Review Article

Surveillance strategies in the management of penile cancer

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Abstract: Penile cancer is a rare disease and can be associated with a high risk of recurrence in regional lymph nodes and distant sites. Surveillance strategies geared towards early detection and treatment are recommended given the significant morbidity and mortality associated with recurrences. Although physical examination is the single most important surveillance strategy, imaging is an important adjunct in high-risk disease and certain clinical scenarios.

Keywords: Penile cancer; penile cancer surveillance; penile cancer imaging

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Introduction

Penile cancer is uncommon, accounting for an estimated 2,120 new cases and 360 deaths in 2017 (1). Because of the rarity of the disease, there is limited level I evidence on management approaches. Although surgery is the mainstay of treatment of both the primary and regional nodal metastatic disease, conservative treatment approaches, such as laser ablation or local excision, are often employed for low risk disease (Tis, T1, Grades 1 and 2) and occasionally for high risk disease (T2) (2-4). Thus, the surveillance strategy largely depends on the disease severity and treatment administered. Given that recurrences may be curable if detected early, close follow up is recommended (5). Herein, we present a review of general surveillance principles and strategies for the penis, the inguinal and pelvic group of lymph nodes, and potential distant recurrence sites. We also examine the evidence for utilizing imaging modalities as adjuncts to clinical evaluation. Lastly, we present a summary surveillance schedule for penile cancer.

General principles of surveillance

Penis

The risk of recurrence after primary therapy for penile cancer is grade and stage dependent. Therefore, a grade and stage appropriate surveillance strategy is imperative in all patients including those treated with organ-preservation, such as phallus-sparing surgeries (e.g., local excision, glansectomy and distal corporectomy), laser ablation, topical therapies and radiation therapy. The incidence of local recurrence after organ-preserving treatment of the primary tumor is as high as 50% within 5 years depending on the stage of the disease (2,3). In a large series of patients with invasive (pT1–T4) disease, the 5-year cumulative incidence of local recurrence was 27% for those treated with penile preservation versus 3.8% for those treated with partial penectomy; despite this though, there was no difference in cancer-specific survival (4). Other studies, however, reported that local recurrence after partial penectomy portends poor prognosis (4,6). The incidence of local recurrence with partial or total penectomy is generally low (0–7%) but may approach 50% in patients treated with more conservative approaches (7-11). However, if local recurrence is detected and treated early, the cancer specific survival may be unaffected (12). Thus, clinical evaluation—history and physical examination—aimed at early detection of recurrent lesions at the site of the treated primary tumor or elsewhere on the penis should be performed. Palpation of the penis

provides an important initial assessment of the extent of the disease (13). Imaging modalities such as magnetic resonance imaging (MRI) and ultrasound (US) may be used as adjuncts to the physical exam to determine the extent of disease and assist with surgical planning. Evidence for their routine utilization is inconclusive and should be used at the discretion of the treating physician (14-18). Any suspicious penile lesion or abnormality detected during surveillance warrants further evaluation with an incisional biopsy for adequate histopathological evaluation (17).

Inguinal lymph node

As with the primary tumor, the surveillance protocol for the inguinal lymph nodes depends on the findings and management at the time of initial diagnosis. The approach to the inguinal nodes is dictated by the pathological stage and grade of the primary penile tumor (19-22). A detailed discussion of measures proposed to manage the inguinal nodes is beyond the scope of this article. Briefly, patients with low risk of lymph node metastasis or recurrence, such as those with *in situ* or Ta disease, can be managed conservatively. Although some patients have clinically negative inguinal lymph nodes at diagnosis (i.e., impalpable and negative imaging), they may harbor micro-metastatic disease and risk development of a clinically evident recurrence in the inguinal lymph nodes. In a review by Busby and Pettaway, 6% of patients with T1, grades 1–2 primary tumors had lymph node metastasis at the time of bilateral inguinal lymph node dissection (ILND) (23). Hence, while this group of patients may be observed without upfront ILND, early detection of nodal recurrence is critical to avoid a poor outcome (24).

