

Overview

Stereotactic Body Radiotherapy for Liver Metastases

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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.

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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

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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 radio-sensitivity 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

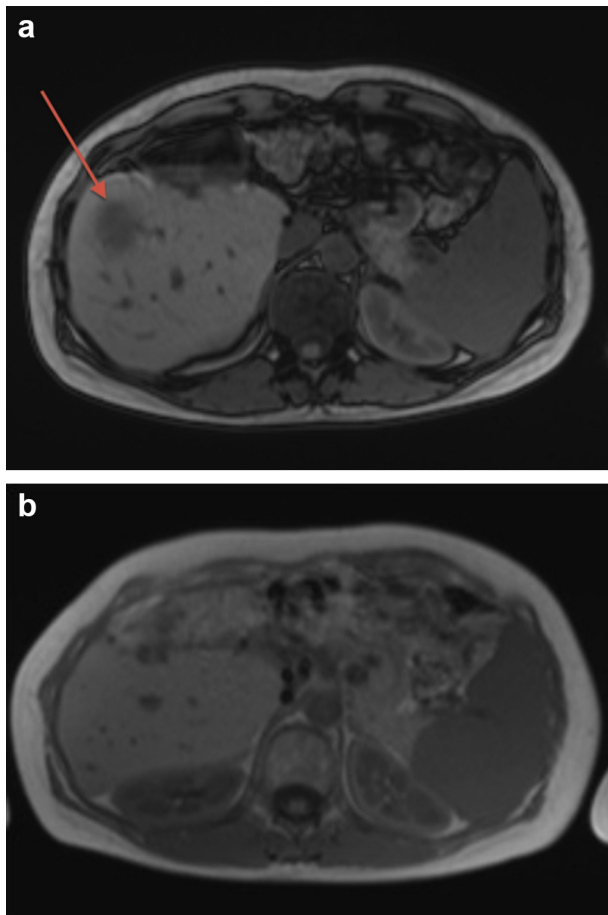


Fig 1. (a) T1-weighted axial magnetic resonance imaging of a colorectal liver metastasis before stereotactic body radiotherapy. The red arrow denotes lesion. (b) Resolution of the lesion 12 months after treatment.

used. A variety of motion management techniques can be used, including abdominal compression [22], gating [23] and breath-hold techniques [24], or alternatively accounted for by the use of four-dimensional computed tomography to individualise treatment margins at treatment planning. For respiratory gating or tracking, between three and five fiducial markers are inserted around the tumour to enable intrafraction tracking of tumour motion using kV-kV (kiloVoltage) imaging during treatment.

Daily radiotherapy patient set-up is made difficult by the fact that the position of liver tumours relative to bony anatomy has been shown to change between fractions by up to 1 cm [25]. In addition, liver tumours are often of similar density with respect to adjacent normal liver tissue, therefore making daily localisation of the tumour with three-dimensional cone beam computed tomography challenging. In view of this, the three-dimensional positions of the whole liver and diaphragm are usually used as surrogates for tumour position [26]. The use of fiducial markers to aid localisation is an alternative solution and has been shown to improve confidence in daily tumour visualisation before treatment [27].

The liver may also undergo deformation between fractions of radiotherapy. This may be due to temporal

