 50% in circumcised men, with higher rates of infection with increasing numbers of sexual partners, lack of condom use, and smoking.[10] Some 60 genotypes of HPV virus have been identified that involve the genital tract.[11] Virus types 6, 11, and 42 to 44 are associated with gross condylomata and low-grade dysplasia. Types 16, 18, 31, 33, 35, and 39 have a higher association with malignant disease. Immunocompromised men with human immunodeficiency virus (HIV) infection are more susceptible to development of penile lesions and squamous carcinoma with high-risk HPV types.[12]

An increased incidence of penile intraepithelial neoplasia has been found in the male partners of women with cervical intraepithelial neoplasia. A recently available quadrivalent vaccine (Gardasil, Food and Drug Administration, June 2006) protects against HPV types 5, 11, 16, and 18 and is recommended in females aged 9 to 26 years. Although approved for use in young males, vaccination rates in Australia and North America are far below those for females. Vaccine use in males still targets high-risk populations such as organ transplant recipients and homosexual men.[13] Successful HPV vaccination programs are necessary to combat the rising incidence of HPV-related neoplasms for which effective screening programs are lacking, including squamous carcinomas of the penis, anus, and oropharynx.[14,15]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The overall incidence of HPV in penile carcinoma is 40% to 45%, as detected by polymerase chain reaction (PCR) amplification of DNA. HPVs 16 and 18 are the most frequent subtypes detected.[16,17] The frequency of HPV detection depends on histopathologic subtype; HPV association is seen in 80% to 100% of basaloid and warty penile cancers but in only approximately 35% of verrucous or squamous cell carcinomas. The difference in prevalence of HPV in these two groups suggests different pathogenesis. Penile lesions can be classified into HPV-induced (HPV 16 in 76%, followed by HPVs 33, 31, 45, and 18) and HPV-independent, often in the background of chronic inflammation (lichen sclerosis, bowenoid papulosis). HPV presence in a tumor may confer a better prognosis.

The presence of p53 is found in 41% to 75% of invasive penile cancers.[18,19] Nuclear expression of p53 is seen in tumor cells and basal keratinocytes of p-16(ink4a) negative non-HPV induced lesions.[7] In multivariate analysis, p53 positivity and lymphatic embolization are predictive of lymph node metastases.[18,20]

PATHOLOGY AND PATHWAYS OF SPREAD

Premalignant lesions are associated with invasive cancers in 20% to 30% of cases. Intraepithelial neoplasia such as bowenoid papulosis, Bowen disease, and erythroplasia of Queryat[21] are precursor lesions of warty and basaloid penile cancers. Lichen sclerosis (balanitis xerotica obliterans) is associated with non-HPV variants of penile carcinoma.[22,23] Condylomata, Buschke-Löwenstein disease, Kaposi's sarcoma, and leukoplakia are also associated with penile cancer.

The primary tumor most frequently occurs on the glans (48%) or prepuce (25%), with the glans and prepuce involved in 9%, the coronal sulcus in 6%, and the shaft in only 2%. Squamous cell carcinomas represent 95% of invasive cancers of the penis. Other histopathologic primary tumor types are malignant melanoma, transitional cell carcinoma, basal cell carcinoma, and sarcoma.

The lymphatics of the prepuce and the skin of the shaft drain into the superficial inguinal nodes located above the fascia lata. The glans and the deep penile structure drain into the superficial or deep inguinal nodes from which they spread along the femoral vessels to the external iliac, common iliac, and paraaortic regions. The sentinel nodes are located above and medial to the junction of the inferior epigastric and saphenous veins.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

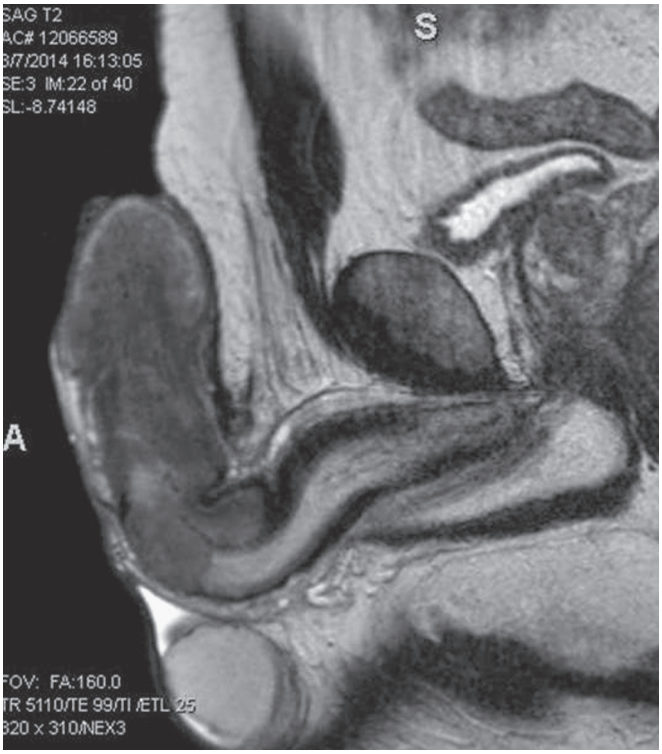
General Approach

Because of the rarity of carcinoma of the penis, reported series often span several decades. Four different staging systems are encountered in a review of the literature of the past three decades[24-27] (Table 57-1).

As clinical staging of carcinoma of the penis is subjective, it may be difficult to distinguish T1 (i.e., invasion of subepithelial connective tissue) from T2 (i.e., invasion of corpus spongiosum or cavernosum). For this reason, techniques that treat less than the full thickness of the penis must be restricted to carefully selected cases. High-resolution MRI is the gold standard for evaluating the primary tumor and local extension.[28,29] Although small-volume lesions on the glans can be adequately staged by palpation in most cases, MRI especially with artificial erection by intracorporal injection of prostaglandin E1 improves staging of the primary tumor where invasion of the corpus cavernosum is suspected (eFigure 57-1).[30,31] Any patient who presents with phimosis and chronic discharge, bleeding, balanitis, or swelling in the region of the coronal sulcus or glans under an unretractable foreskin should have a dorsal slit of the foreskin to allow inspection of the glans, followed preferably by a full circumcision. Any suspicious lesions should be sampled. Figure 57-1 shows the diagnostic algorithm for a patient with clinically node-negative disease.

Lymph Node Assessment: The N0 Patient

Management of the patient with clinically negative groins has been considerably clarified in the past decade. Although many RT series have advocated a "wait-and-see" policy, with no systematic staging investigations such as CT or fine-needle



eFigure 57-1 MRI of the penis. The erectile bodies are normally bright white on MRI. This image shows dark tumor invasion of the shaft.
MRI, Magnetic resonance imaging.