Conversely, patients with ≥ T2 disease have a 59% risk of inguinal lymph node metastasis (23). Although dynamic sentinel node biopsy (DSNB) is being performed at some institutions for high risk patients, bilateral ILND (open or endoscopic) remains the treatment of choice at most North American tertiary care centers due in large part based on the paucity of expertise using this diagnostic modality (20,25-32). A rigorous follow up schedule, especially in the first 2 years, should be implemented in patients with negative DSNB given the relatively high false negative rates (33). In addition, patients with non-visualization following DSNB but with high risk disease (≥ T1G2) should be considered for repeat DNSB given the risk of metastatic disease (34). While a modified template ILND is recommended as a reasonable alternative to standard lymph node dissection in high risk patients, some may choose observation (35). Additionally, patients who underwent a modified template ILND with negative results still harbor the risk of inguinal recurrences; up to 15% within the first 2 years of follow up (36,37). Patients with pathologically node positive (pN+) disease may have poorer cancer specific survival compared to men with pathologically node negative (pN0) disease (35). Thus, continued long term surveillance is recommended in all patients given the high risk of recurrence—a predictor of poor overall survival (38).

Advanced and systemic disease

Locally advanced or widely metastatic primary penile cancer is fairly uncommonly seen within the United States but is unfortunately associated with a high cancer specific mortality rate. Neoadjuvant chemotherapy followed by surgery may render some patients disease-free, though, with a 5-year survival up to 50% (39-42). Regardless of the treatment offered, a more intense surveillance schedule is warranted when compared to low-risk disease, adding periodic cross-sectional imaging as an adjunct to the physical examination.

Surveillance strategies

History and physical examination

A history and physical examination should be performed on patients treated for penile cancer during surveillance. In addition to evaluations by a physician, it is crucial to teach patients how to perform monthly self-exams of the penis (if a penile conserving treatment was performed) and of the inguinal region. Patients should alert their provider if they identify any concerning findings. Recurrence has been reported in distant and uncommon sites such as the brain, cervical lymph nodes, lungs, prostate, and perineum even in patients with pN0 disease, highlighting the importance of a comprehensive clinical evaluation (43,44).

Imaging modalities

Enhanced imaging techniques (e.g., MRI and US) serve as adjuncts to clinical assessment of the penis. The role of MRI and US was evaluated in the staging of primary penile cancer with conflicting results (14-16,18). Although cross-sectional imaging may be indicated in the primary tumor setting, physical examination alone performs just as well or even superior to MRI in a head-to-head comparison (45).

Table 1 Suggested follow-up protocol following partial or total penectomy in men at low-risk with clinically negative inguinal lymph nodes managed with surveillance

Item	Months										
	3	6	9	12	18	24	30	36	48	60	>5 years
Physical examination	X	X	X	X	X	X	X	X	X	X	Every 1–2 years

Low-risk is defined as Tis, Ta T1 grades 1–2, no vascular invasion. Reproduced and modified with permission from Sanchez-Ortiz and Pettaway [Reference (61); Table 5]. The "X" indicates that the specific item should be obtained at that time point.

Inducing an artificial erection, however, may improve the performance of MRI in evaluating the depth of invasion of penile tumors (46,47). Regardless of the MRI or US finding, any suspicious penile lesion or abnormality detected during surveillance warrants further evaluation with an incisional biopsy for adequate histopathological evaluation (17).

