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Overview

Stereotactic Body Radiotherapy for Liver Metastases

K.L. Aitken *, M.A. Hawkins †

* Department of Radiotherapy, Royal Marsden NHS Foundation Trust, London, UK
† CRUK MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, UK

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Abstract

The role for local ablative therapies in the management paradigm of oligometastatic liver disease is increasing. The evidence base supporting the use of stereotactic body radiotherapy for liver metastases has expanded rapidly over the past decade, showing high rates of local control with low associated toxicity. This review summarises the evidence base to date, discussing optimal patient selection, challenges involved with treatment delivery and optimal dose and fractionation. The reported toxicity associated with liver stereotactic body radiotherapy is presented, together with possible pitfalls in interpreting the response to treatment using standard imaging modalities. Finally, potential avenues for future research in this area are highlighted.

Key words: Ablative therapy; liver; metastases; SABR; SBRT; stereotactic

Statement of Search Strategies Used and Sources of Information

Data for this review article were identified and selected after a search of PubMed using a combination of the terms 'liver', 'metastases', 'radiotherapy', 'radiation', 'stereotactic', 'SBRT' and 'SABR' using the PRISMA systematic review guidance criteria (*Br Med J* 2009;339:b2535). Only articles published in English were selected. The search also included the reference list for these articles and selected additional articles and webpages that were judged to be relevant.

Introduction

Liver metastases arise commonly in many solid organ malignancies. Colorectal cancer, which drains initially to the liver via the portal circulation, is the most frequent primary site to give rise to metastatic liver disease, and where the role for local therapy has been most thoroughly evaluated. Historically, the development of liver metastases was considered an incurable disease state; however, advances in imaging, systemic treatment, surgery and locally ablative techniques over the past two decades have provided evidence for a more aggressive approach, especially in patients with oligometastatic disease. Hellmann and Weichselbaum [1,2] proposed two oligometastatic scenarios in which radical therapy may improve outcome. First, in patients with a limited number of metastases, where extirpation is potentially curative. The second scenario where local treatment may be used, is to manage 'remnant disease' after downstaging systemic therapy. This has ignited further interest in ablative approaches. There is a lack of consensus in the optimal number and location of metastases that constitutes a truly oligometastatic state, as well as the best imaging modality to define this [3]. Investigations through randomised prospective trials will hopefully validate some of the concepts emerging from institutional series reviews.

Surgery is the current gold standard for treating liver metastases, with colorectal cancer, melanoma and sarcoma being the most common types of primary tumour for which metastasectomy is used. About 50% of patients diagnosed with colorectal cancer will either present with metastatic liver disease or develop metachronous liver metastases later in their disease course [4], translating to about 20 000 patients per year in the UK [5]. The benefits of adopting a radical treatment approach in patients with oligometastatic

Author for correspondence: M. Hawkins, CRUK MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Old Road Campus Research Building, Oxford OX3 7DQ, UK. Tel: +44-1865-857042.
E-mail address: maria.hawkins@oncology.ox.ac.uk (M.A. Hawkins).

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liver disease are now well established. In colorectal cancer, the combination of hepatic resection and systemic chemotherapy has improved 5 year survival rates to 50–60% [6]. However, only a minority of patients will be appropriate for surgery (about 25–30%), due to unfavourable disease distribution within the liver, comorbidities precluding surgery or the presence of extrahepatic disease [7]. Of these, it is estimated that about 2000 patients per year in the UK will have inoperable, liver-confined disease. For other tumour sites, such as breast and lung, the concept of radical therapy for oligometastatic liver disease is just emerging [8–11]. For liver-only metastases, a number of non-surgical local ablative therapy options are available, including radiofrequency ablation (RFA), microwave ablation, cryotherapy, selective internal radiation therapy and stereotactic body radiotherapy (SBRT).

