16 Sarcoma

Background

Bone and soft-tissue sarcomas have more than 100 different histological subtypes and should be managed under the guidance of a bone and soft-tissue sarcoma centre. Radiotherapy is commonly used as an adjunct to surgery or used as a primary or palliative treatment.[1] Radiotherapy is an integral part of the multimodality treatment of Ewing sarcoma and rhabdomyosarcoma.[2,3] Clinical experience reports sarcomas vary widely in radiosensitivity, and this can influence its application in the timing of radiotherapy. The standard of care is to deliver radiotherapy with conventional fractionation when treatment is with curative intent. However, hypofractionated schedules are considered in selected cases. Intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) or proton therapy may be appropriate when optimal dose fractionation is not achievable with conventional techniques. The principles of stereotactic body radiotherapy (SBRT) for oligometastatic disease follow the guidance in SBRT guidelines.[4,5]

Extremity soft-tissue sarcomas

Surgery is the primary treatment modality in most soft-tissue sarcomas. Radiotherapy is recommended as an adjunct to limb-conservation surgical approaches. For large, deep-seated, high-grade tumours, radiotherapy is recommended as an adjunct in the preoperative or postoperative settings to improve local control rates to greater than 80%.[6] The Canadian Sarcoma Group SR-2 trial randomised patients to preoperative radiotherapy with 50 Gray (Gy) in 25 daily fractions compared with postoperative radiotherapy with 66 Gy in 33 daily fractions.[7] Preoperative radiotherapy and postoperative radiotherapy have comparable local control rates, but preoperative radiotherapy is associated with increased wound complications (predominantly in the distal lower limb) and postoperative radiotherapy leads to increased limb fibrosis, joint stiffness, lymphoedema and bone fractures.[8] Tumour location, proximity to critical normal tissues and ability to resect widely impact on the decision regarding the use and timing of surgery and radiotherapy. International consensus is to recommend radiotherapy to be delivered in the preoperative setting. This allows smaller volumes to be treated to a lower total dose, which translates to a potential decreased functional morbidity.[1,9,10]

Histopathological subtypes differ in their risk for local recurrence and responsiveness to radiotherapy. Myxoid liposarcomas are relatively sensitive to radiotherapy and may have a significant reduction in size with preoperative radiotherapy.[11] Myxofibrosarcomas have a high propensity for local recurrence as they are highly infiltrative and have higher rates of positive margins after surgery.[12] Given this increased risk of local recurrence associated with myxofibrosarcomas, radiotherapy is recommended to improve local control.

Patients with localised unresectable disease may be considered for radical radiotherapy with the aim of achieving local control. A total dose of 64 Gy at 2.0 Gy per fraction is recommended.[13,14</]

16
Sarcoma

Technique

IMRT-based treatment is preferred over conventional techniques in the majority of cases, providing dose homogeneity and reduced incidence of high-grade toxicities, such as fibrosis.

Alternative preoperative radiotherapy schedules

Modern radiotherapy and surgical techniques have improved outcomes for extremity soft-tissue sarcomas applying conventional fractionation schedules. Preoperative hypofractionated schedules have been evaluated but are yet to report comparable local control rates and toxicity profile.[15] The safety and efficacy of dose de-escalation for myxoid liposarcoma continues to be under investigation following an initial phase II study demonstrating comparable local control to historical controls.[10] Further, a randomised study is evaluating a postoperative dose of 50 Gy in 25 daily fractions for patients with negative resection margins.

Recommendations

Preoperative radiotherapy:

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

Postoperative radiotherapy:

- 50 Gy in 25 fractions over 5 weeks plus 10 Gy in 5-fraction boost over 1 week for average risk (Grade C)
- For postoperative treatment, a boost of up to 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)

Unresectable: primary radiotherapy

- 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.[16]

Retroperitoneal soft-tissue sarcomas

Surgery is the mainstay of treatment for retroperitoneal sarcomas (RPS), but locoregional recurrence remains the predominant pattern of disease recurrence. An international expert consensus panel concluded that preoperative radiotherapy is preferable to postoperative radiotherapy when radiotherapy is recommended as an adjunct to surgery. The EORTC STRASS trial investigated the addition of radiotherapy to the surgical management of RPS. This trial randomised patients to preoperative radiotherapy (50.4 Gy in 28 daily fractions)

16
Sarcoma

followed by surgery versus surgery alone. The primary outcome was abdominal recurrence-free survival. The trial did not show a statistically significant abdominal recurrence-free survival benefit for the addition of radiotherapy to surgical resection. Surgical morbidity was not statistically different between the two arms.[17] Exploratory analyses suggested that preoperative radiotherapy might improve the local control in grades 1–2 liposarcoma, whereas there did not appear to be a radiotherapy benefit for leiomyosarcoma and high-grade de-differentiated liposarcoma. The STRASS trial investigators also collected data, known as STREXIT, on non-enrolment cases. The STREXIT study also demonstrated improved outcome in G1–2 liposarcoma.[18] In conclusion, preoperative radiotherapy is recommended in selected cases in discussion with sarcoma surgical colleagues where concern is raised of a high risk of local recurrence following an anticipated close resection margin.