TABLE 57-1 Staging Systems for Carcinoma of the Penis

Stage	Description
JACKSON STAGING SYSTEM*	
1	Tumor limited to the glans or prepuce
2	Tumor extending into the shaft or corpora but without node involvement
3	Tumor confined to the shaft but with malignant but operable lymph nodes
4	Invasion beyond the shaft with inoperable lymph nodes or distant metastases
TNM (UICC, 1978)†	
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 5 cm
T3	Tumor > 5 cm or deep invasion including urethra
T4	Tumor invades adjacent structures
N1	Metastases in unilateral inguinal lymph nodes
N2	Metastases in bilateral inguinal lymph nodes
N3	Fixed inguinal lymph nodes
TNM (UICC, 1987-2002)‡	
T1	Tumor in subepithelial connective tissue
T2	Tumor in corpus spongiosum or cavernosum
T3	Tumor in urethra or prostate
T4	Tumor in other adjacent structures
N1	Tumor in one superficial inguinal lymph node
N2	Tumor in multiple or bilateral superficial inguinal lymph nodes
N3	Tumor in deep inguinal or pelvic lymph nodes
TNM UICC 7TH EDITION 2009§	
Tis	Carcinoma in situ
Ta	Non invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue T1a: without lymphovascular invasion; not poorly differentiated or undifferentiated T1b: with lymphovascular invasion or poor differentiation
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

UICC, *Union Internationale Contre le Cancer (International Union Against Cancer).*
**From Jackson S: The treatment of carcinoma of the penis. Br J Surg 53:33-35, 1966.*
†From Harmer M: Penis (ICD-0187). In TNM classification of malignant tumours, ed 3, Berlin, 1978, Springer-Verlag, pp 126-128.
‡From Hermanek PS, Sobin LH: Penis (ICD-0187). In Hermanek PS, Sobin LH, editors: TNM classification of malignant tumours, ed 4, Berlin, 1987, Springer-Verlag, pp 130-132.
§From Sobin L, Gospodarowicz M, Wittekind C: Penis (ICD-O C60). In Sobin L, Gospodarowicz M, Wittekind C, editors: TNM classification of malignant tumours, ed 7, Oxford, 2010, Blackwell Publishing, pp 239-242.

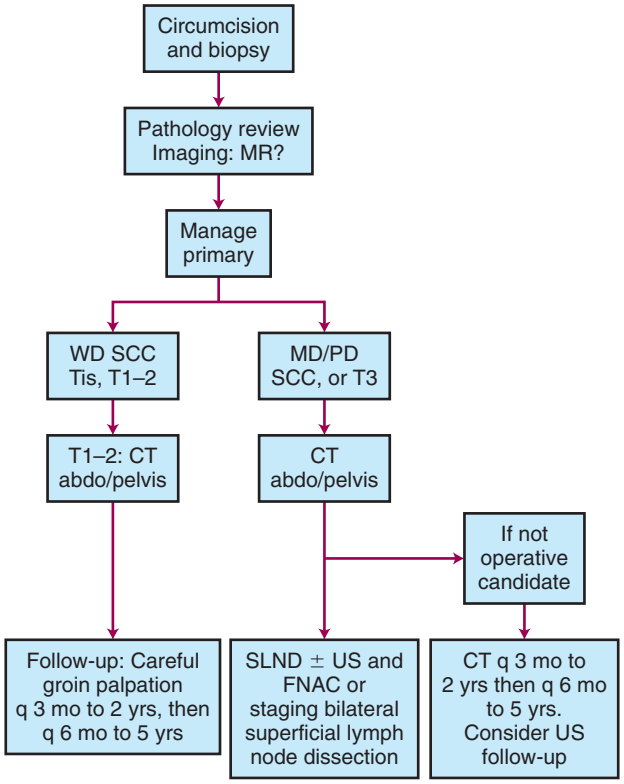


Figure 57-1 Diagnostic algorithm for penile cancer: A patient with clinically node-negative cancer. *CT,* Computed tomography; *FNAC,* fine-needle aspiration cytology; *MR,* magnetic resonance; *MD,* moderately differentiated; *mo,* month; *q,* every; *SCC,* squamous cell carcinoma; *SLND,* sentinel lymph node dissection; *US,* ultrasound; *WD,* well differentiated; *yrs,* year.

aspiration cytology (FNAC),[3,32-35] the predictive factors for lymph node involvement have been established and allow the practitioner to selectively offer surgical staging. Overall, only about 20% of clinically negative nodes have micrometastases, so staging lymph node dissection is not warranted for all patients; traditional inguinal node dissection may be complicated in one third of cases by infection, skin flap necrosis, deep vein thrombosis, or severe leg edema.[36-38] Nodal status is, however, the strongest predictive factor for overall survival (OS) and lymph node dissection may be curative for men with microscopic regional spread. Several surgical series have identified that *therapeutic* node dissection confers an inferior survival compared with *prophylactic* node dissection.[39] McDougal[40] found a 5-year OS after inguinal node dissection of 92% for patients with clinically N0 disease, compared with 33% for those with clinically involved nodes. Modified inguinal lymphadenectomy, sparing the saphenous vein, and limiting the dissection laterally, distally, and proximally, may reduce morbidity.[36]

The reliability of physical examination is diminished markedly in the patient who is obese, so imaging is paramount. Both CT and MRI will demonstrate gross lymph node enlargement but will not detect a small metastasis in a normal-sized node. Nonetheless, CT is the imaging modality recommended to examine the inguinal regions and pelvis as well as to rule out more distant metastases, with a sensitivity and specificity of 36% and 100%, respectively. The combination of positron emission tomography (PET)/CT using the radiopharmaceutical fluorodeoxyglucose (^{18}F-FDG) has been shown[41] to increase sensitivity to 80%. The combination of ultrasound and FNAC has been shown to detect 80% of metastatic disease in

nonpalpable nodes (12 out of 15) with an overall sensitivity and specificity of 87% (48 out of 55) and 99%, respectively.[42]

Stage and histopathologic factors should be used to identify patients at high risk for microscopic regional spread to selectively offer surgical staging of lymph nodes. Chaux and Cubilla[43] have published a stratification system to estimate the likelihood of lymph node metastases based on grade, extent and depth of invasion, and the presence of perineural invasion. T category and lymphovascular invasion are also reported to be predictive for nodal relapse.[44,45] The risk of nodal involvement in patients at high-risk is 64% to 83%, 20% to 33% in intermediate risk, and 0% to 8% in low risk.

The difficulty with applying histopathologic information to decision making in RT is that the primary tumor is not available for complete examination. Invasion of the corpora may be underappreciated clinically. Diagnostic biopsies are often superficial and unreliable in determining the depth of invasion, the presence of lymphovascular invasion, or the ultimate tumor grade.[46] However, if the biopsy shows high-risk features, surgical assessment of regional lymph nodes is recommended. Ultrasound-guided FNAC is a valuable tool to evaluate suspicious inguinal nodes,[47] with reported sensitivity and specificity more than 90%.[48] A 4- to 6-week trial of antibiotics is no longer recommended.