Ablative Therapies for Liver Metastases

RFA is the most established local therapy, with a recent meta-analysis reporting a wide range of 5 year survival (14–55%) and local control (3–60%) [12]. RFA is most effective when reserved for treating three or fewer lesions, <3.5 cm in diameter, which are not in close proximity to large blood vessels due to the heat-sink effect [13]. Although historically high local recurrence rates with RFA have been reported, the combination of better patient selection, improved operator experience and technological advances in computed tomography guidance imaging and RFA probes has reduced recurrence rates to 5.2–8.8% [14]. No randomised trials comparing surgery with RFA have taken place and attempts to organise such a trial have failed. However, in a non-randomised comparison between two arms of prospective trials evaluating RFA and surgery, respectively, there was no significant difference in local lesion recurrence rate between the two approaches in lesions <3 cm in size [14]. Microwave ablation shows an apparent benefit as it generates a larger ablation zone and has a diminished heat-sink effect [15]. However, a review of 450 patients with lesions >3 cm showed a propensity for early recurrence, regardless of histology [15]. Therefore, although surgery remains the gold standard, RFA and microwave ablation are increasingly being accepted as valid treatment alternatives. This in turn, will probably help to promote the acceptance and integration of alternative techniques, such as SBRT, into the treatment pathway, if equivalent efficacy can be robustly demonstrated.

Despite the lack of randomised comparative evidence, small (<3 cm), favourably located lesions will probably be successfully ablated by a number of ablative techniques with similar local control outcomes. More challenging, however, is the management of large volume lesions and those situated adjacent to critical structures, such as the stomach or small bowel, where many of these techniques are either unsuitable or are known to result in inferior local control results. For this patient group, SBRT provides an attractive non-invasive alternative local therapy that can produce excellent rates of local control. It has low morbidity and may be used to treat lesions up to 6 cm in size, including those situated close to large vessels, in contrast to techniques such as RFA [16].

Development of Liver Stereotactic Body Radiotherapy

Despite liver tumours being sensitive to the effects of radiation, historically radiotherapy has not played a significant role in treatment. This is primarily due to the relative radiosensitivity of the liver, such that delivering sufficient dose to the target to achieve local control without causing unacceptable toxicity has been challenging. Although the tolerance of the whole liver to radiotherapy is low, as a parallel organ it can tolerate high doses to small volumes as long as the mean dose to the uninvolved liver is low enough not to cause functional compromise [17,18]. As a result of technical advances in radiation delivery over the past decade, the safe delivery of radiation to the liver has become a realistic prospect, prompting an expansion in its use [19,20]. Highly conformal dosimetry, together with a steep dose gradient allowing relative sparing of normal liver tissue, makes SBRT a particularly attractive technique for liver irradiation.

Liver SBRT can be safely and effectively delivered using either a linear accelerator (linac) or an SBRT-specific delivery platform, such as the robotic CyberKnife (Accuray™). These have relative advantages and disadvantages over one another, although broadly the plan quality that can be achieved with either technique is similar. Linac-delivered SBRT enables three-dimensional volumetric imaging acquisition for patient set-up, does not mandate fiducial marker insertion and generally has shorter treatment times, especially if intensity-modulated arc therapy is used. In contrast, treatment times with CyberKnife are significantly longer, on average being 30–60 min per fraction due to the large number of non-coplanar non-isocentric beams used and respiratory tracking of the mandatory fiducial markers (Figures 1–3).

Technical Challenges of Delivering Liver Stereotactic Body Radiotherapy

By delivering the dose in a small number of high-dose fractions, SBRT allows significant dose escalation. Although this will probably be advantageous in improving local control rates, it has the potential to cause late toxicity, particularly if the delivered dose distribution does not accurately reflect that intended at treatment planning. As such, the liver as a target organ for SBRT presents several specific challenges.

The first is intrafraction motion, predominantly due to the effects of respiration. The degree of intrafraction motion can be significant, with intrafraction liver excursions of up to 39.5 mm (mean 17.6 mm) being reported [21]. Tumour motion is usually predominantly in a cranio-caudal direction due to diaphragmatic movement. Strategies to mitigate for intrafraction motion depend on the delivery platform

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