Ultrasound may be useful in evaluating the groin for recurrence. Though with limited sensitivity and specificity, US may detect evidence of metastasis in inguinal lymph nodes and may guide fine-needle aspiration (FNA) for cytological or histological diagnosis (48-50). Especially in the obese or in patients with a history of prior inguinal surgery who are at risk metastasis, CT or MRI scans of the abdomen and pelvis should be performed periodically to detect recurrence in inguinal and pelvic nodes. Patients with positive inguinal lymph nodes at diagnosis are at higher risk of pelvic lymph node involvement and thus warrant close surveillance (51). Furthermore, PET-CT may improve detection of nodal recurrence (52). The role of lymphotropic nano-particle-enhanced MRI using ferumoxtran-10 is promising but requires further evaluation (53). Other sites, such as the chest/lungs, bones and brain, may be imaged depending on findings from the clinical assessment or other imaging studies. Chest X-ray may be used to evaluate the lungs, and any abnormality can be evaluated further with a chest CT.

Molecular diagnostics and biomarkers

Currently, there is no available penile cancer biomarker to detect disease recurrence or response to treatment. However, certain markers have been associated with recurrence or poor prognosis. For example, HPV expression; lack of p16 expression; nuclear accumulation of p53; EGFR, MYC and CCND1 amplifications were found to be associated with poorer overall survival (54-57). The evidence for association of Ki67 expression with poor outcome is inconclusive (57-59). Testing of these markers in the primary tumor may be considered in patients at higher risk of recurrence to guide surveillance strategies or perhaps inform decision-making for prophylactic lymphadenectomy and/or adjuvant treatment.

Intensity and duration of surveillance

In general, surveillance after a diagnosis of penile cancer is life-long as these patients have the potential to develop recurrent disease or a new primary tumor at any point along their course. The intensity of follow-up, however, is dependent on the pathological stage and grade of disease and the treatment performed (60). Sanchez-Ortiz and Pettaway proposed a risk-adapted strategy for follow-up (61). They proposed three target groups for surveillance, namely: (I) patients treated with phallus-sparing strategies; (II) patients with high-risk primary tumors (pT2–3, grade 3, vascular invasion) and clinically negative inguinal lymph nodes without lymphadenectomy performed; and (III) patients with positive lymph nodes at lymphadenectomy. Two follow up schedules were recommended, a rigorous follow up for patients at high risk of local or regional recurrence and a less rigorous schedule for patients with a low risk of recurrence (*Tables 1,2*).

Most guidelines, including the European Association of Urology© and the National Comprehensive Cancer Network© guidelines recommend follow-up visits every 3 months in the first 2 years, every 6 months for years 3 to 5, and annually thereafter (20,22,62). These recommendations are based on an observational study that showed that 92% of the recurrences occurred within the first 5 years after primary treatment (63). These recommendations, though, do not take disease stage and grade into account. Life-long follow-up is recommended because recurrence can occur beyond 5 years (64). Most surveillance strategies proposed, though, end after year 10 from primary treatment. It is reasonable to refer patients to their primary care provider with instructions for yearly evaluations moving forward after year 10.

Table 2 Suggested follow-up protocol following penile-conserving surgery[#] and for high-risk patients following partial or total penectomy with clinically negative inguinal lymph nodes managed with surveillance or pathological negative or positive nodes

Item	Months														
	3	6	9	12	15	18	21	24	30	36	42	48	54	60	>5 years
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	–	X	Every 1–2 years
Chest X-radiograph	X	–	–	X	–	–	–	X	–	X	–	–	–	–	As indicated
CT pelvis*	X	–	–	X	–	–	–	X	–	X	–	X	–	X	As indicated

High-risk is defined as T1 grade 3, T2–T3, vascular invasion. Reproduced and modified with permission from Sanchez-Ortiz and Pettaway [Reference (61); Table 6]. *, Obtained in obese men, after inguinal surgery, or as indicated; #, chest X-radiograph not indicated. The "X" indicates that the specific item should be obtained at that time point.

Conclusions

Penile cancer is a rare disease, with certain patients having a high risk of recurrence in the inguinal and pelvic lymph nodes. Because of the morbidity and mortality associated with recurrences, a risk-adjusted surveillance strategy geared towards early detection and treatment is recommended. Physical examination is the single most important component of surveillance, but imaging modalities may be used as adjuncts.

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Footnote

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