The current European Association of Urology (EAU) guideline recommends observation of the lymph nodes for carcinoma in situ (Tis), verrucous (Ta), and T1-grade 1 tumors because these are associated with less than a 10% incidence of lymph node positivity.[49] T1 grade 2 tumors are classified as intermediate risk and observation is recommended only for those with a superficial growth pattern and no vascular invasion. Category T2 or higher or grade-3 tumors and those with vascular invasion have a higher than 50% risk of lymph node involvement and should have surgical staging. Patients with T1 grade 2 tumors with high-risk features such as tumor thickness or vertical growth should also be considered for surgical staging. Close follow-up of patients at high risk is important.[50]

Dynamic sentinel lymph node mapping uses a gamma probe after intradermal peritumoral injection of technetium-99m and is becoming more widely available for detection of early lymph node involvement (eFigure 57-2). False-negative rates, although initially in the 18% to 25% range, have fallen to 5% to 7% in the recent literature from high-volume centers with experienced surgeons.[51,52] Complication rates of 5% are reported.[53] Lam et al[54] described long-term follow up of 500 inguinal basins in 264 patients with T1G2 or higher disease and nonpalpable nodes managed with ultrasound or FNAC and DSNB. Sensitivity of DSNB alone per inguinal basin was 92% and with ultrasound with or without FNAC 95%. Routine serial sectioning along with cytokeratin immunohistochemistry, exploration of groins with low or no signal, and ultrasound with FNAC to detect positive lymph nodes that may have altered lymphatic flow[55] have helped to decrease false-negatives. The use of PET/CT may further decrease the risk of false-negatives from tumor blockage and rerouting of lymphatics.[56] Superficial inguinal lymph node dissection is still considered the gold standard in centers lacking the expertise for Dynamic Sentinel Node Biopsy (DSLB) because the consequences of a false-negative may be an increased risk of death from disease.

PRIMARY THERAPY

Surgery

Circumcision is generally the first step. Small tumors that are limited to the prepuce can be treated by circumcision alone. Penis-conserving surgical techniques, such as laser or Moh's surgery, may be suitable for selected tumors. Moh's surgery[57] for carcinoma in situ or superficial tumors involves excision of tissue in successive layers until margins are histologically clear. Complete microscopic scanning of each horizontally cut layer identifies any tumor outgrowths that may extend beyond the visible or palpable lesion.

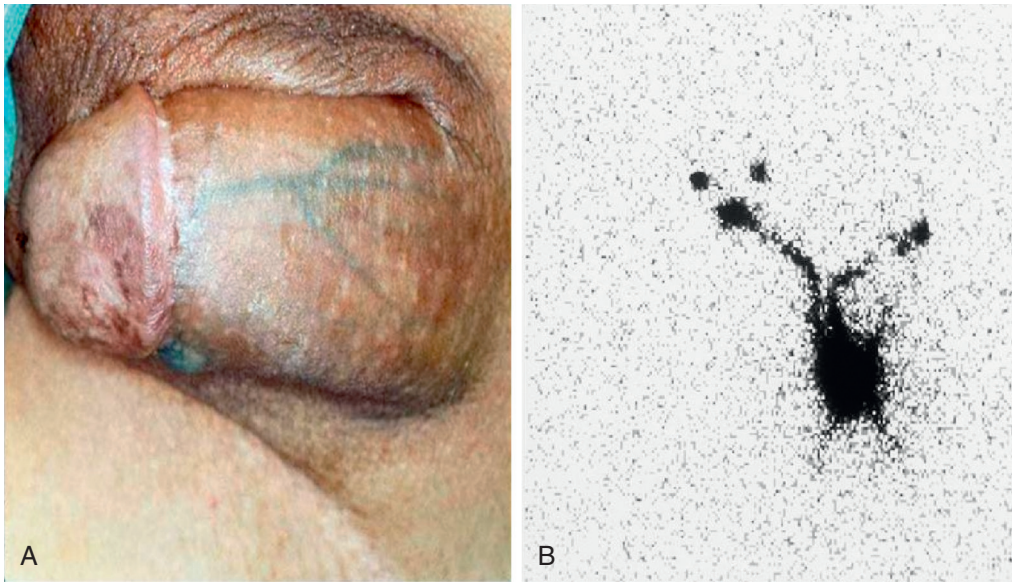
Laser surgery using carbon dioxide or neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers has been reported to provide a superior functional and cosmetic result compared with standard surgical techniques for selected premalignant and malignant lesions (Tis/T1).[58-61] Both carbon dioxide laser (depth of penetration 0.1 mm) and Nd:YAG laser (penetration 6 mm) are used. Tumor-base biopsies to ensure negative surgical margins will reduce failures.[61] High rates of resumption of sexual activity and overall satisfaction are reported. Although local recurrence rates are 17% to 19% at 10 years, many can be retreated with laser, reducing the ultimate amputation rate to about 5%.[59,62] Extended, careful follow-up is required because only 57% of local recurrences occur within the first 2 years, 30% between 6 and 10 years, and 15% after 10 years. Whether these late failures represent true local recurrences or new primary tumors is unknown.

Selected cases, especially those involving only skin, can be treated by wide excision, but local wedge excision is associated with a high recurrence rate. Limited excision of the glans, and glansectomy with reconstruction by a split-thickness skin graft to spare the penile shaft represent surgical strategies to maintain function and penile length.[63] Although Veeratterapillay 2012[64] has reported a 6% local recurrence rate at 40 months in 65 patients, many with T2 disease and intermediate to poor differentiation, local failures increase with longer follow up; 25% occur after 5 years.[65] Traditionally, an adequate resection margin is considered to be 2 cm, but closer margins of 10 mm or less may be acceptable if tumor-free on frozen section. Agrawal et al[66] reported that tumor grade correlated with microscopic spread, with the maximum extent being 5 mm for grade-1 to grade-2 tumors and 10 mm for grade 3. Limited excision is not appropriate for deeply invasive and high-grade tumors. All patients managed with penile-sparing surgical techniques remain at a higher risk for local recurrence. Total or partial penectomy is indicated for tumors greater than 4 cm in diameter, grade 3, or deeply invading. Partial penectomy is possible when the tumor involves the glans or the distal shaft, and the penile remnant will allow the patient to direct the urinary stream. Total amputation and perineal urethrostomy is indicated for larger or proximal tumors.

Radiation Therapy

Radical RT in the form of brachytherapy or EBRT is effective in achieving local control in a high percentage of patients (Table 57-2). Often, series span several decades, during which time treatment techniques and dose prescriptions have evolved. Staging systems have also undergone significant modifications (see Table 57-1).

Interstitial brachytherapy yields a 5-year local control rate of 77% to 87%, with penile preservation rates at 5 years ranging from 72% to 88%. For EBRT, local control rates are less favorable, 41% to 70% at 5 years, and the consequent increase in surgical salvage decreases penile preservation rates to 36% to 66%. Careful extended follow-up is recommended because local failures can occur several years after treatment. Crook et al[75] found that although five of eight local failures in a series of 67 men occurred in the first 2 years, the remaining three occurred at 4.5, 7, and 8 years. Similarly, Mazeron et al[33] reported that 18% of local failures occurred between years 5 and 8, and de Crevoisier et al[68] reported 20% after 8 years. This late recurrence pattern is strikingly similar to that seen after



eFigure 57-2 Sentinel lymph node study: **A,** Blue dye is seen in the lymphatic vessels of the shaft; **B,** radiotracer is seen in the primary tumor and then branching right and left to bilateral inguinal nodes.