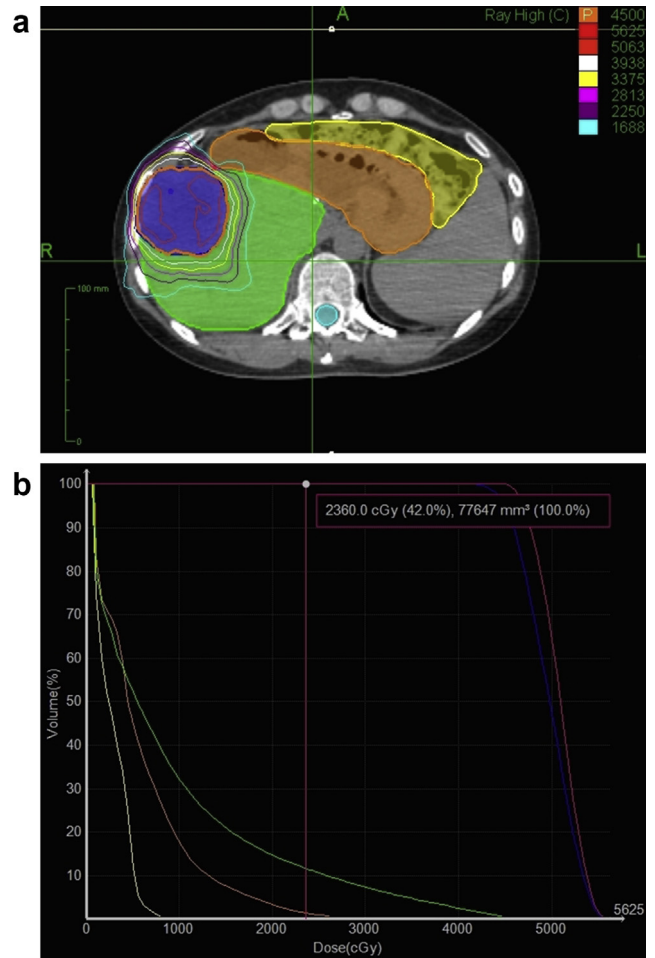


Fig 2. (a) Example of a CyberKnife stereotactic body radiotherapy plan. The planning target volume is denoted in blue. The orange line denotes the 45 Gy prescription isodose line (80% isodose). Adjacent organs at risk are contoured in orange (stomach) and yellow (bowel). Normal liver is contoured in green. (b) Dose volume histogram showing dose to planning target volume (blue), clinical target volume (pink), normal liver (green), bowel (yellow) and stomach (orange).

alterations in the position of the liver with respect to other abdominal organs, or due to differences in patient positioning at set-up. This has been shown to cause discrepancies >5% in the dose delivered to the tumour and normal

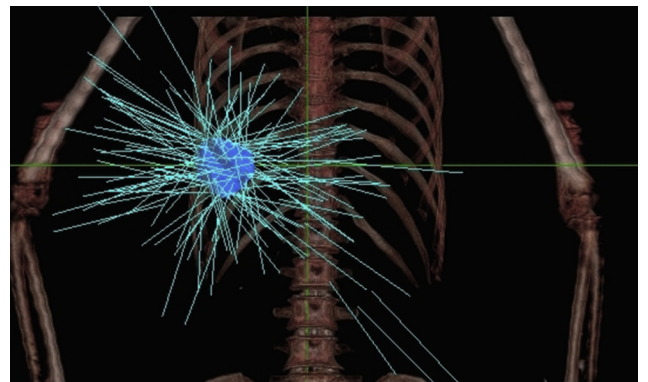


Fig 3. Example of a CyberKnife stereotactic body radiotherapy beam arrangement.

tissues compared with that expected from treatment planning, despite using daily cone beam computed tomography for patient set-up [28]. These uncertainties in the delivered dose distribution are particularly relevant when considering dose-escalation strategies for liver tumours, as the normal tissue dose volume histograms calculated at planning may not reflect the delivered dose.

Clinical Outcomes of Liver Stereotactic Body Radiotherapy

A variety of retrospective and prospective studies of SBRT for the treatment of metastatic liver disease have been reported in the literature. The results of these are summarised in Tables 1 [29–36] and 2 [37–44]. Currently, no randomised phase III data have been reported, although an international multicentre phase III trial comparing RFA with SBRT in lesions <4 cm in size is open and recruiting, Radiofrequency Ablation Versus Stereotactic Radiotherapy in Colorectal Liver Metastases (RAS01) (trial, CI: M Hoyer NCT01233544) [45]. Within the UK, liver SBRT is not currently commissioned for reimbursement despite the existence of national guidance for SBRT indications and treatment guidelines [46]. As securing treatment costs has therefore relied on applying on an individual funding basis, its use to date has generally been reserved for patients ineligible for surgery and unsuitable for RFA/alternative ablative techniques on the basis of either lesion size (≥ 3.5 cm) or location. The treatment indications are likely to expand as the evidence base for efficacy continues to grow, and with the outcome of comparative trials such as RAS01 [45].

Interpretation of the reported survival rates is confounded by the significant heterogeneity in the included patients. In many of the earlier trials the patients were heavily pre-treated with systemic chemotherapy before receiving SBRT. In addition there is significant variation in primary tumour histology, the volume of metastases treated and radiotherapy dose and fractionation. However, in general, reported local control rates are high, ranging from 70 to 100% at 1 year and 60 to 90% at 2 years [16].

Prognostic Factors Related to Local Control

In general, smaller tumour volumes are reported to have better local control [40,42,47], together with a higher delivered dose [48,49]. In addition, those with a longer disease-free interval and absence of chemotherapy [39], adenocarcinoma histology and metachronous disease presentation seem to have better outcomes [39,50].

