

## 14. Sarcoma

### Background

Radiotherapy is widely used as an adjunct to surgery in the management of soft tissue sarcomas as the risk of failure in the surgical bed can be high. For bone sarcomas, radiotherapy is only occasionally employed in the management of osteosarcomas; indications include incompletely resected or unresectable primary disease.<sup>1</sup> By contrast, radiotherapy remains an integral part of multimodality treatment for Ewings sarcoma. Clinical experience suggests that sarcomas vary widely in radiosensitivity. Radiotherapy is delivered with conventional fractionation, with no established role for hypo- or hyperfractionation in treatment with curative intent.<sup>2</sup> Intensity-modulated radiotherapy (IMRT) or proton therapy may be appropriate when optimal dose fractionation is not achievable with conventional techniques.

### Resectable extremity soft tissue sarcomas

Surgery is the primary treatment modality in the majority of soft tissue sarcomas. Adjuvant radiotherapy is used to reduce the probability of local recurrence and facilitate surgical sparing of function.<sup>3,4</sup> There are no randomised trials in soft tissue sarcomas dealing purely with dose-fractionation. External beam radiotherapy (EBRT) can be delivered pre- or postoperatively. The Canadian Sarcoma Group SR-2 trial randomised patients to preoperative radiotherapy with 50 Gray (Gy) in 25 fractions compared with postoperative radiotherapy with 66 Gy in 33 fractions.<sup>4</sup> The results suggest that local control is similar with pre- or postoperative radiotherapy, but that preoperative treatment is associated with an increased rate of acute wound complications (predominantly in the lower limb) and that postoperative treatment leads to increased limb fibrosis, joint stiffness, oedema and bone fractures.

Local control is superior with total postoperative doses >64 Gy in the presence of high-risk features for local failure or positive margins.<sup>5,6</sup> If preoperative radiotherapy is delivered, there is no evidence to support a role for a subsequent postoperative boost in the event of positive resection margins.<sup>7,8</sup>

#### Recommendations

##### **Preoperative radiotherapy:**

50 Gy in 25 fractions over 5 weeks (Grade C)

##### **Postoperative radiotherapy:**

50 Gy in 25 fractions over 5 weeks plus a 10 Gy in 5 fraction boost over 1 week for average risk (Grade C)

For post-operative treatment, a boost of 16 Gy in 8 fractions over 1.5 weeks is recommended for disease considered at higher risk of local recurrence due to positive margins (Grade C)

This boost may be limited to 10 Gy in 5 fractions at certain anatomical sites (for example, across joints, Achilles tendon, brachial plexus)

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>9</sup>

## Unresectable extremity soft tissue sarcomas

Where there are no metastases at presentation, patients may be considered for radical radiotherapy with the aim of achieving local control. There is Level 2+ evidence to support a total dose to tumour of  $\geq 63$  Gy.<sup>9,10</sup>

### Recommendation

66 Gy in 33 fractions over 6.5 weeks (Grade C)

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>9</sup>

## Retroperitoneal soft tissue sarcomas

Surgery is the mainstay of treatment for retroperitoneal sarcomas, however, locoregional recurrence remains the predominant pattern of disease recurrence. The role of radiotherapy remains unproven, with limited supporting data.<sup>11–13</sup> Preoperative radiotherapy is deliverable with minimal toxicity.<sup>11,12</sup> An international expert consensus panel recently concluded that preoperative radiotherapy is preferable to postoperative and provided guidelines on which patients this may be appropriate for, while acknowledging the limited evidence base (Level 4).<sup>9,13</sup>

### Recommendations

#### Preoperative radiotherapy:

50 Gy in 25 fractions over 5 weeks or  
50.4 Gy in 28 fractions over 5.5 weeks (Grade C)

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>9</sup>

## Desmoid tumours

These rare tumours are locally aggressive but do not metastasise. Consensus now supports a multidisciplinary specialist approach to management, with a period of observation most frequently recommended as initial management.<sup>14</sup> For patients with inoperable disease for whom radiotherapy is judged to be indicated, there is evidence to support the use of 56 Gy in 28 fractions in an attempt to delay progression (Level 4).<sup>9,15,16</sup> Radiotherapy may also be used, at similar doses, to prevent or delay recurrence in patients who have residual disease after surgical excision, if clinically indicated. However, it should be noted that positive margins do not necessarily result in disease progression, so this is not an absolute indication for radiotherapy.

