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Current Concepts in Penile Cancer

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Abstract

This review highlights the significant advances made in the diagnosis and management of penile cancer. This often-aggressive tumor phenotype has been characterized by its poor prognosis, mostly attributable to its late presentation and heterogeneity of surgical care because of the paucity of cases treated at most centers. Recent advances in understanding of the risk factors predisposing to penile cancer, including its association with the human papilloma virus (HPV), have brought forth the socioepidemiologic concept of HPV vaccination in certain high-risk populations and countries, which remains highly debated. The management of penile cancer has evolved in recent years with the adoption of penile-sparing and minimally invasive surgical approaches to the inguinal lymph nodes, which are a frequent site of regional spread for this malignancy. Lastly, this review highlights the importance of adopting a multimodal approach consisting of neoadjuvant systemic chemotherapy followed by consolidative surgical resection in patients presenting with bulky/locally advanced nodal metastases from penile cancer. (*JNCCN* 2013;11:617–624)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Identify the risk factors associated with penile cancer.
- Discuss the rationale for adopting a multimodal approach consisting of neoadjuvant systemic chemotherapy followed by consolidative surgical resection in patients presenting with bulky/locally advanced nodal metastases from penile cancer.

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In 2013, an estimated 1570 new cases of penile cancer are expected within the United States, with 310 predicted cancer-specific deaths.[1] Penile cancer represents 0.4% to 0.6% of all malignant neoplasms in the United States and Europe, but up to 10% of cancers in men in the developing countries of Asia, Africa, and South America.[2] Early diagnosis is paramount in improving a patient's prognosis. The 5-year survival rate ranges from 0% to 66%, depending on the extent of regional and distant lymph node metastatic dissemination.[3] Complete clinical staging requires a thorough metastatic workup. The single most important prognosticator of cancer-specific survival is the presence and extent of regional inguinal lymph node (ILN) metastases.[2,4] Because of the paucity of penile cancer cases treated at individual centers, a significant heterogeneity in management remains. This lack of consensus is the reason behind the collaborative effort by the NCCN to provide guidelines for the diagnosis and treatment of penile cancer (available in this issue; to view the most recent version of these guidelines, visit NCCN.org). This evidence-based approach hinges on a critical appraisal of peer-reviewed scientific literature and is consistent with guidelines developed by the European Association of Urology (EAU) and the International Consensus of the Société Internationale d'Urologie/International Consultation on Urological Diseases (SIU/ICUD).

Epidemiology and Risk Factors

Patients typically present with penile cancer between the ages of 50 and 70 years, with a median age at diagnosis in the United States of 68 years.[5,6] As with any other disease entity, the assessment of a patient begins with a thorough history and physical examination, focusing on potential risk factors for penile squamous cell carcinoma (SCC). Risk factors include an uncircumcised phallus, especially in the presence of phimosis and/or poor hygiene, tobacco use, psoriasis treatment with ultraviolet light A to the genital area, and lichen sclerosis.[7–10] Also at increased risk are patients with a history of sexually transmitted diseases, including human papillomavirus (HPV; types 16 and 18) and HIV.[6,7,11] Patients with HIV have an 8-fold increased risk, which may be secondary to the higher incidence of HPV among men with HIV.[12] On physical examination, it is essential to characterize the primary penile lesion and assess the presence and extent of ILN.

Clinical Staging and Risk Stratification

The AJCC updated its penile cancer TNM staging system in 2010, and recognizes 4 subtypes of SCC: verrucous, papillary squamous, warty, and basaloid ("see Staging Table, in the NCCN Clinical Practice Guidelines in Oncology for Penile Cancer, available online at NCCN.org [ST-1]"). Adenosquamous and sarcomatoid variants carry a worse prognosis.[13,14] The degree of cellular differentiation is an important predictor of metastatic nodal cancer dissemination and is assigned a pathologic grade, with grade GX indicating that grade cannot be assessed; G1 indicating a well-differentiated tumor (no evidence of anaplasia); G2 a moderately differentiated tumor (<50% anaplasia); G3 a poorly differentiated tumor (>50% anaplastic cells); and G4 an undifferentiated tumor.[13] Additional tumor characteristics of importance are: 1) the distinction between corpus spongiosum and corpus cavernosum involvement, 2) lymphovascular invasion, 3) the size of the largest lymph node metastasis and the number of involved lymph nodes, and 4) a history of HPV infection, if known.[13]

