21 Extracranial oligometastases

Background

This document is intended to provide an outline of the evidence-based dose fractionation schedules published in the latest UK SABR Consortium guidelines[1] and should be read in conjunction with these guidelines.

The metachronous oligometastatic state can be defined as 1–5 metastatic sites, typically occurring more than 6 months after successful treatment of primary disease.[2,3] At present NHS commissioning allows treatment of up to 3 metachronous oligometastases.

Oligometastases can occur at different sites including bone (including spine), lymph node, lung, liver and adrenal. In colorectal cancer (in addition to sarcoma and other sites), surgical treatment of oligometastatic disease (most frequently liver metastases) is associated with prolonged overall survival.[4] The SABR-COMET phase II trial randomised 99 patients, across multiple locally controlled primary cancers, using stereotactic ablative body radiotherapy (SABR) to treat 1–5 oligometastases occurring more than 3 months after primary treatment.[5] This trial showed improved 5-year overall survival with the addition of SABR (42% versus 18%).

Other randomised trials have supported the benefit of metastasis-directed therapy in metachronous oligometastatic prostate cancer[6,7] and painful spinal metastases.[8–11] The UK has completed a Commissioning through Evaluation programme review, finding very low rates of severe G3+ toxicity (≤2% for any toxicity) across 1,422 patients treated for 1–3 extracranial metachronous oligometastases.[12] Meta-analysis of 21 prospective SABR studies has suggested grade 3–5 toxicity rates of 1.7% for acute and 1.2% for late effects respectively.[13] Thus, although phase III data are awaited, metastasis-directed therapy may be deployed for metachronous oligometastatic disease, as an alternative to surgery or where surgery is not possible or deemed too high risk.

Research is ongoing into the role of SABR for oligometastases in both the synchronous[14,15] and oligoprogressive settings,[16] but the NRG BR002 randomised data[17] for synchronous oligometastatic breast cancer have failed to show a benefit, so SABR is not currently recommended in the oligoprogressive or synchronous settings outside a clinical trial.

There is no established consensus on dose fractionation for oligometastatic disease. Recommendations have been derived from systematic reviews of non-randomised studies (prospective and retrospective [Level 3a]), along with expert consensus from the Commissioning through Evaluation Service Specification (Level 5).[1] For all sites, it is recommended that the critical organ dose constraints agreed by the UK SABR Consortium should be considered.[18]

The dose fractionation recommendations here provide guidance only, and when delivering SABR clinicians must balance the priorities of delivering an ablative tumour dose while respecting dose constraints to the surrounding organs at risk. Therefore, the total dose may be lowered at the discretion of the treating clinician and radiotherapy team dependent on individual patient and dosimetric factors. Even at reduced SABR doses, the equivalent dose in 2 Gy per fraction will often exceed the common total doses used for palliative radiotherapy.

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The dose fractionation regimes recommended are independent of the platform used to deliver SABR.

Oligometastases: bone (including spine) and lymph nodes

In this setting, treatment can expect to achieve local control in around 80% and progression-free survival (PFS) of approximately 20% at 2–3 years.[2] Treatment is, in general, well tolerated with myelopathy rates for spinal treatments being less than 1% in most series.[19,20]

Contouring for spinal treatment should be based on the expert consensus guidelines by Cox *et al* (Level 5).[21] Similarly, expert consensus contouring guidelines for non-spinal bone oligometastases and sacral oligometastases can be considered.[22,23]

Recommendations

Initial treatment

Spine (excluding sacrum):

- 18–24 Gy single dose (Grade B)
- 24 Gy in 2 fractions (Grade B)
- 24–27 Gy in 3 alternate day or daily fractions (Grade C)

Sacrum:

- 27–30 Gy in 3 alternate day or daily fractions (Grade C)

Bone:

- 30 Gy in 3 fractions over 1 week (10 Gy per fraction given on alternate days or daily) (Grade C)
- 30 Gy in 5 fractions over 1 week (Grade C)
- 20 Gy in 1 fraction (Grade C)

Nodes:

- 30–45 Gy in 3 fractions over 1 week (10–15 Gy per fraction given on alternate days or daily) (Grade C)
- 30 Gy in 5 fractions over 1 week (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.[24]