### Recommendation

#### **Definitive or postoperative radiotherapy:**

56 Gy in 28 fractions over 5.5 weeks (Grade C)

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>9</sup>

### Ewing's-type tumours and primitive neuroectodermal tumour (PNET)

When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. Where a radical surgical margin is not achieved, then there is evidence to suggest that postoperative radiotherapy at a dose of 54–60 Gy in 28–30 fractions for gross disease, and at least 45 Gy in 25 fractions for microscopic disease, might be beneficial. Surgical resection may not be feasible or appropriate for certain anatomical sites (for example, spine, pelvis), in which case radiotherapy can be used as a radical treatment, although evidence suggests that it is not quite as effective as surgery in achieving local tumour control; evidence indicates that doses of 55–56 Gy in 1.8 Gy fractions can be effective (Level 2b).<sup>9,17–20</sup>

### Recommendations

Doses are based upon the current Euro Ewing 2012 radiotherapy protocol.<sup>21</sup>

#### **For preoperative treatment:**

50.4 Gy in 28 fractions as a single phase. Dose may be reduced to 45 Gy in 25 fractions if necessary due to proximity to organs at risk (Grade C)

#### **Unresectable disease or incomplete macroscopic clearance:**

54 Gy in 30 fractions. A phase 2 boost of 5.4 Gy in 3 fractions may be used respecting organ at risk constraints (Grade C)

#### **For paraspinal tumours:**

50.4 Gy in 30 fractions either as a single phase or an initial phase of 45 Gy in 25 fractions followed by a boost of 5.4 Gy in 3 fractions

#### **For patients at risk of microscopic disease following surgery:**

54 Gy in 30 fractions, delivered with an initial phase of 45 Gy in 25 fractions followed by a 9 Gy in 5 fraction boost (Grade C)

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>9</sup>

## Lung metastases

Curative intent multimodality treatment for patients with lung metastases includes whole-lung radiotherapy (in patients who have not received busulphan).<sup>22</sup> Recommended doses for whole-lung radiotherapy in the EURO EWING 99 study were 15 Gy (for patients <14 years of age) or 18 Gy (patients >14 years) delivered with 1.5 Gy daily fractions or alternatively using bi-daily fractionation with 1.25 Gy per fraction.<sup>23,24</sup> An appropriate bi-daily fractionation schedule would be 17.5 Gy in 14 fractions of 1.25 Gy per fraction over two weeks with a minimum of a six-hour inter-fraction interval. Other centres have reported that a dose of 15 Gy in ten fractions over three weeks is well tolerated in an adult population.<sup>22</sup> Whole-lung radiotherapy should be computed tomography (CT) planned with an inhomogeneity correction.

### Recommendations

#### Whole-lung radiotherapy:

Doses are based on the current Euro Ewing 2012 radiotherapy protocol.<sup>21</sup>

#### <14 years of age:

15 Gy in 10 fractions over 2 weeks (Grade C)

#### ≥14 years of age:

18 Gy in 12 fractions over 2.5 weeks (Grade C)

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>9</sup>

## Palliation

Radiotherapy is used to palliate locally uncontrolled and distant disease. With little evidence available, the selection of dose-fractionation schedules is individualised. Higher total doses maybe appropriate for selected patients with local disease to obtain more durable local control. In patients with metastatic soft tissue sarcoma, a recent series reported a high rate of durable pain control with a dose of 39 Gy in 13 fractions (Level 4).<sup>9,25</sup>

### Recommendations

8 Gy in a single fraction (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

30 Gy in 5 fractions over 5 weeks (Grade D)

30 Gy in 10 fractions over 2 weeks (Grade D)

36 Gy in 12 fractions over 2.5 weeks (Grade D)

39 Gy in 13 fractions over 2.5 weeks (Grade D)

40 Gy in 15 fractions over 3 weeks (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>9</sup>

---

## References

1. DeLaney TF, Park L, Goldberg SI *et al.* Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys* 2005; **61**(2): 492–498.
  2. Dickie CI, Haas R, O'Sullivan B. Adjuvant radiation for soft tissue sarcomas. *Am Soc Clin Oncol Educ Book* 2015; e634–e642.
  3. Yang JC, Chang AE, Baker AR *et al.* Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998; **16**(1): 197–203.
  4. O'Sullivan B, Davis AM, Turcotte R *et al.* Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002; **359**(9325): 2235–2241.
  5. Zagars GK, Ballo MT. Significance of dose in postoperative radiotherapy for soft tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2003; **56**(2): 473–481.
  6. Delaney TF, Kepka L, Goldberg SI *et al.* Radiation therapy for control of soft-tissue sarcomas resected with positive margins. *Int J Radiat Oncol Biol Phys* 2007; **67**(5): 1460–1469.
  7. Al Yami A, Griffin AM, Ferguson PC *et al.* Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys* 2010; **77**(4): 1191–1197.
  8. Pan E, Goldberg SI, Chen YL *et al.* Role of post-operative radiation boost for soft tissue sarcomas with positive margins following pre-operative radiation and surgery. *J Surg Oncol* 2014; **110**(7): 817–822.
  9. [www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009](http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009) (last accessed 30/9/16)
  10. Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2005; **63**(3): 852–859.
  11. Jones JJ, Catton CN, O'Sullivan B *et al.* Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. *Ann Surg Oncol* 2002; **9**(4): 346–354.
  12. Pisters PW, Ballo MT, Fenstermacher MJ *et al.* Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma. *J Clin Oncol* 2003; **21**(16): 3092–3097.
  13. Baldini EH, Wang D, Haas RL *et al.* Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. *Int J Radiat Oncol Biol Phys* 2015; **92**(3): 602–612.
  14. Kasper B, Baumgarten C, Bonvalot S *et al.* Management of sporadic desmoid-type fibromatosis: a European consensus approach based on patients' and professionals' expertise – a sarcoma patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative. *Eur J Cancer* 2015; **51**(2): 127–136.
  15. Keus RB, Nout RA, Blay JY *et al.* Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis – an EORTC STBSG and ROG study (EORTC 62991-22998). *Ann Oncol* 2013; **24**(10): 2672–2676.
  16. Kriz J, Eich HT, Haverkamp U *et al.* Radiotherapy is effective for desmoid tumors (aggressive fibromatosis) – long-term results of a German multicenter study. *Oncol Res Treat* 2014; **37**(5): 255–260.
  17. Indelicato DJ, Keole SR, Shahlaee AH *et al.* Definitive radiotherapy for ewing tumors of extremities and pelvis: long-term disease control, limb function, and treatment toxicity. *Int J Radiat Oncol Biol Phys* 2008; **72**(3): 871–877.
-

- 
18. La TH, Meyers PA, Wexler LH *et al.* Radiation therapy for Ewing's sarcoma: results from Memorial Sloan-Kettering in the modern era. *Int J Radiat Oncol Biol Phys* 2006; **64**(2): 544–550.
  19. Casey DL, Meyers PA, Alektiar KM *et al.* Ewing sarcoma in adults treated with modern radiotherapy techniques. *Radiother Oncol* 2014; **113**(2): 248–253.
  20. DuBois SG, Krailo MD, Gebhardt MC *et al.* Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. *Cancer* 2015; **121**(3): 467–475.
  21. <http://www.isrctn.com/ISRCTN92192408> (last accessed 10/10/16)
  22. Casey DL, Alektiar KM, Gerber NK, Wolden SL. Whole lung irradiation for adults with pulmonary metastases from Ewing sarcoma. *Int J Radiat Oncol Biol Phys* 2014; **89**(5): 1069–1075.
  23. Ladenstein R, Pötschger U, Le Deley MC *et al.* Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol* 2010; **28**(20): 3284–3291.
  24. <http://www.controlled-trials.com/ISRCTN61438620> (last accessed 10/10/16)
  25. Soyfer V, Corn BW, Kollender Y *et al.* Radiation therapy for palliation of sarcoma metastases: a unique and uniform hypofractionation experience. *Sarcoma* 2010; **2010**: 927–972.
-