PENILE CANCER

Date Developed: January, 2011

Date Revised: February, 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Penile cancer is rare in developed countries, occurring annually in approximately 1 in 100,000 men \(^1\). This type of cancer occurs most often in older men (i.e. those 60 years of age and older). An association with human papilloma virus (HPV) has been suggested \(^2\). There are several types of penile cancer, nearly all of which are of squamous cell origin, including verrucous carcinoma, basaloid carcinoma, warty carcinoma (verruciform), and neuroendocrine carcinomas \(^3-6\).

Staging of penile cancer is based on the 7\(^{th}\) edition of American Joint Committee on Cancer (AJCC) manual \(^7\). A detailed description of staging can be found in the Appendix. In stage I disease, carcinoma in situ (CIS) of the penis that occurs on the glans is referred to as *erythroplasia of Queyrat*, whereas when CIS occurs on the penile shaft it is referred to as *Bowen disease*. The five year survival rate for CIS of the penis is over 90%. With lymph node involvement, the five year survival rate declines to 60%. The prognosis with stage IV disease is a five year survival rate of approximately 20% \(^8\).

GUIDELINE QUESTIONS

What are the appropriate management and follow up strategies for penile cancer?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

Entries to Medline, EMBASE, and Cochrane (January 2000 to December 2011) and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: penile cancer OR cancer of the penis OR carcinoma of the penis OR penile carcinoma, limited to studies published in English.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with penile cancer. Different principles may apply to pediatric patients.

RECOMMENDATIONS

These recommendations have been adapted from the European Association of Urology’s *Guidelines on Penile Cancer* \(^9\), the National Cancer Institute’s *Penile Cancer Treatment* guidelines \(^10\), and the BC Cancer Agency’s *Cancer Management Guidelines* on cancer of the penis \(^11\).
Institutional Approach

A multi-disciplinary approach encompassing collaboration between the members of the clinical team, especially the surgeon and the radiation oncologist, is recommended for all patients undergoing treatment for penile cancer.

Tis, Ta N0 M0 (Stage 0)

Management Options

- Surgical excision with an adequate margin. In order to minimize scarring, deformity, and impaired function, Mohs micrographic surgery is preferred. During Mohs procedure, successive horizontal layers of tissue are excised and examined microscopically.
- Brachytherapy.
- Laser therapy in selected cases, using Nd:YAG or CO2 lasers.
- Topical treatment with 5-fluorouracil cream in cases of erythroplasia of Queyrat and Bowen disease.
- Topical treatment with Imiquimod 5% cream, an immune response modifier.
- Cryosurgery in patients with erythroplasia of Queyrat and verrucous penile carcinoma.

T1 N0 M0 (Stage I)

Management Options

- Circumcision is standard therapy.
- Wide local excision.
- Partial penectomy (1 cm proximal to the lesion) for infiltrating tumours of the glans.
- Brachytherapy for tumours that infiltrate the glans (T1, T2, and selected, well differentiated T3 tumours).
- External beam radiotherapy for larger tumours or those extending onto the shaft.

T2 N0 M0 (Stage II) and T3 N0 M0 (Early Stage III)

Management Options

- Partial penectomy or radical penectomy, depending on the extent and location of the neoplasm.
- Antibiotic therapy for a short period then reassessment at six weeks.
- Bilateral superficial inguinal dissection could be considered, upon direction by biopsy and imaging findings. Clinically evident regional lymph node metastasis without evidence of distant spread is an indication for groin node dissection.
Patients with positive lymph nodes in the specimen may be considered for radical radiation therapy.

Surgery to inguinal lymph nodes and radiation therapy may only be considered as an alternative to radical surgery if patient declines.

Post-operative adjuvant radiation therapy may be considered to decrease the risk of recurrence.

Patients who are either not candidates for or who refuse surgery may be considered for radical radiation therapy to lymph nodes.

**T4 or N3 or M1 (Stage IV)**

**Management Options**

- Exenterative surgery in select cases.
- Palliative radiotherapy and/or chemotherapy.