TABLE 57-2 Summary of Literature Results for Brachytherapy and External Beam Radiation Therapy

Study	Year	No. Pts	Dose (Gy)	Follow-Up (range, mo)	5-year Local Control	5-year CSS	Complications	Penile Preservation
BRACHYTHERAPY								
Crook et al[67]	2009	67	60	48 (6-194)	87% 72% (10-year)	83.6%	12% necrosis 9% stenosis	88% (5-year) 67% (10-year)
DeCrevoisier et al[68]	2009	144	65	68 (6-348)	80% (10-year)	92% (10-year)	26% necrosis 29% stenosis	72% (10-year)
Delannes et al[35]	1992	51	50-65	65 (12-144)	86% (crude)	85%	23% necrosis 45% stenosis	75%
Delaunay et al[69]	2013	47	60 (42-70)	80 (13-190)	60%	87.6%	Not stated	66%
Kiltie et al[34]	2000	31	64	61.5	81%	85.4%	8% necrosis 44% stenosis	75%
Mazeron et al[33]	1984	50	60-70	36-96	78% (crude)	—	6% necrosis 19% stenosis	74%
Rozan et al[32]	1995	184	59	139	86%	88%	21% necrosis 45% stenosis	78%
Soria et al[3]	1996	102	61-70	111	77%	72%	Not stated	72% (6-yr)
EXTERNAL BEAM IRRADIATION								
Gotsadze et al[70]	2000	155	40-60 at 2 Gy/Fx	Four decades' experience	65%	86%	1% necrosis 7% stenosis	65%
McLean et al[71]	1993	26	35/10 Fx to 60/25 Fx	116 (84-168)	61.5%	69%	28% unspecified	66% (crude)
Neave et al[72]	1993	24	56/84 hr (12 hr/day) (mold)	36-mo minimum	69.7%	67%	13% stenosis	55%
		20	50-55/20-22 Fx (external)	36-mo minimum	69.7%	58%	10% stenosis	60%
Ozsahin et al[73]	2006	33	52	62 (6-450)	44%	—	10% stenosis	52%
Sarin et al[2]	1997	59	60/30 Fx	62 (2-264)	55%	66%	3% necrosis 14% stenosis	50% (crude)
Zouhair et al[74]	2001	23	45-74/25-37 Fx	12 (5-139)	41%	—	10% stenosis	36%

CSS, *Cause-specific survival;* Fx, *fractions;* Pts, *patients;* mo., *months.*

penile-conserving laser treatment[59] and necessitates careful long-term follow-up because the majority can be successfully salvaged.

Surgery for Salvage

Surgery for salvage is successful in more than 80% of failures.[32,74] Local excision is rarely appropriate. The choice between total and partial penectomy[32,34,35,74] depends on penile length and the proportion of shaft irradiated by the primary treatment. The localized nature of brachytherapy should result in less radical salvage operations.

Patient Selection for Radiation Therapy

Several prognostic factors have been identified for penile preservation. For EBRT, a total dose of less than 60 Gy, a protracted treatment time of more than 45 days, and a daily fraction size of less than 2 Gy are all associated with an increased risk of local failure.[2,74]

For brachytherapy, the volume of tumor and depth of invasion are predictive of local control. The ideal tumor for brachytherapy should be less than 4 cm in its maximum diameter, with less than 1 cm of invasion.[3,33,34,76] Local failure rates of 50% to 60% for tumors larger than 4 cm in diameter have been reported, compared with 14% to 30% for those less than 4 cm. Use of more than six brachytherapy needles and tumor volumes greater than 8 mL are also associated with an increased risk of failure.[3,32,34] Crook et al[67] found that wider needle spacing was associated with a decreased risk of failure ($p = 0.006$). Wider spacing results in a wider lateral margin, ensuring more generous margins around the tumor (Figure 57-2).

Histopathology does not appear to be a factor in local control. Moderate to poor differentiation influences OS and the risk of nodal involvement[77] but does not preclude a penile-conserving approach.

LOCALLY ADVANCED DISEASE AND PALLIATION

Although a penile-sparing approach may be warranted for a T3 tumor in a younger patient, most locally advanced tumors require a primary surgical approach with partial or total penectomy, perineal urostomy, and bilateral groin dissection.

Node-Positive Disease

Involved nodes should be resected if possible. As in squamous cancers of the vulva, patients with pathologic findings of multiple positive nodes or extracapsular spread should be offered postoperative RT.[77-79] If dissection of deep pelvic nodes is negative, treatment can be limited to the involved groin. A direct anterior electron field of suitable energy to deliver a dose of 45 Gy to 50 Gy over 5 weeks to the depth of the nodes is

