

## 10. 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.<sup>1,2</sup> Approximately 20–30% of patients with positive inguinal nodes have positive pelvic nodes.<sup>1</sup> Lymph node status is a major prognostic factor for penile cancer.<sup>1</sup> Surgery is the mainstay of locoregional treatment.<sup>3</sup> There is a lack of high level evidence to guide management.

### Radical radiotherapy for primary lesion

Primary disease is rarely managed non-surgically in the current era, with the development of penile-preserving and reconstruction surgical techniques and the need for surgical lymph node management.<sup>4</sup> Radiotherapy remains an effective penile-sparing alternative and may be delivered with external beam radiotherapy (EBRT) with tissue equivalent bolus (Level 3) or brachytherapy (Level 3).<sup>5</sup> 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.<sup>6,7</sup> 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.<sup>8–12</sup>

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

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)<sup>11</sup>

55 Gy in 20 fractions over 4 weeks (Grade D)

60 in 30 fractions over 6 weeks (Grade C)<sup>10</sup>

66 in 33 fractions over 6.5 weeks (Grade C)<sup>10</sup>

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.<sup>5</sup>

### Unresectable primary and lymph node disease or locoregionally recurrent tumour

For patients with resectable primary and lymph node disease, up front 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.<sup>13,14</sup> The use of either neoadjuvant or definitive radiotherapy or radiotherapy with concomitant chemotherapy are alternative approaches.<sup>4</sup> The radiotherapy target volume is individualised, but may include

the whole pelvis with a boost to sites of gross disease; intensity-modulated radiotherapy (IMRT) may have a role in improving the tolerability of treatment (Grade D).<sup>5</sup> One reported schedule is 45 Gy in 20 fractions to the whole pelvis and inguinal regions followed by a 12 Gy in five fraction boost to gross disease.<sup>15</sup> Combining radiotherapy with concurrent chemotherapy can be considered, although there is no direct evidence to support the combination in penile cancer (Level 4).<sup>5</sup>

### 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.<sup>5</sup>

### 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  $\geq 2$  inguinal lymph nodes are positive or in the presence of extracapsular spread (ECS).<sup>4</sup> The subsequent role of adjuvant radiotherapy is controversial based on limited data (Level 2, Grade D), with the rationale provided by the observation of a significant rate of lymph node recurrence in patients treated with lymphadenectomy with positive lymph node rates varying between 25% and 77%.<sup>5,16–18</sup>

Two recent series have reported on the use of adjuvant radiotherapy for  $\geq 2$  lymph nodes or extracapsular spread.<sup>15,19</sup> In the series of 161 patients from The Netherlands Cancer Institute, 67 patients received adjuvant radiotherapy to a dose of 50 Gy in 25 fractions, delivered to the involved inguinal lymph nodes  $\pm$  involved pelvic lymph node regions; analysis identified high-risk patients as having  $\geq 3$  unilateral inguinal lymph nodes, extracapsular spread or pelvic lymph node involvement.<sup>19</sup> In a series from Leeds, the target volume include the whole pelvis and inguinal regions to a dose of 45 Gy in 20 fractions followed by a boost to gross disease of 12 Gy in five fractions.<sup>15</sup> In both of these series, outcomes were superior to a series which reported on ECS without adjuvant radiotherapy.<sup>2</sup> One small series reported the adjuvant treatment of nine patients to a conventionally fractionated dose of 54 Gy after dissection of pathological lymph nodes, with only one regional recurrence compared with three of five patients who did not receive adjuvant radiotherapy.<sup>20</sup>

The role of concurrent chemotherapy remains an important unanswered question, extrapolated from other disease sites, with the caution that toxicity will be increased in a cohort of patients who are usually elderly. A forthcoming trial of chemoradiation, (International Advanced Penile Cancer Trial, InPACT) will provide more data.<sup>21</sup>

The use of IMRT can be considered (Grade D).<sup>5</sup>

### Recommendations

#### **Based on the forthcoming InPACT chemoradiotherapy trial are:<sup>21</sup>**

54 Gy in 25 fractions over 5 weeks to inguinal regions

Boost sites of residual disease to 57 Gy (Grade D)

#### **Pelvic dose:**

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

#### **Other schedules in use include:**

45 Gy in 25 fractions over 5 weeks or  
50.4 Gy in 28 fractions over 5.5 weeks

to pelvis/inguinal regions, with the option of a boost in 1.8–2 Gy per fraction to high-risk areas up to total of 55–66 Gy depending upon the size of boost volume/risk factors (Grade D).

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

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