**Metastatic Disease and Adjuvant Therapy**

Chemotherapy has been largely ineffective in treating patients with large disease burden. Options that have been used in clinical trials include: bleomycin, vincristine, and methotrexate +/- radiotherapy and ifosfamide, paclitaxel, and cisplatin, followed by surgery. There is no established role for adjuvant chemotherapy in patients who have completely resected disease.

**Follow-Up**

Follow-up of patients who have completed treatment for penile carcinoma allows for the detection of a potential recurrence, which may be curable if the recurrence is regional or loco-regional, as well as the assessment of early or late complications from treatment. Follow-up also allows for the periodic review and improvement of current treatment policy.

Follow-up traditionally consists of inspection and physical evaluation. Diagnostic imaging with ultrasound and PET scan are also useful modalities. As approximately 92% of all recurrences occur within the first five years after which recurrences tend to be local or new primaries, it is important to provide intensive follow-up for the first two years with less frequent follow-up thereafter.

The following schedule of follow-up intervals is recommended:

- For patients who have received penile-preserving treatment of primary tumour:
  - Years 1 and 2: every 3 months regular physician or self-examination.
  - Years 3, 4, and 5: every 6 months regular physician or self-examination.
  - Minimum follow-up: 5 years.
  - Follow-up following penile brachytherapy will be more frequent initially and at the discretion of the treating physician.

- For patients who have received amputation as treatment of primary tumour:
  - Years 1 and 2: every 6 months regular physician or self-examination.
  - Years 3, 4, and 5: every 1 year regular physician or self-examination.
  - Minimum follow-up: 5 years.

- For patients undergoing a ‘wait-and-see’ approach with respect to the inguinal lymph nodes:
Years 1 and 2: every 3 months regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.

Years 3, 4, and 5: every 6 months regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.

Minimum follow-up: 5 years.

For patients who are pN0 with respect to the inguinal lymph nodes:
- Years 1 and 2: every 6 months regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.
- Years 3, 4, and 5: every 1 year regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.
- Minimum follow-up: 5 years.

For patients who are pN+ with respect to the inguinal lymph nodes:
- Years 1 and 2: every 3 months regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.
- Years 3, 4, and 5: every 6 months regular physician or self-examination; ultrasound with fine-needle aspiration biopsy.
- Minimum follow-up: 5 years.

DISCUSSION

Management Strategies

Based on evidence from well-designed comparative studies, correlation studies, and case reports, the choice to provide conservative surgical treatment is dependent largely upon the potential morbidity of the procedure and the surgeon’s experience. Depending upon the size of the excised area, skin grafts can be used to improve cosmetic results in conservative procedures. For partial or radical penectomies, a spatulated repair is recommended in order to avoid stenosis.

Radiotherapy can afford T1-2 patients a greater chance of penile preservation. This can be provided as external beam irradiation (EBRT; i.e. high-energy photons, 4-6 MV), using a CT scan to define the target volume and optimise dosage distribution, or as brachytherapy (BRT; i.e. external isotope, low dose rate BRT, pulse-dose rate BRT, or high-dose rate BRT). These modalities are considered equivalent, as there are no studies to date that suggest one is more effective than another. As compared with partial penectomy, radiotherapy results in higher local and regional failure rates. However, salvage surgery is an option.

A recent study by Crook, et al. (2009) demonstrated that in patients (n=74) with T1 (58%), T2 (32%), selected T3 (7%), and Tx (3%) tumors who were treated with brachytherapy (60 Gy as either pulse dose rate brachytherapy or Iridium192) for primary management, the five- and ten-year actuarial rates of penile preservation were 88% and 69%, respectively (eight local failures occurred). The actuarial ten-year overall survival rate for that study was 61%. The risks associated with radiotherapy include soft tissue necrosis and urethral stenosis, at rates of 10-20% and 20-35%, respectively. Differentiation (well differentiated versus moderately or poorly differentiated) was shown to be a positive predictive factor of failure free survival in T1, T2, and T3 patients.