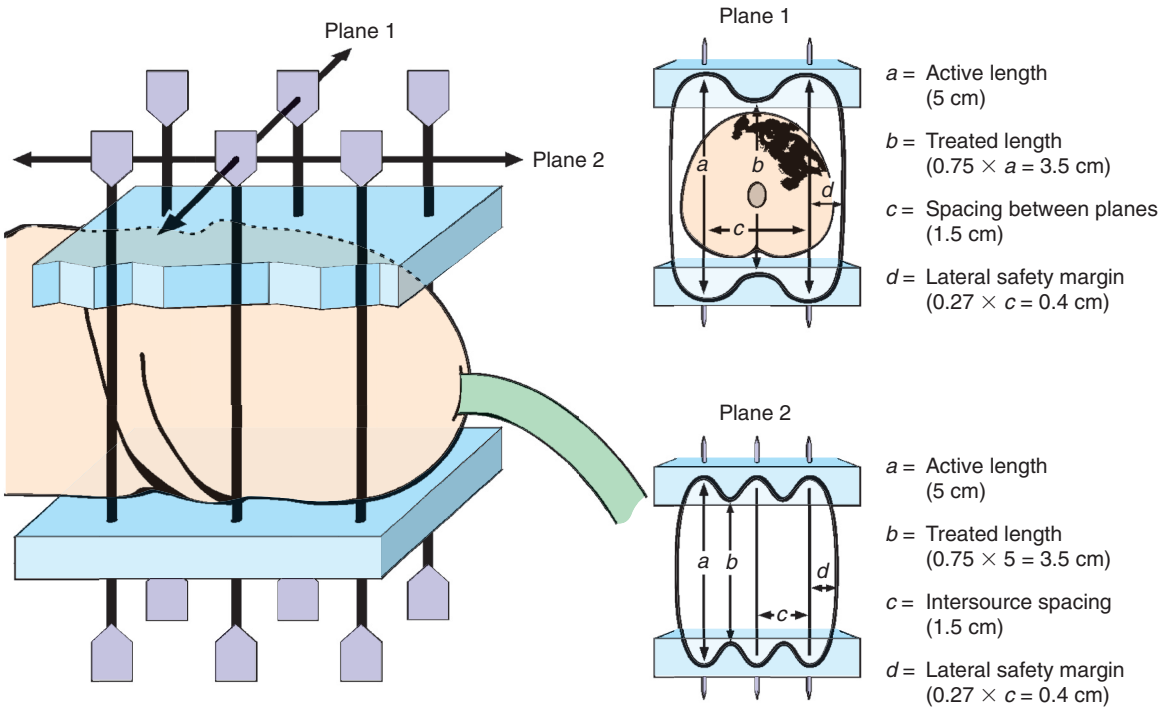


Figure 57-2 Schematic of Paris system of dosimetry for two-plane interstitial implants. Dimensions of treatment isodose can be predicted from length and spacing of radioactive sources.
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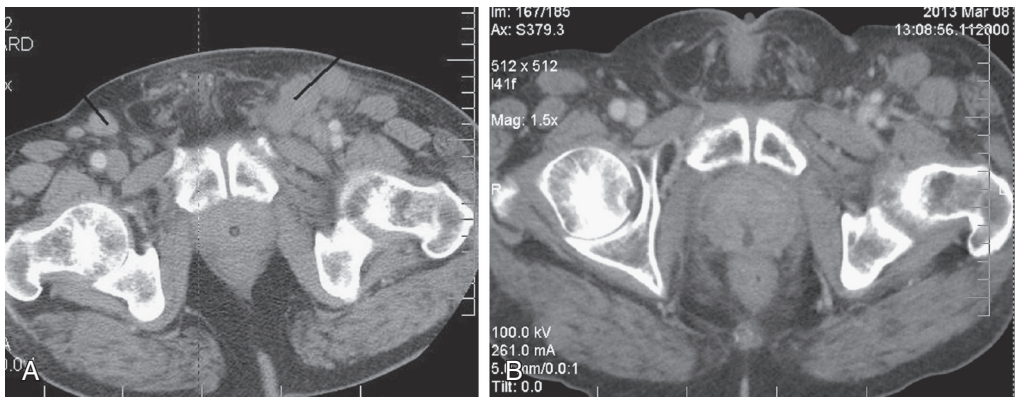

Figure 57-3 Locoregionally advanced penile cancer treated with EBRT and weekly cisplatinum. **A,** diagnostic CT. **B,** Follow-up scan 2.5 years later. *CT,* Computed tomography.

appropriate. If the status of the pelvic nodes is unknown, they should be included in the treatment volume.

Unresectable nodes are rarely controlled by RT alone but can be palliated. A combined approach of concurrent chemotherapy and radiation should be considered (Figure 57-3) in view of the improved local control in other squamous carcinomas when compared with either EBRT alone (cervical cancer) or sequential chemoradiation (CRT; head and neck cancers). One such site is locally advanced squamous cell carcinoma of the vulva,[79] in which the American College of Radiology Appropriateness Criteria[80] recommend the use of neoadjuvant chemotherapy alone only if radiotherapy is not available. The Gynecology Oncology Group (GOG) trial 101 reported that 95% of 41 women with unresectable N2-3 disease who completed CRT subsequently underwent surgical resection with 41% histologically negative. A subsequent Phase II trial (GOG 205) used weekly platinum with daily fractionated RT to a dose of 57.6 Gy in 58 patients. Of 40 who completed the treatment, 37 had a complete clinical response and 29 (50% of the entire series) were histologically negative at subsequent surgery. The role of CRT with or without surgery will be explored in an upcoming international trial for locally advanced penile cancer (InPACT) sponsored by the International Rare Cancers Initiative, using weekly cisplatinum as a radiation sensitizer.

Response rates for neoadjuvant chemotherapy are, at best, 50%. A trial of neoadjuvant paclitaxel, ifosfamide, and cisplatin at the M. D. Anderson Cancer Center has reported a response rate of 50% in 30 patients with N2 or N3 penile cancer. Surgery, CRT, or both, can be used after a response to chemotherapy.[81]

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Irradiation

EBRT has several advantages in that it is widely available, delivers a homogeneous dose, and does not require the specific expertise of brachytherapy. Well-localized carcinoma in situ (Tis) may be treated effectively using 125-kV orthovoltage beams or 9-MeV electrons with suitable bolus, using fractionation schemes commonly employed for skin cancer such as 35 Gy in 10 fractions over 2 weeks[71]; however, most such lesions would be treated by a penile-conserving surgical technique. Most cases referred for RT require irradiation to the full thickness of the penis with a full dose to the skin surface. Fraction sizes less than 2 Gy are suboptimal[2] and fraction sizes larger than 2 Gy may be associated with increased long-term sequelae.[72] Doses range from 60 Gy in 25 fractions over 5 weeks to 74 Gy in 37 fractions over 7.5 weeks, avoiding interruptions because of acute reactions (e.g., edema, pain, desquamation). A reproducible setup, easily verified by technologists, which is comfortable for the patient despite increasing local reaction, is essential.

Successful application of megavoltage EBRT to treat penile cancer must overcome the technical challenge of positioning the penis in such a way that other tissues will not be exposed to irradiation and counteracting the skin-sparing of megavoltage x-rays. Several techniques have been developed.

A 10- × 10-cm to 10- × 15-cm wax block can be constructed in two halves with a central cylindrical chamber.[71,74] The patient is positioned supine on the treatment couch, and the penis is supported in a vertical position, encased in the wax block. Tissue-equivalent material must be placed in the distal portion of the cylindrical chamber to maintain full dose to the glans. Parallel-opposed beams of cobalt 60 or 4- to 6-MV photons treat the entire length of the penis (Figure 57-4). As treatment progresses, penile swelling may require modification of the wax block. Verification of penile position within the wax is not possible, but a snug fit will prevent the penis from "slumping" inside the wax.

Perspex is a good alternative to wax and provides full buildup to the skin surface while allowing treatment by parallel-opposed beams.[2] Preconstructed blocks in a range of sizes of the central cylindrical chamber can be sterilized for reuse. Penile swelling can be accommodated easily by choosing the next larger size, and penile position within the transparent block can be easily verified visually.

An alternative approach has been described with the patient positioned prone and the penis suspended in a *water* bath. This approach is not appropriate in patients who are obese and day-to-day set up can be challenging because the penis tends to float and position itself too close to adjacent tissues.[82]

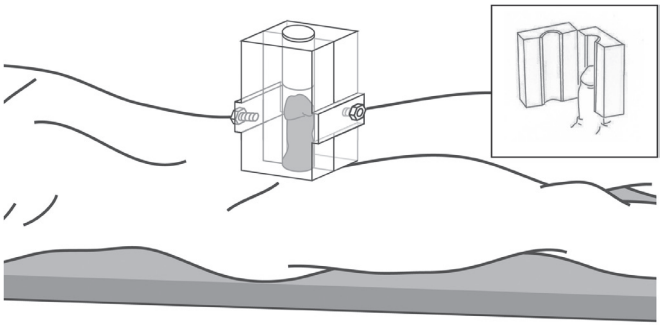

Figure 57-4 Patient positioned with Perspex block in place. Block provides full buildup and is transparent for verification of penile position. The blocks are bivalved and can be made in a range of sizes to accommodate penile swelling as treatment progresses.

Brachytherapy

The penis is well suited to brachytherapy. For centers with appropriate expertise, surface molds or interstitial techniques can be used with good effect. Circumcision should be performed before brachytherapy to ensure complete exposure of the tumor and prevent subsequent phimosis or annular fibrosis of the foreskin.