Physical examination should assess the diameters, number, and laterality of ILNs, and their relationship to adjacent structures, all of which assist in assessing the locoregional extent of penile SCC.[4] If the physical examination is difficult to perform because of body habitus or prior surgery, imaging studies such as contrast-enhanced MRI or PET/CT can help determine the extent of disease.[15]

For clinically node-negative patients, the risk of occult metastasis can be estimated based on the characteristics of the primary lesion, with an average of 25% (range, 11%–62%) of patients harboring micrometastatic disease.[16] The NCCN Penile Cancer Panel recommends a modified ILN dissection or dynamic sentinel lymph node biopsy (DSNB) in the absence of palpable nodes (≤pT1G2 disease with superficial growth pattern), and a standard ILND for high-risk patients with a primary lesion of pT1G3 or greater, or those whose primary tumor exhibits lymphovascular invasion or greater than 50% poorly differentiated cancer. Slaton et al[16] reported that these patients are at significantly increased risk (42%–80%) of nodal metastases.

The EAU guidelines panel defined prognostic stratification groups for inguinal metastases among patients with nonpalpable disease, with the low-risk group defined as patients with pTis, pTaG1–2, or

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pT1G1 disease; intermediate-risk patients as those with pT1G2 disease; and high-risk patients as those with pT2 and higher or G3 disease.[4] Similar risk groups have also been defined by the SIU guidelines panel.[17]

Management

Primary Penile Tumor

Tis or Ta: Management of patients with Tis or Ta disease who are at lower risk of metastasis encompasses penile-preserving techniques, namely: 1) topical imiquimod (5%) or 5-FU, 2) circumcision and local excision, and 3) laser ablative therapy with carbon dioxide (CO_2) or neodynium:yttrium-aluminum-garnet (Table 1).[4,18,19] Topical treatments are generally prescribed as first- and second-line treatments for Tis or Ta penile cancer lesions, particularly in patients not seeking surgical resection. In those deemed not suitable surgical candidates, lesions on the foreskin are readily excised, whereas lesions on the glans are more amenable to laser ablation.

T1G1–2: For patients with T1G1–2 disease, penile-preserving techniques are preferred but patient compliance with follow-up is essential. These techniques include local wide excision plus reconstructive surgery, laser therapy, radiotherapy (external-beam radiotherapy), or brachytherapy with interstitial implant.[20–22] Notably, a circumcision should be performed before radiotherapy for full exposure of the lesion and to avoid radiation-related complications. The reason for close follow-up stems from the 2-year recurrence rate reaching up to 50%[23] with some techniques. Historically, a 2-cm surgical margin was recommended with local resection; however, recent studies have shown that surgical margins of 5 to 10 mm provide favorable oncologic outcomes and low recurrence rates (4% and 3%, respectively) with short duration of follow-up. Nevertheless partial/total penectomy remains the gold standard if the lesion is not amenable to penile-preserving approaches, depending on the extent of disease.[24]

T1G3–4, T≥2: Patients exhibiting these lesions should be carefully counseled, because the mainstay surgical option consists of partial or total penectomy, depending on the characteristics of the tumor and whether complete tumor eradication can be completed while leaving a functional penile stump to direct the urinary stream and potentially maintain sexual activity.[25] A more conservative approach, such as brachytherapy or external-beam radiotherapy, may be considered if the patient agrees to undergo close observation. The patient should understand that he is at an increased risk of recurrence and/or metastatic progression, and should be aware of the importance of a commitment to stringent follow-up (year 1–2 every 2 months; year 3 every 3 months; year 4 every

Table 1 Literature on the Management of Penile Squamous Cell Carcinoma Using Penile-Preservation Techniques or Partial or Total Penectomy

