Multimodal Therapy in the Management of Advanced Penile Cancer

Praful Ravi, MBBChir[a], Lance C. Pagliaro, MD[b,*]

KEYWORDS

• Penile cancer • Adjuvant chemotherapy • Neoadjuvant chemotherapy • Survival • Radiotherapy

KEY POINTS

- A multimodal approach to therapy is increasingly used in treating men with advanced penile cancer.
- Adjuvant chemotherapy is associated with improved outcomes in chemotherapy-naïve men with node-positive penile cancer.
- Neoadjuvant systemic chemotherapy may downstage regional lymph node metastases sufficiently to permit surgery while imparting a potential improvement in long-term disease-free survival.
- International collaboration in clinical trials is required to optimize treatment and improve survival in men with advanced penile cancer.

INTRODUCTION

Squamous cell carcinoma (SCC) of the penis is a rare disease, with an estimated 2020 cases and 340 deaths in the United States this year.[1] Prognosis is good if disease is diagnosed at a localized stage, but up to 40% of patients present with locally advanced or metastatic disease and outcomes for these patients have historically been poor.[2,3] The disease typically spreads in a locoregional manner, first to the draining inguinal lymph nodes, then to pelvic nodes, and then to viscera. The organized nature of spread makes the disease a candidate for a multimodal therapeutic approach, which has been successfully used to treat other SCCs, such as head and neck,[4] anus,[5] or vulva.[6] The rarity of penile cancer in the United States and Western Europe, however, has hampered clinical study into the treatment of locally advanced or metastatic disease and there are currently no randomized data in this setting.

The TNM staging system for penile cancer is shown in **Table 1**. Advanced disease implies spread beyond the local tissues (ie, T3-4 and/or N1-3 and/or M1 disease); 28% to 64% of men with penile cancer present with clinically palpable inguinal lymph nodes. In such cases, metastatic disease underlies lymphadenopathy in 47% to 85% of such individuals, with the remainder due to inflammatory nodal reaction, and the risk of pelvic nodal metastases is 22% to 56% if the inguinal nodes are involved.[7–9] The most important prognostic factor in penile cancer is the presence of inguinal lymph node metastases, with the number of positive lymph nodes, bilateral inguinal nodal disease, pelvic nodal involvement, and extranodal metastatic extension imparting a worse prognosis.[10] When inguinal lymphadenopathy is not clinically apparent, micrometastatic disease is present in approximately 25% of cases, with predictive risk factors including tumor stage, grade, and lymphovascular invasion.[11]

ADJUVANT CHEMOTHERAPY IN NODE-POSITIVE DISEASE

A multimodal approach can be used to treat men who are found node-positive after undergoing

The authors declare no conflicts of interest and no funding source.
[a] Department of Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA;
[b] Department of Oncology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
* Corresponding author.
E-mail address: pagliaro.lance@mayo.edu

Urol Clin N Am 43 (2016) 469–479
http://dx.doi.org/10.1016/j.ucl.2016.06.008

Table 1
TNM staging system for penile cancer

T – primary tumor
- Tx: Cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- Ta: Noninvasive carcinoma
- T1a: Tumor invades subepithelial tissue without LVI and is not poorly differentiated/undifferentiated
- T1b: Tumor invades subepithelial tissue with LVI or is poorly-differentiated/undifferentiated
- T2: Tumor invades corpus spongiosum and/or cavernosum
- T3: Tumor invades urethra
- T4: Tumor invades other adjacent structures

N – regional lymph nodes
- Nx: Cannot be assessed
- N0: No palpable or visibly enlarged inguinal lymph node
- N1: Palpable mobile unilateral inguinal lymph node
- N2: Palpable mobile multiple unilateral or bilateral inguinal lymph nodes
- N3: Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral

M – distant metastasis
- M0: No distant metastasis
- M1: Distant metastasis

Pathologic classification
- pNX: Cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Metastasis in a single inguinal lymph node
- pN2: Metastasis in multiple or bilateral inguinal lymph nodes
- pN3: Extranodal extension of lymph node metastasis or pelvic lymph node(s) metastasis

Anatomic staging

Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1-3	N1	M0
Stage IIIB	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Abbreviation: LVI, lymphovascular invasion.

Adapted from Sobin LH, Gospodariwicz M, Wittekind C, editors. TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edition. Oxford: Wiley-Blackwell; 2009. p. 336.

radical inguinal lymphadenectomy. Although there is evidence to support the use of adjuvant chemotherapy in men with pN2 or pN3 disease, this is based on small numbers of patients and single-center or multicenter retrospective data.

The largest patient series reporting outcomes of adjuvant chemotherapy for penile cancer was recently published and combined data from 4 tertiary centers in the United States, Netherlands, Italy, and China.[12] The investigators identified 84 men who underwent lymph node dissection for SCC of the penis between 1978 and 2013 and who were found to have positive pelvic lymph nodes (ie, pN3). In this cohort, 36 men received adjuvant chemotherapy, with a majority (78%) treated with platinum-based regimens (most commonly docetaxel, cisplatin, and 5-fluorouracil [TPF]), whereas 48 were not. At a median follow-up of just over 12 months, median overall survival was significantly greater in those who had received chemotherapy compared with those who had not (21.7 months vs 10.1 months, $P = .048$) (**Fig. 1**). Furthermore, receipt of adjuvant chemotherapy (hazard ratio [HR] = 0.40 [0.19–0.87], $P = .021$) was the sole independent predictor of overall survival in a multivariable analysis adjusting for age, pathologic stage, bilaterality of nodal disease, and timing of pelvic surgery.

There are several important limitations of this study, however, the most important being that men who had received salvage chemotherapy after disease recurrence were excluded, which may have led to a systematic bias. The group who had not received adjuvant chemotherapy likely included men who had been unable to receive it owing to rapid postoperative disease recurrence or poor postoperative recovery. In contrast, the group who did receive adjuvant chemotherapy was probably enriched by men who had recovered quickly after surgery (and were thus able to tolerate chemotherapy) and then never recurred, thereby never requiring salvage chemotherapy. In addition to this and potentially other selection biases, the study was inadequately powered for a multivariable analysis.

Other data on the role of adjuvant chemotherapy for pathologic node-positive penile cancer come from smaller, single-center studies. The earliest data on adjuvant treatment came from a pilot study in Milan, Italy, that was published in the late 1980s.[13] Twelve men who had undergone unilateral or bilateral lymphadenectomy for penile cancer, including 5 who had pelvic nodal disease, received weekly vincristine, bleomycin, and methotrexate (VBM) for 12 weeks, with 11 of the 12 patients (92%) alive and disease-free at a median