Molds

Unlike interstitial brachytherapy, a mold is not invasive and does not require anesthesia.[72] The acute reaction develops after the treatment is finished. A surface dose of 55 Gy to 60 Gy is prescribed, with a central axis dose of 46 Gy to 50 Gy over 84 hours (12 hr/day) and may be delivered using a Perspex tube or silicon monomer.[72] Application is limited to superficial tumors of known depth of invasion.

Interstitial Brachytherapy

There is experience with interstitial brachytherapy for T1 or T2 penile carcinoma from many European countries and from Canada. A joint consensus guideline has recently been published by the American Brachytherapy Society and Groupe Europeen de Curiethérapie.[83] Ideally patients should have tumors less than 4 cm in diameter with no or limited invasion of the corpora or involvement beyond the coronal sulcus. Implants can be performed with the patient under general or local anesthesia. The Paris system of dosimetry[84] is applicable to manually afterloaded implants and remote afterloading pulse-dose-rate systems, although for the latter some optimization can be introduced.

Circumcision should always precede penile brachytherapy to allow full visualization of the tumor and to remove any portion involving the foreskin. The foreskin is prone to necrosis and if left in situ during brachytherapy the ensuing painful ulceration can be slow to heal and result in a chronically adherent or phimotic foreskin.

Penile brachytherapy is generally performed as a "volume" or multiplane implant delivering irradiation to the full-thickness of the penis. Only well-selected, superficial tumors may be treated with a single-plane implant. A video of penile brachytherapy is available on the Expert Consult website. For volume implants, two or three parallel planes of sources are inserted, with two or three needles in each plane. Intersource and interplane spacing should be equal, in the range of 12 mm to 18 mm. The distribution, spacing, and total number of needles depend on tumor size. Planes are usually oriented with the needles passing from the dorsal to the ventral surface of the glans, but a left-to-right orientation may work for some tumor locations. Visual verification of coverage can be readily accomplished. Needle placement should be planned such that the prescription isodose will cover 10 mm beyond visible or palpable tumor. Care must be taken to adhere to the rules of the Paris system[66] and to be aware of the relationship of the treated volume to the needles such that placement ensures that the entire tumor and desired margin are within the high-dose volume (Figure 57-5). Specific considerations of needle placement for meatal tumors or unilateral tumors have been described.[53]

Needle placement requires 30 minutes to 45 minutes in the operating room. Catheterization aids in identification of the urethra so as to avoid transfixing it with implant needles. For manually afterloaded iridium-192 wire, 19.5-gauge needles

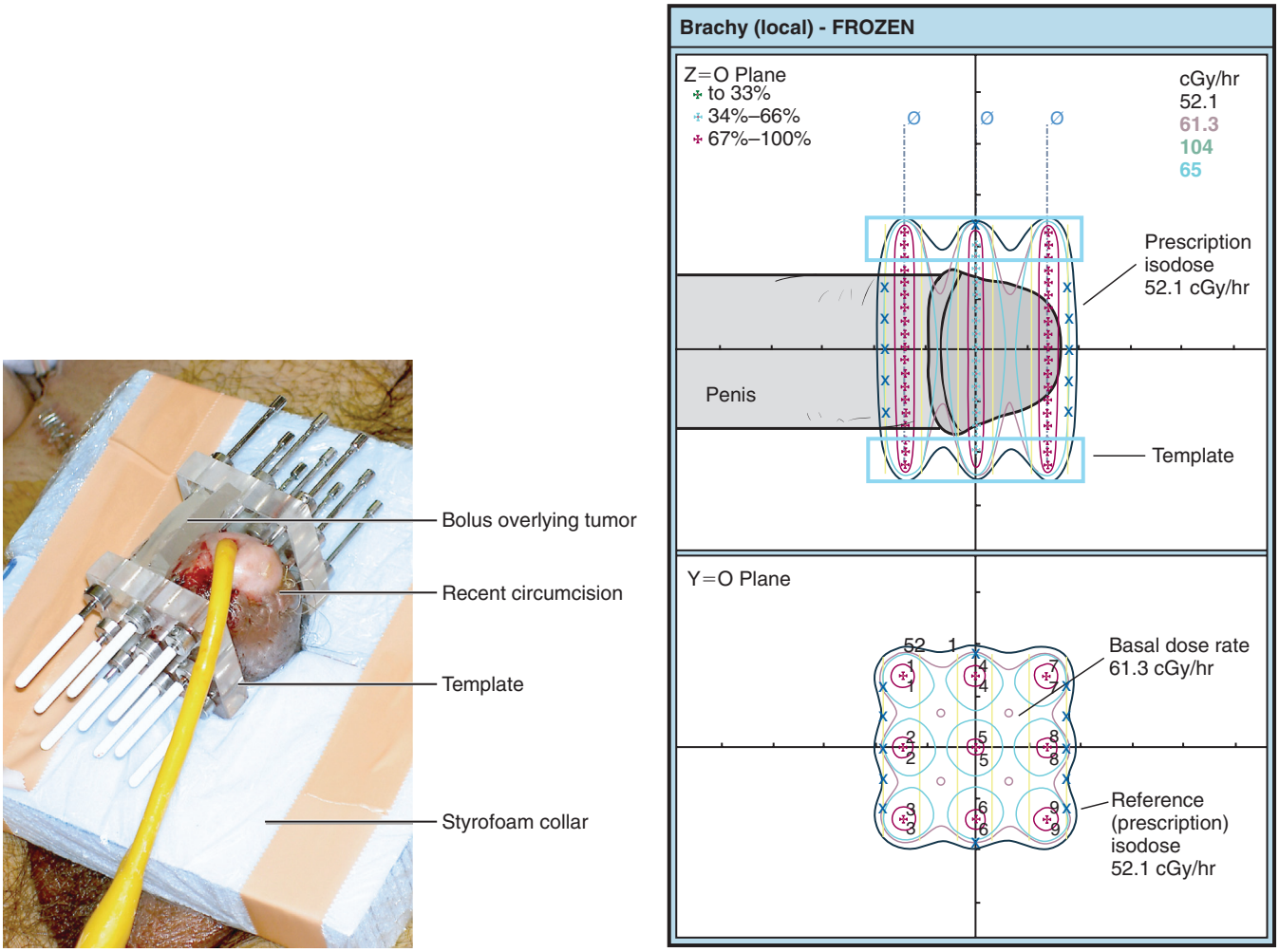

Figure 57-5 Interstitial brachytherapy according to the Paris system of dosimetry.[66] **A,** Six-needle, two-plane implant. **B,** Nine-needle, three-plane implant. **C,** Dose distribution for B. According to the Paris system, dose rate minima in the central plane (61.3 cGy/hr in this case) are the basal dose rate. The prescription isodose is 85% of the basal dose rate (52.1 cGy/hr in this case).

are appropriate, whereas, for a pulse-dose-rate remote afterloader, 17.5-gauge needles are compatible. The needles are stabilized through the duration of treatment with predrilled Plexiglas templates. The prescribed dose is generally 60 Gy at a dose rate of 50 cGy/hr to 60 cGy/hr over 100 to 120 hours (4 days to 5 days). No dose rate correction is required for pulse-dose-rate therapy (hourly fractions) compared with continuous low-dose-rate therapy. A Styrofoam or sponge collar positioned around the base of the penis proximal to the needles supports the penis, distances the implant from the testes, and minimizes unnecessary irradiation of adjacent tissue. A thin sheet of lead can be inserted into the supporting collar to decrease transmitted dose to the testes if subsequent fertility is an issue.