Author	N	Procedure	Number of Recurrences	Mean Follow-Up
Laser				
Tietjen and Malek[50]	44 (T1–2)	CO_2/Nd:YAG	5 (11.4%)	58 mo
Frimberger et al[51]	29: 12 (T1–2), 17 (Tis)	Nd:YAG	2 (6.8%): 2 (17.2% T1–2), 0 (Tis)	46.7 mo
Penile-Preservation Procedures				
Brown et al[52]	174	Glans/partial resurfacing	23 (13%)	72 mo
Hadway et al[53]	10 (Tis)	Glans skinning + resurfacing	0	30 mo
Partial or Total Penectomy				
Ornellas et al[54]	522	Partial penectomy	25 (4%)	11 mo
	98	Total penectomy	0	—
Leijte et al[55]	214	Partial penectomy	15 (5.1%)	60.6 mo
	71	Total penectomy	0	—

Abbreviations: CO_2, carbon dioxide; Nd:YAG, neodynium:yttrium-aluminum-garnet.

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6 months; and annually thereafter) should be emphasized, along with the potential requirement for a repeat surgical resection should a locoregional recurrence be detected.[26]

Role of Radiotherapy: Radiation is an effective treatment for penile SCC, with more than 5 decades of reported experience. Either external-beam radiotherapy or brachytherapy can be used, but when technically feasible, brachytherapy gives superior results, with 5-year penile preservation rates of 75% to 88% and 10-year rates of 67% to 70%. Series that span several decades often use a range of techniques, doses, and dose rates, making it difficult to develop guidelines for the modality (Table 2). Most patients included in published series had T1–T2 lesions, with occasional T3 tumors. Both local recurrences and complications, such as soft tissue ulceration increase, have been associated with larger tumor sizes and larger volume implants.[27–29] However, Crook et al[30] found no size effect up to 5 cm using a consistent interstitial technique and a narrow range of dose rates between 50 and 60 cGy/h, provided the tumor was limited to the glans. When the tumor is larger than 4 cm and extends beyond the coronal sulcus and onto the shaft, a surgical approach may be preferable.[31] The most common side effects are soft tissue ulceration (6%–26%) and meatal stenosis (8%–45%). Soft tissue ulceration or necrosis can be minimized in larger tumors by using a moderate dose rate of 50 to 60 cGy/h.[31] Nonhealing ulcerations will often respond well to hyperbaric oxygen treatments.[32]

All of the large reported brachytherapy series used classic low-dose-rate techniques, with the radiation dose delivered at between 30 and 100 cGy/h over approximately 3 to 6 days. One recent report from Petera et al[33] used the much more widely available high-dose-rate (HDR) technology, delivering 54 Gy over 9 days, with 2 fractions per day of 3 Gy each. These excellent results require validation in other centers, but guidelines on HDR fractionation for penile cancer will make penile brachytherapy much more widely available, because HDR "afterloading" machines are present in most radiation departments.

Reports on external-beam radiation show an equally large range of total dose and fractionation schemes. Penile preservation rates at 5 years are 50% to 65% at best, and less if the total dose is less than 60 Gy, the fraction size is less than 2 Gy per fraction, or the total course is prolonged beyond 45 days.[22,34]

Radiation therapy for penile SCC, as for so many other squamous carcinomas (eg, cervix, head and neck, anal canal), is a highly effective treatment modality. The site presents certain technical challenges, which can be overcome in a center of excellence with sufficient case volumes.

Inguinal Lymph Nodes

Inguinal Lymph Node Dissection: Penile cancer typically metastasizes in a predictable fashion to the ILNs; therefore, early surgical management of nonbulky nodal metastasis (<4 cm) has been shown to have a favorable impact on survival.[35] However, because not all palpable lymphadenopathy at diagnosis warrants an immediate ILN dissection (ILND), careful evaluation based on the primary penile lesion's risk factors is warranted. Up to 70% of patients with palpable lymph nodes at diagnosis will not have metastatic disease. Fine-needle aspiration is the favored approach among many leading penile cancer experts in lieu of a course of antibiotics in low-risk men with a palpable node after primary tumor therapy.[36]

Cabanas et al[37] used lymphangiograms and dissection targeting specific anatomic areas to define the sentinel node in an area superior and medial to the junction of the saphenous and femoral veins along the superficial epigastric vein. Because of high false-negative rates (9%–50%), this technique is no longer recommended as a diagnostic or therapeutic approach.[4,38] To more accurately identify the sentinel node, researchers from the Netherlands Cancer Institute developed the concept of a DSNB using a patent blue dye and gamma emission, most recently reducing the false-negative rate from 18% to 4.9%.[39] Because of the technical expertise necessary, DSNB is recommended only at high-volume centers.