Palpable inguinal nodes should be examined with ultrasound and fine-needle aspiration biopsy. Early bilateral lymphadenectomy should be performed. In contralateral non-palpable lymph nodes, surgical
staging is recommended either by dynamic sentinel node biopsy or lymph node dissection. Radiotherapy is not recommended in N0 patients, as this treatment does not prevent lymph node metastases, is associated with complications, and can cause fibrotic changes to occur, making follow-up more difficult. In addition, neoadjuvant therapy, such as radiotherapy, may be required for patients with inguinal masses prior to surgery.

A variety of agents and treatment schedules have been used in treating patients with metastatic disease beyond the inguinal and pelvic nodes. The most commonly used agents include cisplatin, bleomycin, methotrexate, paclitaxel, and 5-fluorouracil. Response rates to single agent cisplatin ranges from 15-32% and is often of short duration. Overall, chemotherapy has been largely ineffective in treating patients with large disease burden. The largest prospective clinical trial (SWOG) in metastatic penile cancer, in which patients were treated with cisplatin, bleomycin, and methotrexate, demonstrated an overall response rate of 32.5% with a median survival time of 28 weeks; mortality from this trial was 13.9%. In another study, ten patients with inguinal and pelvic node metastases were treated with a combination of ifosfamide, paclitaxel, and cisplatin, followed by surgery. Clinical benefit was demonstrated in nine patients (three complete responses, one partial response, and five stable disease), with a median survival time of 26 months. Finally, a trial involving 30 patients with stage III or stage IV (N2 or N3) disease, but no distant metastasis, treated with four courses of paclitaxel, ifosfamide, and cisplatin on a three-week cycle, showed that among patients who went on to surgery (n=22), there were three complete responses. The overall response rate for the whole group (surgery or chemotherapy only) was 50% and the median time to progression and overall survival were 8.1 months and 17.1 months, respectively. No deaths were attributed to treatment, 17 deaths were attributed to progressive, metastatic disease. There is no data to support a role for adjuvant chemotherapy in patients who have completely resected disease.

Institutional Approach

A multi-disciplinary approach encompassing collaboration between the members of the clinical team, especially between the surgeon and the radiation oncologist, is recommended for all patients and is essential for patients with tumours classified as T2 or higher with nodal involvement (i.e. two or more involved lymph nodes, bilateral involvement, evidence of extranodal extension, and pelvic nodal metastases). For these patients, adjuvant therapeutic strategies may be required.

Given the relative rarity of penile cancer, there are limited clinical trials to test the efficacy of various therapies or combinations of therapies in patients. Furthermore, clinicians practicing at a given cancer centre may treat as few as one to two patients per year. Therefore, it is important to develop expertise within the cancer centre by centralizing the care of these patients to one or two designated surgeons and radiation oncologists who can then garner more extensive experience in treating the disease.
GLOSSARY OF ABBREVIATIONS

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<tr>
<td>BRT</td>
<td>brachytherapy</td>
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<tr>
<td>CIS</td>
<td>carcinoma in situ</td>
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<td>ERT</td>
<td>external beam irradiation</td>
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<td>HPV</td>
<td>human papilloma virus</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>UICC</td>
<td>International Union Against Cancer</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2012. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


APPENDIX

The American Joint Committee on Cancer (AJCC) staging for penile cancer (7th edition, 2010):

Tumour
- **Tx**: Primary tumour cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **Ta**: Noninvasive verrucous carcinoma
- **T1a**: Tumour invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
- **T1b**: Tumour invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated
- **T2**: Tumour invades corpus spongiosum or cavernosum
- **T3**: Tumour invades urethra
- **T4**: Tumour invades other adjacent structures

Regional lymph nodes
- **Nx**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in a single inguinal lymph node
- **N2**: Metastases in multiple or bilateral inguinal lymph nodes
- **N3**: Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

Distant Metastasis
- **Mx**: Metastasis can not be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis