12 Penile cancer

Background

Squamous cell carcinoma of the penis is rare; treatment needs to consider both the primary lesion and the potential for lymphatic dissemination. Bilateral lymph node involvement is common due to the rich penile lymphatic drainage. Lymph node spread generally occurs in a predictable manner, involving superficial inguinal, then deep inguinal and then pelvic lymph nodes.[1,2] Approximately 20–30% of patients with positive inguinal nodes have positive pelvic nodes.[1] Lymph node status is a major prognostic factor for penile cancer.[1] Surgery is the mainstay of locoregional treatment.[3] There is a lack of high-level evidence to guide management.

Radical radiotherapy for primary lesion

Primary disease is rarely managed non-surgically, with the development of penile-preserving and reconstruction surgical techniques and the need for surgical lymph node management.[4] Radiotherapy remains an effective penile-sparing alterative and may be delivered with external beam radiotherapy (EBRT) with tissue-equivalent bolus (Level 3) or brachytherapy (Level 3).[5] Brachytherapy provides good control rates with acceptable morbidity and can be considered for T1/2 and selected T3 lesions according to the 2013 American Brachytherapy Society–Groupe Européen de Curiethérapie–European Society of Therapeutic Radiation Oncology (ABS–GEC–ESTRO) guidelines.[6,7,8,9] Only a limited number of series have reported outcomes with EBRT; a higher risk of local failure has been associated with a total dose <60 Gray (Gy) (dose per fraction <2 Gy, treatment time >45 days), T3 or greater disease and higher tumour grade.[10–14]

Lymph nodes are managed with either a sentinel lymph node biopsy or dissection.[4] Elective irradiation of clinically and radiologically N0 inguinal lymph nodes is of unproven efficacy and is not performed.[4]

If a primary penile cancer is treated non-surgically, either interstitial brachytherapy or EBRT are appropriate.

Recommendations

- 50 Gy in 16 fractions over 3 weeks (Grade C)[11]
- 55 Gy in 20 fractions over 4 weeks (Grade D)
- 60 Gy in 30 fractions over 6 weeks (Grade C)[10]
- 66 Gy in 33 fractions over 6.5 weeks (Grade C)[10]
- 70 Gy in 35 fractions over 7 weeks (Grade C)[15]

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[5]

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Unresectable primary and lymph node disease or locoregionally recurrent tumour

For patients with resectable primary and lymph node disease, primary surgery is the standard approach. For unresectable disease, there is interest in the use of multimodality treatment, although there is no standard approach. Neoadjuvant chemotherapy is an option with a view to downstaging the disease to facilitate surgery.[16,17] The use of either neoadjuvant or definitive radiotherapy or radiotherapy with concomitant chemotherapy are alternative approaches.[4] The radiotherapy target volume is individualised, but may include inguinal and pelvic lymph node regions with a boost to sites of gross disease using intensity-modulated radiotherapy (IMRT). Combining radiotherapy with concurrent chemotherapy can be considered, although there is no direct evidence to support the combination in penile cancer (Level 4).[5]

Recommendations

Dose to pelvis/inguinal regions:

- 45–50 Gy in 25 fractions over 5 weeks (Grade D)
- 50.4 Gy in 28 fractions over 5.5 weeks (Grade D)
- 45 Gy in 20 fractions over 4 weeks (Grade D)
- Boost dose to gross disease: up to a total of 55–66 Gy depending on tumour volume/site (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[5]

Adjuvant radiotherapy

The current European Society for Medical Oncology (ESMO) guidelines recommendation for patients with mobile inguinal lymph nodes is an inguinal dissection with a subsequent pelvic lymph node dissection if ≥2 inguinal lymph nodes are positive or in the presence of extracapsular spread (ECS).[4]

The rationale for considering adjuvant radiotherapy is provided by the observation of a significant rate of lymph node recurrence in patients treated with lymphadenectomy with positive lymph nodes recurrence rates varying between 25% and 77%[5,18–20] and extrapolation from other HPV-driven squamous cell carcinoma (SCC) tumour sites. The role of adjuvant radiotherapy in penile cancer is controversial based on limited data (Level 2, Grade D) due to rarity of this disease and the lack of randomised controlled trial data.

Two previous series have reported on the use of adjuvant radiotherapy for ≥2 lymph nodes or ECS[21,22] using doses of 45–57 Gy over 20–25 fractions. In both series, outcomes were superior to those that reported on ECS without adjuvant radiotherapy.[2]

A recent UK multi-institutional case series of adjuvant radiotherapy of 146 patients with pN3 disease reported its outcomes.[23] The ipsilateral pelvis received radiotherapy if extranodal extension was present following pelvic lymph node dissection or if pelvic lymph node dissection was not performed. Radiotherapy doses used were 45–54 Gy over 20–27 fractions and typically given in combination with weekly low-dose platinum-based chemotherapy.

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Rates of 5-year recurrence-free survival, cancer-specific survival and overall survival were better than previously documented for pN3 disease without adjuvant treatment.[23]

A multi-institutional retrospective analysis was carried out to review the benefit of adjuvant radiotherapy in addition to adjuvant chemotherapy after inguinal surgery for penile cancer.[24] This study looked at 93 patients across 9 centres and reported longer cancer-specific survival with additional radiotherapy (28.5%) compared with adjuvant chemotherapy alone (16.2%, p=0.036).[24] Further prospective studies would be required to confirm these findings.

A current trial of chemoradiation (International Penile Advanced Cancer Trial, InPACT, NCT02305654) is still recruiting and aims to determine prospectively the relative benefits and sequencing of surgery, chemotherapy and chemoradiotherapy in the management of patients with inguinal lymph node positive penile cancer.[25,26]

Recommendations

Inguinal dose:

- 54 Gy in 25 fractions over 5 weeks[21]
- Boost sites of residual disease to 57 Gy (Grade D)

Pelvic dose:

- 45 Gy in 25 fractions over 5 weeks; consider boost up to 54 Gy in 25 fractions to sites of residual disease or external iliac lymph nodes in high-risk patients (Grade D)

or

- 45 Gy in 20 fractions over 4 weeks to pelvis/inguinal regions with 10–12 Gy in 5-fraction boost (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[5]

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