In 1988, Catalona et al[40] described a modified ILND approach using a shorter incision, limiting the field of ILND by excluding the area lateral to the femoral artery and caudal to the fossa ovalis, preserving the saphenous vein and eliminating the need to transpose the sartorius muscle while maintaining favorable oncologic outcomes. This technique reduces the morbidity associated with traditional ILND, and is an attractive alternative for clinically negative groins at increased risk of metastases based on primary penile tumor characteristics. Although the modified ILND has reduced surgical morbidity compared

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Table 2 Literature on Radiotherapy for Penile Cancer

Author, Year	Treatment Period	N	Stage	Dose, Gy (range)	F/U, y (range)	LC by RT	CSS	Penile Preservation	Notes
Chaudhary et al,[56] 1999	1988–1996	23	T1: 7, T2: 7 Rec: 9	50 (40–60)	2 (0.3–9.8)	18/23 70% at 8 y	NS	70% at 8 y	
Crook et al,[30] 2009	1989–2007	67	T1: 56%, T2: 33% T3: 8%; 38% >3 cm	60	4 (0.5–16.0)	87% at 5 y 72% at 10 y	83.6% at 5 & 10 y	88% at 5 y 67% at 10 y	No effect of size (to 5 cm) or grade on LF
de Crevoisier et al,[31] 2009	1970–2006	144	100% Jackson stage 1 Med diam, 20 mm 81% sup/19% inf/ulc	65 (37–75)	5.7 (0.5–29.0)	80% at 10 y	92% at 10 y	70% at 10 y	Not BT if extends beyond glans ↓ dose rate if large
Delannes et al,[27] 1992	1971–1989	51	T1: 14, T2: 28 T3: 6	60 (50–65)	5.5 (1–12)	44/51 crude 86% at 5 y	85% at 5 & 10 y	67% 71% T1–2	↑ LF if ↑ size >4 cm or volume
Kiltie et al,[28] 2000	1980–1997	31	Jackson stage 1: 27 Jackson stage 2: 4	63.5 (60.0–66.5)	5.1 (0.3–14.0)	25/31 81%	85.4% at 5 y	75% at 5 y	↑ LF if ↑ size >4 cm, T2, or ↑ volume
Mazeron et al,[29] 1984	1970–1979	50	T1: 9, T2: 27 T3: 14	65 (60–70)	3–8+	78% crude		74%	↑ LF if size >4 cm, or deep infiltration
Rozan et al,[57] 1995	1959–1989	184	Jackson stage 1: 93% Jackson stage 2: 7%	63 (10–87)	11.6 (2.5–32.0)	86%	88% at 5 & 10 y	78%	
Soria et al,[58] 1997	1973–1993	72	T1: 67, T2: 24 T3: 6	61–70	9.3 (2.5–32.0)	77%	72% at 5 y 62% at 10 y	75% at 5 y 68% at 10 y	Probable overlap with de Crevoisier et al[31]
Petera et al,[33] 2011	2002–2009	10	T1–T2	HDR BT 54/18/9 d	2	100%	100%	100%	
External-Beam Radiotherapy									
Gotsadze et al,[59] 2000	1959–1997	155	T1: 37%, T2: 55% T3: 8% (12 N1, 13 N2–3)	40–60	4 decades	65%	86%	65%	CR 89% in T1, 53% in T2
Sarin et al,[34] 1997	1960–1990	59	T1: 89%, T2: 9% T3: 3%	60/30 (40–78)	5.2 (0.2–22.0)	55% at 10 y crude	57% at 10 y	50% crude	↑ LF if dose <60 Gy, fraction <2 Gy
McLean et al,[60] 1993	1970–1985	26	T1: 19, T2: 4 T3: 2, T4: 1 (2 N2, 4 N3)	35/10–60/20	9.6 (7–14)	61.5%	69%	66% crude	

Abbreviations: BT, brachytherapy; CR, complete response; CSS, cancer-specific survival; F/U, follow-up; HDR, high-dose-rate; inf/ulc, inferior/ulceration; LC, local control; LF, local failure; med diam, median diameter; NS, not stated; Rec, recurrent; RT, radiotherapy; Sup, superficial.