Optimal Dose and Fractionation for Liver Stereotactic Body Radiotherapy

A variety of dose regimens have been used, varying from single fractions of up to 30 Gy to six fraction regimens where the dose is individualised according to the predicted

risk of liver toxicity. Several studies have shown a dose response, with local control improving with higher doses [40,47,51]. A meta-analysis concluded that a dose of 46–52 Gy in three fractions or higher is required to achieve 90% local control at 1 year for the treatment of colorectal liver metastases (equivalent to a biologically equivalent dose > 117) [48]. Therefore, more recent studies have pursued a dose-escalation strategy, using doses of up to 75 Gy in three fractions, reporting local control rates of 94% at 1 year [44]. It should be noted, however, that the mean gross tumour volume in this series was small at 18.7 cm³ (mean planning target volume 54.9 cm³, maximum 209.4 cm³), with 60% of lesions being ≤ 3 cm in size. The feasibility of delivering such high doses to larger lesions is unproven. In general, most SBRT series have included lesions up to a maximum size of 6 cm.

For larger volume lesions (>6 cm), achieving ablative doses using a three to five fraction regimen is challenging without exceeding normal liver constraints. For this group of patients, an alternative approach is to use a risk-stratified individualised prescription technique using a normal tissue complication probability model. This effectively allows individualisation of tumour dose according to the modelled risk of radiation-induced liver disease (RILD) for each patient, a toxicity of particular concern when treating large lesions. The prescribed dose is dependent on the volume of normal liver tissue exposed to radiation and has been previously described [40,52]. Outcomes of using this approach in six to 10 fraction regimens have reported 1 year local control rates varying from 65 to 71% [34,40]. Although the use of these more protracted dose fractionation regimens does not meet some definitions of SBRT (e.g. five or fewer fractions), this approach provides a useful option for the safe treatment of larger lesions or when multiple sites are treated [53].

Toxicity of Liver Stereotactic Body Radiotherapy

Most series have reported low rates of treatment-related toxicity, with rates of CTCAE grade 3 or 4 toxicity ranging from 1 to 10%. Historically, the most common toxicity with liver radiotherapy has been RILD. The risk of RILD is known to be proportional to the mean dose delivered to the normal liver [52] and is more common in patients with hepatocellular carcinoma, as underlying liver dysfunction is known to be a risk factor for both the disease and RILD. Most studies have reported rates of $<1\%$ of RILD after SBRT for liver metastases. It should be noted that in most reported studies, only one metastasis was treated per patient. Therefore, although the definition of oligometastases allows for the treatment of multiple lesions, the toxicity profile for this approach is less well defined. Other significant reported toxicities include luminal gastrointestinal complications, such as duodenal ulceration and intestinal perforation [39]. In view of this, it has been recommended that the ideal lesions for SBRT are >8 mm away from visceral organs at risk and that respecting organ at risk tolerances should always take priority over planning

Table 1
Summary of reported retrospective studies of stereotactic body radiotherapy for liver metastases

Reference	No. patients	Tumour volume	Primary site	Radiotherapy dose	Prescription isodose line	Delivery platform	Toxicity	Outcome
[29]	14	3–260 ml	CRC (11)	7.7–45 Gy (1–4 fractions)	Periphery of PTV	Linac	2 haemorrhagic gastritis	50% response rate
[30]	5	NR	NR	45 Gy (3 fractions)	90–100%	Linac	No serious toxicity	2 year LC 71.2%
[31]	44	9–335 ml	CRC (23) Breast (11) Ovarian (4) Other (13)	30–37.5 Gy (3 fractions) 26 Gy (1 fractions)	65%	Linac	No grade 2–4 toxicity	1 year LC 92% 2 year LC 66% 1 year OS 72% 2 year OS 32%
[32]	69	0.6–12.5 cm	CRC (20) Breast (16) Pancreas (9) Lung (5) Other (19)	30–55 Gy (5–15 fractions)	80%	Linac	No grade 3/4 toxicity	10 month LC 76% 20 month LC 57% Median survival 14.5 months
[33]	20	0.7–6.2 cm	CRC (20)	30–37.5 Gy (3 fractions)	95%	Linac	2 grade 3 late liver enzyme changes 1 grade 2 rib fracture	1 year LC 100% 2 year LC 74% Median survival, 34 months
[34]	34	2–614 ml	CRC (27) Breast (4) Sarcoma (2) Anal (1)	30–60 Gy (10 fractions)	100%	Linac	1 grade 3 acute liver enzyme changes	1 year 65%, 2 year 45% Median OS 14.5 months
[35]	57	2.5–126 ml	CRC (18) Pancreas (8) Breast (7) Lung (7) Other (17)	39–54 Gy (3–7 fractions)	Isodose encompassing 95% PTV (range 70–85%)	CyberKnife	No \geq grade 3 toxicity	1 year 94.4%, 2 year 89.7% Median OS 37.5 months
[36]	139 (51 liver metastases)	1.3–5.4 cm	CRC (30) Lung (5) Gastric (5) Other (11) HCC (79)	30–60 Gy (3–10 fractions)	NR	Linac	7% grade 2–4 3 grade 3 gastrointestinal bleeds 1 grade 4 gastroduodenal artery rupture 3 grade 2 gastric ulcers	Liver metastases only: 1 year 75%, 2 year 65% 2 year OS 72%