Recommendation

Preoperative radiotherapy:

• 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.[16]

Desmoid tumours

Fibromatosis or desmoid tumour is a proliferation of well-differentiated myofibroblasts and fibroblasts with low to moderate mitotic activity. The process is locally aggressive but does not metastasise. An international consensus recommends a multidisciplinary sarcoma specialist approach with, if clinically suitable, a period of surveillance recommended as initial management.[19] Radiotherapy is considered in very selective cases: unresectable tumours growing rapidly in critical anatomical sites or as adjunct following surgery, especially if further surgery would result in significant morbidity or functional deficit, failed systemic therapy or symptom relief.[20]

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.[16]

16
Sarcoma

Ewing-type tumours and primitive neuroectodermal tumour (PNET)

When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. Ewing sarcoma is a radiosensitive disease. If it is anticipated that surgery will result in a marginal resection, preoperative radiotherapy is considered at 45–50.4 Gy in 1.8 Gy per fraction. Where surgery has been considered as primary local treatment and a radical surgical clear resection margin is not achieved and/or there is >10% residual viable disease remaining 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, head and neck, spine, pelvis), in which case radiotherapy can be used as a primary 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.[21]

Recommendations

Doses are based upon the current Euro Ewing 2012 radiotherapy protocol.[22]

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 fractions boost (Grade C)

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16
Sarcoma

Ewing-type tumours: Lung metastases

Curative intent multimodality treatment for patients with lung metastases includes whole-lung radiotherapy (in patients who have not received busulphan).[23] 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.[24,25] An appropriate bi-daily fractionation schedule would be 17.5 Gy in 14 fractions of 1.25 Gy per fraction over 2 weeks with a minimum of a 6-hour interfraction interval. Other centres have reported that a dose of 15 Gy in 10 fractions over 3 weeks is well tolerated in an adult population.[23] Whole-lung radiotherapy should be computed tomography (CT) planned with an inhomogeneity correction.

Recommendations

Doses are based on the current Euro Ewing 2012 radiotherapy protocol.[21]

Whole-lung radiotherapy:

<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.[16]

Rhabdomyosarcoma

Paediatric-type rhabdomyosarcomas (alveolar and embryonal) are relatively radiosensitive disease. In the current FAR-RMS protocol, disease is classified according to PAX-FOXO1 status (PAX-FOXO1 positive is classified as unfavourable disease). When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. If it is anticipated surgery will result in a marginal resection, preoperative radiotherapy is considered. Where surgery has been considered as primary local treatment and a radical surgical clear resection margin is not achieved then postoperative radiotherapy is recommended. Surgical resection may not be feasible or appropriate for certain anatomical sites (for example, head and neck, spine, pelvis), in which case radiotherapy can be used as a primary radical treatment.[3]

16
Sarcoma

Recommendations

Primary disease and involved lymph nodes where applicable:

- Complete response after induction chemotherapy: 41.4 Gy in 23 daily fractions over 4.5 weeks for preoperative radiotherapy or postoperative radiotherapy
- Incomplete response after induction chemotherapy and inoperable disease: 50.4 Gy in 28 daily fractions over 5.5 weeks

Metastatic disease:

- Favourable disease (PAX-FOXO1 negative): all sites – 41.4 Gy in 23 daily fractions over 4.5 weeks

Additional considerations:

In cases of malignant ascites, or diffuse peritoneal involvement, whole-abdominal radiotherapy should be considered. The usual dose will be 24 Gy in 16 daily fractions (or equivalent), followed by a boost to the primary tumour site (where identifiable) up to a dose of 41.4 Gy (microscopic disease) or 50.4 Gy (macroscopic disease).

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.[16]

Bone sarcomas

Patients should be treated within a dedicated bone sarcoma centre to determine the suitability of radiotherapy.

Osteosarcoma

Radiotherapy is recommended in the management of osteosarcomas, for unresectable primary tumours where surgery would be unacceptably morbid or as adjuvant treatment of tumours at high risk of local recurrence and with limited options for further surgery.[25]

Chondrosarcoma

Radiotherapy can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptom palliation. Modern radiotherapy techniques with the ability to safely deliver high doses, including heavy particle therapy, should be considered whenever felt to be technically appropriate. High-dose radiotherapy is recommended for patients with skull base chondrosarcomas, based on the excellent outcome reported (80–90% local control rates).

16
Sarcoma

Chordoma

Chordomas arise from the persistent notochordal elements in the spine (sacrum 50%, mobile spine 20%) and in the skull base (30%). Extraskeletal cases are extremely rare. Patients with chordoma should be managed within a bone sarcoma multidisciplinary team (MDT). Local control will be with surgery or radiotherapy or both. Base of skull chordoma should be discussed at an appropriate MDT with the necessary expertise.[26–28]

Recommendations

Chordoma:

- Adjuvant radiotherapy: 70.2–75.6 Gy in 39–42 fractions depending on resection margins
- Radiotherapy can also be given as a split preoperative and postoperative schedule
- Definitive radiotherapy: 75.6 Gy in 42 fractions

Chondrosarcoma and osteosarcoma:

- Adjuvant radiotherapy limb: 60–66 Gy in 30–33 fractions depending on margins
- Adjuvant radiotherapy for pelvis and spine: 68.4–75.6 Gy in 38–42 fractions depending on margins and site
- Definitive radiotherapy: 75.6 Gy in 42 fractions

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.[16]

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 may be 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 (biologically effective dose [BED] 68 Gy with $\alpha\beta$=4) (Level 4); this may be limited to 36 Gy in 12 fractions when in close proximity to critical structures.[9,29]

Recommendations

Additional palliative radiotherapy schedules to consider in sarcoma include:

- 36 Gy in 6 fractions over 6 weeks (Grade D)
- 36 Gy in 12 fractions over 2.5 weeks (Grade D)
- 45 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.[16]

16
Sarcoma

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16
Sarcoma

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