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with the standard ILND, a standard ILND approach should be adopted if nodal metastases are detected on frozen section. Traditionally, a standard lymphadenectomy has been offered for resectable metastatic ILNs, although recent data would support neoadjuvant chemotherapy followed by surgical consolidation as the preferred treatment approach in patients with bulky disease.[41,42]

Pelvic Lymph Node Dissection: The presence of pelvic lymph node metastasis on imaging or pathologic staging is an ominous prognostic sign. Patients with 2 to 3 positive ILNs have a 23% probability of pelvic lymph node metastasis, and in those with more than 3 ILNs, this increases up to 56%.[43] Lont et al[44] determined that patients with 2 or more positive ILNs, extracapsular nodal extension, or poorly differentiated ILNs were at increased risk for pelvic metastasis and could benefit from a pelvic lymph node dissection.

Advances in Surgical Approach Minimally Invasive: Recent surgical series have found that minimally invasive techniques for ILND (such as video-assisted laparoscopic ILND) offer encouraging oncologic outcomes comparable to open surgical series with respect to lymph node counts,[45,46] with only 20% of patients developing minor complications. These techniques, however, require validation in large, multicenter, preferably prospective studies with longer follow-up.

Locally Advanced or Bulky/Unresectable Disease

Multimodality Approach: Patients with locally advanced or bulky/unresectable disease require a multidisciplinary approach involving medical, radiation, and urologic oncologists. The preferred approach for patients with 4 cm or larger or fixed ILNs should be neoadjuvant cisplatin-based systemic chemotherapy.[47] Based on a patient's response to systemic chemotherapy (ie, stable disease, partial or complete response), surgical consolidation may be considered thereafter. Pagliaro et al[42] recently reported that neoadjuvant chemotherapy with paclitaxel, ifosfamide, and cisplatin produced complete or partial responses in 50% of patients, with most (73.3%) subsequently undergoing surgery as planned. This finding compares favorably with historical response rates of only 30% to 35% for advanced metastatic disease. In this series, the median follow-up was 34 months, with 30% of the patients alive and with no evidence of disease at their last visit. This treatment approach may redefine the therapeutic paradigm of more advanced penile SCC.

Unresectable or Metastatic Disease: Paclitaxel, ifosfamide, and cisplatin chemotherapy was effective for patients with lymph node metastases (N2–3, M0), and is also a reasonable choice in first-line therapy for patients presenting with distant metastases (M1). Another acceptable first-line therapy is 5-FU and cisplatin, as recently described by Di Lorenzo et al.[48] No standard second-line systemic therapy exists, and depending on the first-line therapy used, the patient may benefit from suitable single-agent treatment, such as capecitabine, carboplatin, docetaxel, 5-FU, irinotecan, methotrexate, or paclitaxel.[49] Additional studies are needed, particularly with newer targeted therapeutics.

Conclusions

The onus is on both the patient and society-at-large for the prevention, education, and early detection of penile cancer. Once diagnosed, the impetus rests with the treating physician to determine the appropriate treatment approach for a given patient based on the primary tumor's characteristics, regional ILNs, metastatic status, and patient compliance with stringent follow-up. The adoption of novel diagnostic and surgical techniques, and of a multidisciplinary approach to suitable cases, is redefining the therapeutic approach to penile SCC.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.
2. Pettaway C, Lynch D Jr, Davis J. Tumors of the penis. In: Wein AJ, Kavoussi L, Novick AC, et al, eds. Campbell-Walsh Urology. 9th ed. Philadelphia: Saunders; 2007:959–992.
3. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. BJU Int 2001;88:473–483.
4. Pizzocaro G, Algaba F, Horenblas S, et al. EAU penile cancer guidelines 2009. Eur Urol 2010;57:1002–1012.
5. Hernandez BY, Barnholtz-Sloan J, German RR, et al. Burden of invasive squamous cell carcinoma of the penis in the United States, 1998-2003. Cancer 2008;113(10 Suppl):2883–2891.
6. Pow-Sang MR, Ferreira U, Pow-Sang JM, et al. Epidemiology and natural history of penile cancer. Urology 2010;76(2 Suppl 1):S2–6.
7. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer 2005;116:606–616.
8. Maden C, Sherman KJ, Beckmann AM, et al. History of circumcision, medical conditions, and sexual activity and risk of

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penile cancer. J Natl Cancer Inst 1993;85:19–24.