CRC, colorectal; NR, not reported; LC, local control; OS, overall survival; HCC, hepatocellular carcinoma; PTV, planning target volume.

target volume coverage [54]. The use of volumetric image guidance, for example with cone beam computed tomography, can be useful to verify organ at risk position when treating lesions in close proximity to organ at risk. This approach is not possible when using fiducial markers in combination with planar imaging. Soft tissue and bone complications such as non-traumatic rib fractures [43] and grade 3 soft tissue toxicity [31] are rarely described. In general, the toxicity of giving SBRT in conjunction with systemic therapy is not well established, although phase I trials of combination drug approaches are ongoing. In general, we would advocate a washout period of 2 weeks before and after SBRT for patients on systemic therapy and novel biological agents, with the exception of endocrine therapy, which can be continued concurrently with radiation. No organ at risk tolerances are well described for either the liver vasculature or gall bladder. A retrospective evaluation investigating patients

who had received >20 Gy to the central biliary tree and/or gall bladder during liver SBRT found rates of toxicity to be low when treating with a five fraction schedule [55]. However, avoiding unnecessary radiation exposure should be considered.

Post-treatment Response Evaluation

Serial computed tomography and/or magnetic resonance imaging (MRI) are the most frequent modalities used to assess local response after treatment. Baseline imaging to assess the treatment response is generally carried out at 3 monthly intervals in the first year, then 6 monthly, although computed tomography imaging at earlier time points may be required to confirm a clinical suspicion of RILD. MRI and positron emission tomography (PET) may bring

Table 2

To summarise prospective studies of stereotactic body radiotherapy for liver metastases

Reference	Design	No. patients	Tumour volume	Primary site	Radiotherapy dose	Prescription isodose line	Delivery platform	Toxicity	Outcome
[37]	Phase I–II	35	1–132 ml (median 10)	NR	14–26 Gy (1 fraction) Dose escalation	80%	Linac	No serious toxicity	1 year LC 71% 18 month LC 67% 1 year OS 72%
[38]	Phase I–II (HCC and metastases)	25 (17 liver)	1.1–322 ml (median 22.2)	CRC (14) Lung (1) Breast (1) Carcinoid (1)	30–37.5 Gy (3 fractions)	65%	Linac	2 grade 3 liver toxicities	2 year LC 86% 2 year OS 62%
[39]	Phase II (CRC oligometastases)	64 (44 liver metastases)	1–8.8 cm (median 3.5 cm)	CRC (44)	45 Gy (3 fractions)	67%	Linac	1 liver failure 2 severe late GI toxicities	2 year LC 79% 1 year LC 95% months
[40]	Phase I–II	68	1.2–3090 ml (median 75.9)	CRC (40) Breast (12) Gallbladder (4) Lung (2) Anal canal (2) Melanoma (2) Other (6)	Individualised dose 27.7–60 Gy (6 fractions)	Periphery of PTV	Linac	No RILD 10% grade 3/4 acute toxicity No grade 3/4 late toxicity	1 year LC 71% Median survival 17.6 months
[41]	Prospective cohort	27	20–165 (median 69)	CRC (11) Other (16)	25–60 Gy (3 fractions)	80%	CyberKnife	No serious toxicity	Crude LC rate 74%
[42]	Phase I–II	47	0.75–97.98 ml (median 14.93)	CRC (15) Lung (10) Breast (4) Ovarian (3) Oesophageal (3) HCC (2) Other (10)	Dose escalation 36–60 Gy (3 fractions)	80–90%	Linac	No RILD Late grade 3/4 toxicity <2%	1 year LC 95% 2 year LC 92% Median survival 20.5 months
[43]	Phase I (HCC and liver metastases)	26 (19 liver metastases)	0.8–146.6 ml (median 32.6 ml)	CRC (6) Pancreatic (3) Gastric (2) Ovarian (2) Other (6)	Dose escalation 18–30 Gy (1 fraction)	Isodose covering PTV	Linac and CyberKnife	No dose limiting toxicity 4 cases of grade 2 late toxicity (2 GI, 2 soft tissue/rib)	1 year local failure 23% 2 year OS 49%
[44]	Prospective phase 2	61	CTV 1.8–134 cm ³ (mean 18.6)	CRC (29) Breast (11) Gynaecological (7) Other (14)	52.5–75 Gy (3 fraction)	Prescribed as mean dose to PTV	Linac (RapidArc)	1 case late grade 3 toxicity	1 year LC 94% 1 year OS 84%

CRC, colorectal; NR, not reported; LC, local control; OS, overall survival; HCC, hepatocellular carcinoma; RILD, radiation-induced liver disease; GI, gastrointestinal; PTV, planning target volume; CTV, clinical target volume.

complementary information if the lesion cannot be reliably visualised on computed tomography. However, accurately determining the treatment response using standard RECIST criteria alone can be difficult. A phenomenon of pseudo-progression on computed tomography has been described, whereby lesions that have responded to treatment may become necrotic and increase in size, therefore being misclassified as a progression event [56]. Serial imaging may be required to clarify the response, but shrinkage of the hypodense region, vessel displacement and distinct patterns of contrast enhancement are considered indicative of local control [57]. FDG-PET may be useful for response imaging, although further evaluation is required in this area. An $SUV_{max} > 6$ (twice the baseline standardised uptake value (SUV)) has been proposed to be suggestive of local failure, assuming an initial SUV response [58]. Strategies to improve diagnostic certainty include assessing enhancement-based lesion characteristics, in conjunction with standard size evaluation criteria [56]. Further work is required in the future to refine imaging-based assessment of the response to liver SBRT.

Future Directions

In the UK, there are currently no clinical trials of SBRT for liver metastases recruiting. However, two recently funded CRUK trials opening in 2015 will be evaluating the role of SBRT, in addition to standard therapy, in the management of oligometastatic disease. The CORE (Conventional care Or Radioablation for Extracranial oligometastases) trial will evaluate the role of SBRT in metachronous presentations of oligometastases in breast, prostate and non-small cell lung cancer. The SARON (Stereotactic Ablative Radiotherapy for Oligometastatic Non-small cell lung cancer) trial will investigate the same question in the management of synchronous oligometastatic non-small cell lung cancer.

Further advances in radiotherapy technology, such as the development of a magnetic resonance linac for treatment delivery has exciting potential applications for SBRT. The magnetic resonance linac will enable detailed evaluation of target and organ at risk motion and be able to track tumour motion. The ability to acquire real-time high resolution imaging, including functional MRI series, will improve the accuracy of both target and organ at risk definition, therefore enabling on-the-fly adaptive therapy, opening up the possibilities for isotoxic dose escalation.

It has been proposed that one of the causative mechanisms of local failure are regions of hypoxia, particularly within large lesions [59]. In colorectal cancer, tumour hypoxia has been shown to be present heterogeneously throughout resected specimens [60]. Van Laarhoven *et al.* [61] have shown, in resected liver metastases with a mean size of 43.9 mm (range 10–100 mm), areas of chronic hypoxia close to areas of proliferation, raising the possibility of high oxygen consumption alongside limited oxygen supply. Combining SBRT with hypoxia-modifying agents is therefore one potential area of research. Given the propensity for patients to fail at distant sites after SBRT, further

work is required to evaluate the optimal sequencing and combination of liver SBRT with systemic therapies. Combining SBRT with concomitant systemic therapy as a means of improving the therapeutic ratio requires further evaluation. This approach has been shown to be feasible in a phase I trial of whole liver radiotherapy in combination with sorafenib, for liver metastases.

A further exciting avenue for SBRT research is the discovery that delivering radiation doses within the ablative range seems to enhance anti-tumour immunity, with activation of the adaptive and innate immune responses. Case reports have described the so-called ‘abscopal effect’, whereby regression of distant metastases outside the radiation field is seen after SBRT [62,63]. This has stimulated research interest into the potential for combining SBRT with immunotherapy in oligometastatic disease, in order to therapeutically exploit this immune response [64].

Conclusion

Ablative techniques provide the option for a minimally invasive treatment approach in a selected group of patients with oligometastatic liver disease. The evidence for SBRT is increasing in magnitude. However, prospective trials and further research are necessary to identify the group of patients that benefit most from this approach. The opportunity for combining systemic agents with SBRT brings a new exciting era of research, evaluating how best to integrate SBRT into current treatment strategies.

Conflict of Interest

None declared.

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