The brachytherapy needles are generally well tolerated. The patient remains catheterized and in bed for the duration of the implant, although with pulse-dose-rate therapy the source cables can be disconnected from the needles to allow the patient to mobilize for brief periods between fractions. Sufficient analgesia is usually provided by acetaminophen, with or without codeine. Leg exercises and embolus prophylaxis are recommended. Removal of the needles occurs at the bedside after premedication with a narcotic analgesic.

Although high-dose-rate (HDR) brachytherapy is becoming widely available, at present there is little evidence on which to base treatment recommendations for penile cancer. One report of 10 patients treated over 8 years used twice-daily fractions of 3 Gy to deliver 54 Gy over 9 days.[85] No necrosis was observed but implants were small volume and the majority was single plane. Limited personal experience with 6 patients, prescribing fractions of 3.2 Gy to 3.75 Gy twice a day for a total prescribed dose of 38.2 Gy to 45 Gy, with needle spacing from 9 mm ($n = 2$) to 14 mm to 17 mm ($n = 4$), resulted in 5 patients being disease free and one local failure. Five of the 6 patients experienced delayed healing and necrosis, including the one with local failure. Of the 5 patients who were NED, one has ongoing ulceration, whereas 3 healed with conservative management including hyperbaric oxygen. CT planning is required with delineation of the gross tumor volume using fine wire. Because of the high rate of troublesome ulceration and necrosis one has to be cautious and preliminary recommendations would be to keep the V_{150} less than 20%, use needle spacing of 9 mm to 12 mm to improve homogeneity, and select cases where the PTV is limited to 30 mL or less. Complications will be worse in patients with diabetes and those who smoke. Further published experience and longer

follow-up is required before any definitive recommendations can be made regarding optimal fractionation for HDR brachytherapy in the management of penile carcinoma.

Tolerance: Acute and Chronic Reactions

Toxicity: Acute Reaction

The acute reaction after brachytherapy is limited to the implant site. Moist desquamation peaks in 2 to 3 weeks but may take 2 to 3 months to heal completely. Local hygiene is important, including frequent soaks in baking soda and water. Sterile distal urethritis is common, but urethral adhesions, causing a divided or deviated urinary stream, should be separated by passing a meatal dilator or an 18-French Foley catheter a few centimeters into the distal urethra. Intercourse can be resumed as soon as the patient is comfortable, but because the healing epithelium is fragile, additional water-based lubricant is recommended.

The acute reaction to EBRT peaks during treatment and may involve edema of the penile shaft and more extensive desquamation. Management is similar to that for patients who had brachytherapy.

Late Reactions

The two most common and significant late complications of RT for penile cancer are soft-tissue ulceration and meatal stenosis. Either can occur with EBRT or brachytherapy (see Table 57-2).

Soft-Tissue Ulceration or Necrosis

Soft-tissue ulceration is reported in 0% to 23% of patients and is more common after brachytherapy than after EBRT. Necrosis (persistent, nonhealing ulceration) is the most common reason for amputation of a tumor-free penis. The risk of necrosis increases with increasing dose more than 60 Gy, stage T3 tumors, larger implant volume (>30 mL; $p = 0.01$), and a greater number of needles ($p = 0.04$) or implant planes (>2; $p = 0.001$).[33,77]

The peak time for soft tissue ulceration is 7 to 18 months after brachytherapy, but it can occur much later. Causative factors include trauma and cold exposure. Areas of ulceration should be treated conservatively, with attention to good hygiene, antibiotics, and topical corticosteroid or vitamin E creams. Biopsy should be avoided unless there is suspicion of concomitant tumor. A deeper or painful area of necrosis may respond well to hyperbaric oxygen treatment[77] (Figure 57-6). If such treatment is available, it should be tried before resorting to amputation.

Urethral Stenosis

Urethral or meatal stenosis is reported in 10% to 45% of patients and tends to occur later in the follow-up period, but usually before 3 years. With EBRT it is more common with higher doses and fraction sizes greater than 2 Gy. For brachytherapy, Rozan et al reported that the only factor predictive of urethral stenosis was the number of needle planes used in the

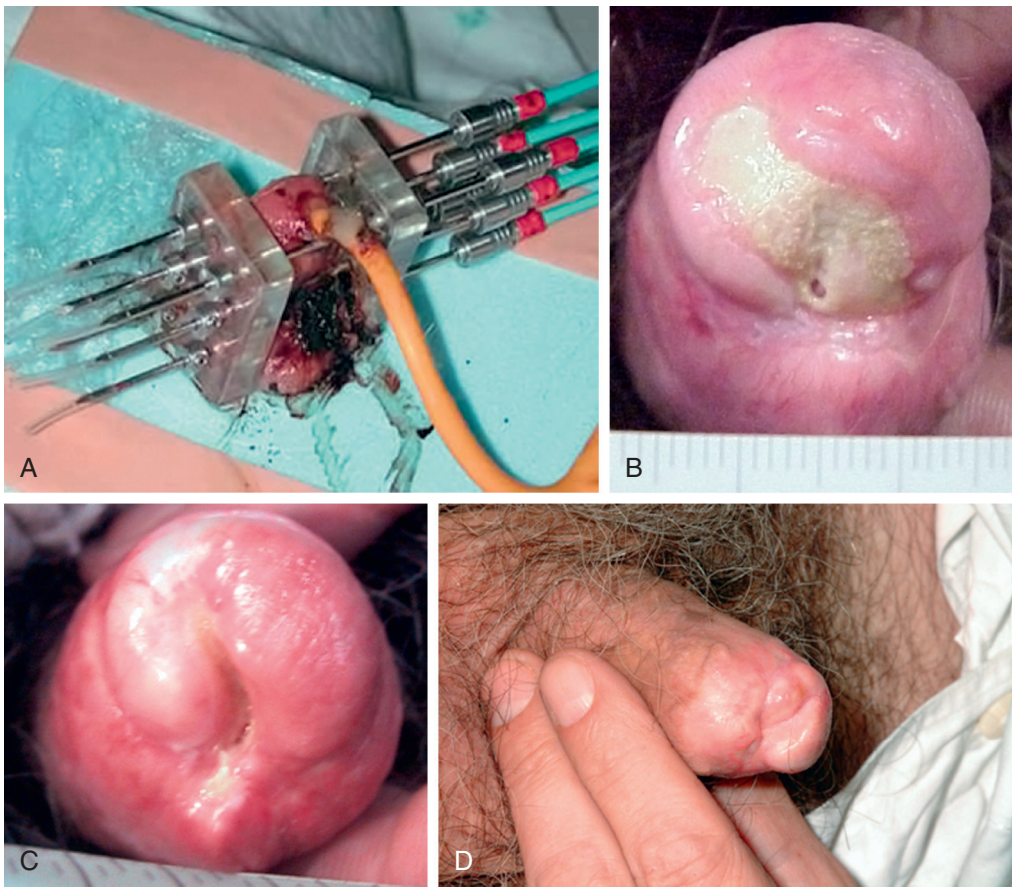

Figure 57-6 **A,** 47 year old man with deeply invasive moderately differentiated SCC, T3pN0 who had staging node dissection but refused penectomy. **B,** The patient suffered a severe necrosis following brachytherapy and tumor response. **C,** Healed with hyperbaric oxygen. **D,** Result shown 5 years later. Patient is potent and disease-free.