9. Minhas S, Manseck A, Watya S, Hegarty PK. Penile cancer—prevention and premalignant conditions. Urology 2010;76(2 Suppl 1):S24–35.
10. Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. N Engl J Med 1990;322:1093–1097.
11. Wiener JS, Walther PJ. The association of oncogenic human papillomaviruses with urologic malignancy. The controversies and clinical implications. Surg Oncol Clin N Am 1995;4:257–276.
12. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS 2006;20:1645–1654.
13. Edge SB, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
14. Cubilla AL, Reuter V, Velazquez E, et al. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. Int J Surg Pathol 2001;9:111–120.
15. Mueller-Lisse UG, Scher B, Scherr MK, Seitz M. Functional imaging in penile cancer: PET/computed tomography, MRI, and sentinel lymph node biopsy. Curr Opin Urol 2008;18:105-110.
16. 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.
17. Pompeo AC, Heyns CF, Abrams P. Penile cancer: Montreal, QC: Société Internationale d'Urologie (SIU); 2009.
18. Schroeder TL, Sengelmann RD. Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. J Am Acad Dermatol 2002;46:545–548.
19. 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.
20. Azrif M, Logue JP, Swindell R, et al. External-beam radiotherapy in T1-2 N0 penile carcinoma. Clin Oncol (R Coll Radiol) 2006;18:320–325.
21. Crook J, Grimard L, Tsihlias J, et al. Interstitial brachytherapy for penile cancer: an alternative to amputation. J Urol 2002;167(2 Pt 1):506–511.
22. Zouhair A, Coucke PA, Jeanneret W, et al. Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur J Cancer 2001;37:198–203.
23. 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.
24. Minhas S, Kayes O, Hegarty P, et al. What surgical resection margins are required to achieve oncological control in men with primary penile cancer? BJU Int 2005;96:1040–1043.
25. Ficarra V, Maffei N, Piacentini I, et al. Local treatment of penile squamous cell carcinoma. Urol Int 2002;69:169–173.
26. Hatzichristou DG, Apostolidis A, Tzortzis V, et al. Glansectomy: an alternative surgical treatment for Buschke-Lowenstein tumors of the penis. Urology 2001;57:966–969.
27. Delannes M, Malavaud B, Douchez J, et al. Iridium-192 interstitial therapy for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys 1992;24:479–483.
28. Kiltie AE, Elwell C, Close HJ, Ash DV. Iridium-192 implantation for node-negative carcinoma of the penis: the Cookridge Hospital experience. Clin Oncol (R Coll Radiol) 2000;12:25–31.
29. Mazeron JJ, Langlois D, Lobo PA, et al. Interstitial radiation therapy for carcinoma of the penis using iridium 192 wires: the Henri Mondor experience (1970-1979). Int J Radiat Oncol Biol Phys 1984;10:1891–1895.
30. Crook J, Ma C, Grimard L. Radiation therapy in the management of the primary penile tumor: an update. World J Urol 2009;27:189–196.
31. de Crevoisier R, Slimane K, Sanfilippo N, et al. Long-term results of brachytherapy for carcinoma of the penis confined to the glans (N- or NX). Int J Radiat Oncol Biol Phys 2009;74:1150–1156.
32. Gomez-Iturriaga A, Crook J, Evans W, et al. The efficacy of hyperbaric oxygen therapy in the treatment of medically refractory soft tissue necrosis after penile brachytherapy. Brachytherapy 2011;10:491–497.
33. Petera J, Sirak I, Kasaova L, et al. High-dose rate brachytherapy in the treatment of penile carcinoma—first experience. Brachytherapy 2011;10:136–140.
34. Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 1997;38:713–22.
35. Kroon BK, Horenblas S, Lont AP, et al. Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. J Urol 2005;173:816–819.
36. Heyns CF, Fleshner N, Sangar V, et al. Management of the lymph nodes in penile cancer. Urology 2010;76(2 Suppl 1):S43–57.
37. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977;39:456–466.
38. Pettaway CA, Pisters LL, Dinney CP, et al. Sentinel lymph node dissection for penile carcinoma: the M. D. Anderson Cancer Center experience. J Urol 1995;154:1999–2003.
39. Leijte JA, Kroon BK, Valdes Olmos RA, et al. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. Eur Urol 2007;52:170–177.
40. 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.
41. Bermejo C, Busby JE, Spiess PE, et al. Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. J Urol 2007;177:1335–1338.
42. Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. J Clin Oncol 2010;28:3851–3857.
43. Culkin DJ, Beer TM. Advanced penile carcinoma. J Urol 2003;170(2 Pt 1):359–365.
44. Lont AP, Kroon BK, Gallee MP, et al. Pelvic lymph node dissection for penile carcinoma: extent of inguinal lymph node involvement as an indicator for pelvic lymph node involvement and survival. J Urol 2007;177:947–952; discussion 952.
45. Sotelo R, Sanchez-Salas R, Carmona O, et al. Endoscopic lymphadenectomy for penile carcinoma. J Endourol 2007;21:364–367; discussion 367.
46. Tobias-Machado M, Tavares A, Ornellas AA, et al. Video endoscopic inguinal lymphadenectomy: a new minimally invasive procedure for radical management of inguinal nodes in patients with penile squamous cell carcinoma. J Urol 2007;177:953–957; discussion 958.
47. Pettaway CA, Pagliaro L, Theodore C, Haas G. Treatment of visceral, unresectable, or bulky/unresectable regional metastases of penile cancer. Urology 2010;76(2 Suppl 1):S58–65.
48. Di Lorenzo G, Buonerba C, Federico P, et al. Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis. BJU Int 2012;110(11 Pt B):E661–668.
49. Di Lorenzo G, Federico P, Buonerba C, et al. Paclitaxel in pretreated metastatic penile cancer: final results of a phase 2 study. Eur Urol 2011;60:1280–1284.
50. Tietjen DN, Malek RS. Laser therapy of squamous cell dysplasia and carcinoma of the penis. Urology 1998;52:559–565.
51. Frimberger D, Hungerhuber E, Zaak D, et al. Penile carcinoma. Is Nd:YAG laser therapy radical enough? J Urol 2002;168:2418–2421; discussion 2421.
52. Brown GM, Khadra, A, Abdelraheem A, et al. Predictors of penile cancer recurrence following conservative surgical resection [abstract]. Eur Urol Suppl 2009;8:369:Abstract 995.
53. Hadway P, Corbishley CM, Watkin NA. Total glans resurfacing for