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Reirradiation

Often patients will have received prior radiotherapy and, in this setting, it is vital to consider the dose previously received by critical organs. As far as possible, cumulative doses to critical organs should be calculated and, allowing for recovery, tolerances described in the UK SABR consensus document should not be exceeded, if necessary modifying prescription doses to the planning target volume (PTV).[18]

In the specific case of remaining spinal cord tolerance, the method described by Sahgal is recommended.[19] Following this, the maximum cumulative point dose to the thecal sac (similar to cord planning organ at risk volume [PRV]), at a minimum of 6 months after initial irradiation, should not exceed a biologically effective dose (BED) of 140 Gy (α/β=2 Gy). Similarly, Nieder *et al* recommend a cumulative cord BED of less than or equal to 135.5 Gy (α/β=2 Gy) when the interval between radiotherapy courses is not shorter than 6 months.[25] For other organs at risk, there is, to date, no robust evidence to guide safe constraints.[26]

Recommendations

Reirradiation

Pelvis:

• 30 Gy in 5 fractions, given on alternate days or daily (Grade C)

Spine:

• 20–30 Gy in 2–5 fractions, given on alternate days (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.[24]

Oligometastases: lung

Lung oligometastases present a similar clinical problem to early-stage primary lung cancer, for which stereotactic treatment is a standard of care.[27] Specifically for patients with oligometastases, a BED >100 Gy is associated with approximately 90% local control at 1–2 years.[27,28] Although Timmerman *et al* found a significant increase in toxicity when treating central lung tumours, other series have found no increase in toxicity when treating with more than 3 fractions.[29–32] The dose fractionation schedules are based on those used for primary lung cancer SABR schedules but lower doses may be acceptable at the discretion of the treating clinician.

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Recommendations

Peripheral lung oligometastases not abutting chest wall:

• 54 Gy in 3 fractions over 1 week given on alternate days (Grade C)

Peripheral lung oligometastases in contact with chest wall, or consider where 3-fraction constraints are challenging:

• 55–60 Gy in 5 fractions over 2 weeks given on alternate days (Grade C)

Lung oligometastases in the central lung/mediastinum:

• 60 Gy in 8 fractions over 3 weeks given on alternate days (Level 4)

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.[24]

Oligometastases: liver

The use of surgery and radiofrequency ablation to treat liver oligometastases is well established for colorectal tumours. A phase II randomised trial reported improved overall survival with radiofrequency ablation (RFA) of liver metastases (CLOCC trial EORTC-NCRI CCSG-ALM Intergroup 40004).[33] For colorectal liver tumours under 6 centimetres (cm) in diameter, local control above 90% at 1 year can be achieved with stereotactic doses of at least 48 Gy in 3 fractions.[34] This analysis included patients who were heavily pre-treated with systemic therapy. Consideration should be given to the functional liver remnant. Further reviews have indicated this dose is effective in other tumour types, with grades 3–4 toxicity, most commonly elevated liver enzymes or gastrointestinal toxicity, of 1–10% (Level 3a).[35,36]

Recommendations

• 24–30 Gy in a single fraction (Grade C)
• 40–60 Gy in 3 fractions over 1 week, on alternate days (Grade C)
• 50–60 Gy in 5 fractions on alternate days or daily (Grade C)

For oligometastases 6 cm or more in size, or where constraints cannot be met:

• 40–60 Gy in 10 daily 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.[24]

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Oligometastases: adrenal

Due to a rich sinusoidal blood supply, adrenal metastases are frequently observed in patients with melanoma, breast, lung, kidney and gastrointestinal tumours. Based on non-randomised observations of enhanced survival in patients undergoing adrenalectomy for oligometastatic disease, stereotactic radiotherapy has also been used. Meta-analysis of 39 studies (2009–2019) has shown pooled local control rates of 82% at 1 year and 63% at 2 years, across a wide range of dose fractionation schedules.[37]

Recommendations

- 30–36 Gy in 3 fractions on alternate days (Grade C)
- 40–45 Gy in 5 fractions on alternate days or daily (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.[24]

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