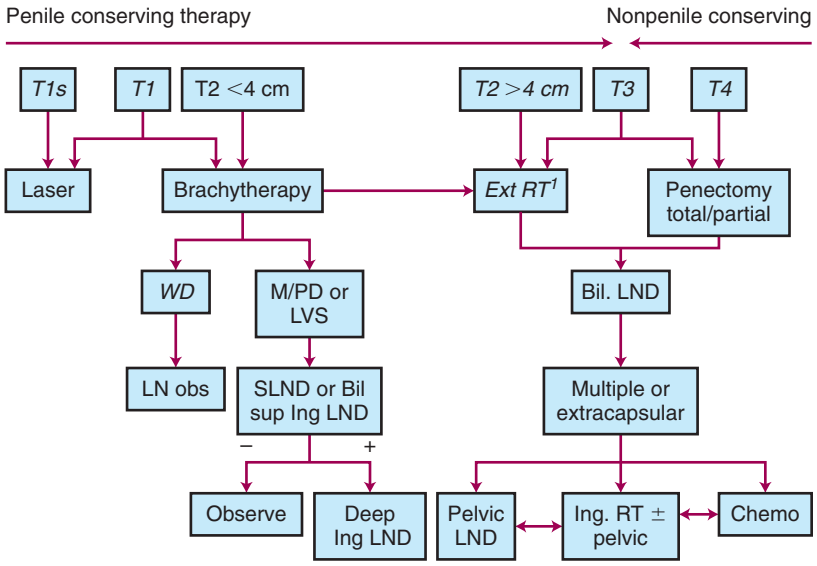

Figure 57-7 Treatment algorithm for penile cancer. External irradiation is a reasonable option for T1 and small T2 tumors if brachytherapy is not available. *Bil sup,* Bilateral superficial; *EXT RT,* external radiation; *Ing,* inguinal; *LN,* lymph node; *LND,* lymph node dissection; *LN Obs,* lymph node observation; *LVS,* lymphovascular space; *M/PD,* moderately/poorly differentiated; *SLND,* sentinel lymph node dissection; *WD,* well differentiated.

implant ($p = 0.001$, if two planes).[32] When a three-plane implant is indicated because of tumor size or morphology, central plane needles will be close to the urethra.[75] A pulse-dose-rate remote afterloader allows optimization of dwell times to limit the urethral dose.

Urethral adhesions in the acute phase should be separated to avoid development of a chronic problem. Patients can be given a meatal dilator at their first follow-up visit with instructions to use it as required. Many late urethral stenoses are low grade and can be managed with repeat dilatations, or even self-dilatations, often at infrequent intervals. Severe cases may require reconstructive surgery, such as urethroplasty or meatoplasty.

Sexual Function

The impact on sexual function often is not assessed. Crook et al[77] found that in a series of 49 men treated with brachytherapy, 22 of 27 who were potent at baseline reported satisfactory potency at last follow-up. Delannes et al[35] observed that apart from one patient who developed painful erections resulting from sclerosis, "sexual function did not appear to be altered by the implant." Sarin et al[2] provided details for only 14 of the 59 patients, commenting that 12 were normal and 2 had minor impairment. Mazeron et al[33] stated that for noninfiltrating or moderately infiltrating tumors less than 4 cm in diameter, "sexual function remained the same as before treatment." A recent systematic survey of 21 French patients (median age 73 years) treated by brachytherapy a median of 80 months previously, 59% remained sexually active, and 79% maintained nocturnal erections. None reported a "loss of manliness," but 53% noted a change in sensitivity of the glans.[69]

Incorporation of a layer of 2 mm of lead into the supporting collar around the penis will limit total dose to the anterior testis to 55 cGy and 26 cGy to the posterior testis during a 60-Gy pulse-dose-rate treatment course[58] as measured by thermoluminescent dosimeter. No data are available on post-brachytherapy sperm counts.

Other Late Sequelae

Mottled hypopigmentation or hyperpigmentation, telangiectasia, and mild to moderate focal fibrosis may occur. Some atrophy of the glans in areas of deep tumor infiltration is common.

TREATMENT ALGORITHM, CONTROVERSIES, AND CHALLENGES

Penile cancer is a rare but psychologically devastating disease. The functional and sexual implications of treatment should be discussed with patients.

Our preferred treatment algorithm is shown in Figure 57-7. For Tis, T1, and T2 tumors less than 4 cm in diameter, a penile-conserving approach as primary management is warranted. Laser surgery can provide satisfactory cosmesis, function, and local tumor control, especially for Tis or small T1 lesions, with the option of retreating local recurrences with further laser surgery. The RT of choice is interstitial brachytherapy, which results in penile preservation in 70% of cases at 10 years. If brachytherapy expertise is not available, EBRT can prevent amputation in 50% to 60% of patients. For more locally advanced lesions (T2 > 4 cm, T3, ? T4), concurrent chemoradiation should be evaluated. With any penis-conserving approach, protracted follow-up is necessary because local failure can occur many years later and surgical salvage can be curative.

Observation of regional nodes is recommended for low-risk T1 and T2 tumors that are well differentiated with no evidence of lymphovascular space invasion. Moderately or poorly differentiated tumors and all T3 tumors should have surgical staging of regional lymph nodes.

Squamous cell carcinoma of the penis remains a clinical challenge. Although it is highly curable in its early stages, the challenge is to minimize the psychosexual morbidity of treatment through less aggressive surgical approaches or alternatives to surgery such as brachytherapy without compromising cure. When diagnosis is delayed and the patient presents with advanced disease, the fatality rate is high.

Rare tumors do not achieve the same level of public awareness as the more common malignancies. Public education and support groups for breast or prostate cancer are well established and successful. For penile cancer there is a need to educate the public and physicians about risk factors, warning signs, and early diagnosis. It is unfortunate that men should ever present with locally advanced disease on such a readily visible and easily examined organ.

Enhanced clinical staging with MRI may prove to be a useful adjunct to physical examination when invasion of the

corpora is suspected but not certain (eFigure 57-2). Dynamic sentinel node mapping spares patients with high-risk disease (G2 to G3 or T3) the morbidity of a staging superficial inguinal node dissection (eFigure 57-2).

Cooperative group efforts such as the upcoming trial from the International Rare Cancers Initiative (InPACT) are required to determine the most effective aggressive multimodality approach for the patient with locally advanced disease.

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