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premalignant lesions of the penis: initial outcome data. BJU Int 2006;98:532–536.

54. Ornellas AA, Kinchin EW, Nobrega BL, et al. Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. J Surg Oncol 2008;97:487–495.
55. Leijte JA, Kirrander P, Antonini N, et al. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. Eur Urol 2008;54:161–168.
56. Chaudhary AJ, Ghosh S, Bhalavat RL, et al. Interstitial brachytherapy in carcinoma of the penis. Strahlenther Onkol 1999;175:17–20.
57. Rozan R, Albuisson E, Giraud B, et al. Interstitial brachytherapy for penile carcinoma: a multicentric survey (259 patients). Radiother Oncol 1995;36:83–93.
58. Soria JC, Fizazi K, Piron D, et al. Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in monocentric study with a conservative policy. Ann Oncol 1997;8:1089–1098.
59. Gotsadze D, Matveev B, Zak B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? Eur Urol 2000;38:306–312.
60. 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.

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PostTest Questions

1. True or False: The single most important prognosticator of cancer-specific survival in penile cancer is the presence and extent of regional inguinal lymph node (ILN) metastases.
2. Which of the following is not a risk factor for penile cancer?
   a. Human papillomavirus
   b. An uncircumcised phallus
   c. Obesity
   d. Tobacco use
3. True or False: Penile cancer typically metastasizes in a predictable fashion to the ILNs; therefore, early surgical management of nonbulky nodal metastasis (<4 cm) has been shown to have a favorable impact on survival.

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