4.x Oligometastases: evidence for dose-fractionation

Background

4.x.1. The oligometastatic state can be defined as 1-3 isolated metastatic sites, typically occurring more than six months after successful treatment of primary disease. 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. Multiple single-arm studies have shown that stereotactic radiotherapy is effective and well tolerated in the oligometastatic setting, in multiple histologies and anatomical sites (see below). Thus, it may be deployed as an alternative to surgery, or where surgery is not possible. However, in this developing field, patients should be treated within clinical trials or Commissioning Through Evaluation processes.

Treatment technique

4.x.2 It is not possible to discuss dose-fractionation without discussing treatment technique. The majority of evidence comes from stereotactic body radiotherapy (SBRT, or SABR – stereotactic ablative radiotherapy). Developments in radiotherapy technology have allowed the safe delivery of an ablative dose in five or fewer fractions, with high-precision. Patients have been treated using dedicated stereotactic systems (such as Cyberknife) and using conventional gantry-based systems with stereotactic capability. The optimal system for delivery is unknown, but image guidance, either with implanted fiducials and/or soft tissue tomography, is essential. Organ dose constraints for 1-5 fractions can be found in the AAPM and Timmerman publications.

Evidence for dose-fractionation:

4.x.3 There is no randomised data, and no established consensus for dose-fractionation in radiotherapy for oligometastatic disease. Recommendations have been derived from systematic reviews of non-randomised studies (prospective and retrospective), along with expert consensus.

Oligometastases: bone (including spine) and lymph nodes

4.x.4 In this setting, treatment can expect to achieve a local control around 80% and progression free survival of approximately 20% at 2-3 years. In this review, patients who received a Biologically Equivalent Dose > 100Gy, and those with tumours ≤ 3cm had better outcomes. Patients have typically received three fractions, but many with spinal disease received a single fraction. Treatment is well tolerated, with myelopathy rates for spinal treatments being less than 1% in most series.

Recommendations (Grade B):

- Three fraction treatment: 30-45Gy (10-15Gy per fraction)
- Single fraction treatment: 18-24Gy
(These doses may need to be reduced dependent on proximity of organs at risk.)

It should be noted that the risk of vertebral compression fracture following spinal treatment rises significantly for dose per fraction above 19Gy (10% vs. 20-40%)\textsuperscript{6} (Grade B).

Contouring for spinal treatment should be based on the expert consensus guidelines by Cox et al\textsuperscript{7} (Grade D).

A number of case series have reported experience in treating metastatic disease occurring in a pelvis or spinal region previously treated with conventionally fractionated radiotherapy\textsuperscript{8}. Treatment appears to provide good local control and is well tolerated, with a low rate of myelopathy.

**Recommendations for retreatment (Grade D):**

<table>
<thead>
<tr>
<th>Location</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Pelvis</td>
<td>30Gy/5#</td>
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<tr>
<td>Spine</td>
<td>20-30Gy/2-5#</td>
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**Lung oligometastatic disease**

4.x.5 Lung oligometastases present a similar clinical problem to early-stage primary lung cancer, for which stereotactic treatment is a standard of care\textsuperscript{9}. Specifically for patients with oligometastases, a BED > 100Gy is associated with approximately 90% local control at 1-2 years\textsuperscript{10}. Although Timmerman et al\textsuperscript{11} found a significant increase in toxicity when treating central lung tumours, other series have found no increase in toxicity when treating with more than three fractions\textsuperscript{12-14}.

**Recommendations:**

- Peripheral lung oligometastases: 48-54Gy/3# (Grade B)
- Central lung oligometastases: 48-55Gy/5# (Grade C)

**Liver oligometastatic disease**

4.x.6 The use of surgery and radiofrequency ablation to treat liver oligometastases is well established. For colorectal liver tumours under 6cm in diameter, local control above 90% at 1 year can be achieved with stereotactic doses of at least 48Gy in 3#\textsuperscript{15}. This analysis included patients who were heavily pre-treated with systemic therapy. Further reviews have indicated this dose is effective in other tumour types, with grade 3-4 toxicity of 1-10\%\textsuperscript{16,17}.

**Recommendation (Grade B):**

- Liver oligometastases: 45-50Gy in 3#

**Adrenal oligometastatic disease**
Due to a rich sinusoidal blood supply, adrenal metastases are frequently observed in patients with melanoma, breast, lung, kidney and gastrointestinal tumours. Based on observations of enhanced survival in patients undergoing adrenalectomy for oligometastatic disease, stereotactic radiotherapy has also been utilised. Local control rates vary from 55% to 90% with doses ranging from 16Gy in 4 fractions to 50Gy in 10 fractions\textsuperscript{18,19}.

**Recommendation (Grade D):**

**Adrenal oligometastases:** 45 Gy in 3#

**Conclusions**

4.x.8 There is good evidence that stereotactic radiotherapy for oligometastatic disease is well tolerated and effective, and that a BED above 100Gy should be the aim of treatment, while respect organ tolerance. However, in the absence of randomised evidence and a clear consensus on dose fractionation, patients should be treated in clinical trials or the Commissioning Through Evaluation process.
References

