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REVIEW

Treatment of metastatic liver tumors using stereotactic ablative radiotherapy

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Abstract

The prognosis of patients with metastatic liver disease remains dismal with a median survival of only 6-12 mo. As 80%-90% of patients are not candidates for surgical therapy, there is a need for effective non-surgical therapies that would improve outcomes in these patients. The body of evidence related to the use of stereotactic ablative radiotherapy (SABR) in metastatic liver disease has substantially grown and evolved over the past decade. This review summarizes the current evidence supporting liver SABR with particular attention given to patient selection, target delineation, organ at risk dose volume constraints, response evaluation imaging and the various SABR techniques for delivering ablative radiotherapy to the liver. Even though it is unclear what dose-fractionation scheme, delivery system, concomitant therapy or patient selection strategy yields the optimum liver SABR outcomes, clear and growing evidence is available that SABR is a safe and effective therapy for the treatment of oligometastatic liver disease.

Key words: Liver; Metastasis; Stereotactic; Radiotherapy; Ablative

Core tip: The body of evidence related to the use of stereotactic ablative radiotherapy (SABR) in metastatic liver disease has substantially grown and evolved over the past decade. This review summarizes the current evidence supporting liver SABR with particular attention given to patient selection, target delineation, organ at risk dose volume constraints, response evaluation imaging and the various SABR techniques for delivering ablative radiotherapy to the liver.

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INTRODUCTION

Metastatic disease to the liver constitutes the most common malignant hepatic tumor, accounting for 45% of all liver tumors followed by hepatocellular carcinoma at 28%[1]. Any clinical or radiological evidence of cancer cells in the liver would deem the patient as stage IV no matter what the primary source of the malignancy is and the intent of treatment traditionally has been palliative. With advances in systemic and local therapies a steady decline in the nihilistic approach to patients with liver metastasis has evolved. The definition of the term "oligometastases" as an intermediate state in the multistep nature of cancer spread between stages of purely localised and widely spread metastases has made its way into the common vernacular of the clinic. The implication is that patients with oligometastatic disease can be cured with metastasis directed therapy before it disseminates further. This appears to be true for liver metastasis

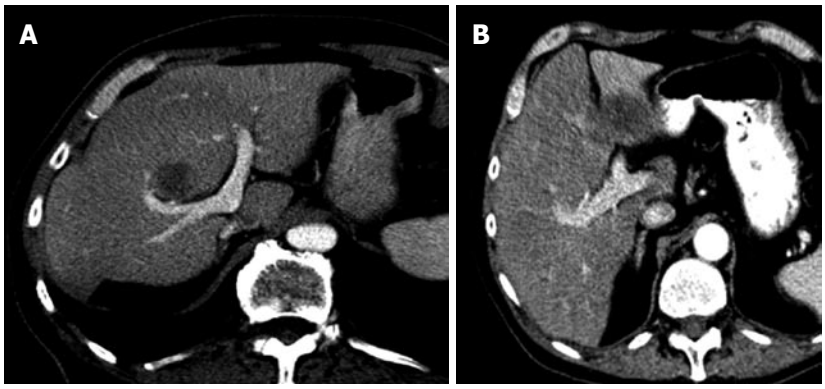

Figure 1 Images demonstrating tumors close to the critical structures. In these cases stereotactic ablative radiotherapy could prove useful than radiofrequency ablation or other alternative non-surgical therapies. A more fractionated regimen would be useful to minimise toxicity when abutting luminal structures. A: tumor abutting vascular trunk; B: Tumor close to luminal gastrointestinal structures (stomach in this case).

arising from cancers of the colon or rectum where the natural history of cancer can be relatively indolent and spread can be paradoxically limited to just one organ (the liver) for a long time before ever metastasizing elsewhere. The majority of the experience with liver metastasis-directed therapies is with colorectal cancer (CRC) liver metastases (CRCLM). Approximately 50% of colon cancer patients will be diagnosed with hepatic metastases, either at the time of initial presentation or as a result of disease recurrence[2]. With improved outcomes with systemic agents in non-colorectal malignancies an increased demand for liver metastasis-directed therapies in other histopathologies that presents with oligometastases is on the rise.

Among the liver metastasis-directed therapies currently available, surgery forms the standard of care. Modern series analyzing post liver resection survival for patients with CRCLM report 5-year survival of 37%-58% and 10-year survival of 22%-28%[3]. This improved survival confirms the hypothesis that there could be a subset of patients with liver metastasis who could benefit from liver metastasis-directed therapy; especially when one considers the fact that the 5 years survival for patients with CRCLM without treatment is less than 10% (median survival 6-12 mo)[4]. In patients with non-CRC, non-neuroendocrine metastasis, a 5- and 10-year survival of 36% and 23% respectively has been reported with resection, with liver metastases originating from breast cancer having the best survival and melanoma and squamous cell cancers or any origin having the worst survival[5]. Despite the benefits of liver metastasis resection, 80%-90% of patients of such patients are not resectable at diagnosis and hence cannot avail this benefit[6]. The quandary in patients with inoperable oligometastatic disease lies in deciding what treatment options would provide the best outcomes. Traditionally chemotherapy would be the next option. Numerous histopathology and biology specific chemotherapy agents and targeted therapies have been developed to improve outcomes. However with neo-adjuvant chemotherapy, only 10%-30% of these tumors are converted into a resectable status[7,8]. Also the high systemic toxicity from most of the therapies precludes many patients from completing their course and generally would seek alternative liver directed therapies especially when they have only 1-5 metastasis confined to liver.

Traditionally, radiation therapy for liver metastases was considered to be a palliative therapy due to the low tolerance of the whole liver (20-30 Gy in 2-3 Gy per fraction) and the potential for radiation induced liver disease (RILD). Also the associated survival was very poor. Though less used, radiotherapy to the whole or partial liver still continues to be used for symptom palliation[9]. Other options for liver metastases are radiofrequency ablation (RFA), cryotherapy, laser-induced thermotherapy, and high-intensity focal ultrasound[10]. However these liver metastasis-directed ablative therapies have some limitations such as maximum diameter of the metastasis, number of metastases and location within the liver, susceptibility to trauma for adjacent intestine or biliary vessels or for RFA specifically loss of effectiveness with large vessels in proximity which may act as a heat sink (Figure 1)[11]. Hence there is demand for a non-surgical therapeutic option which can globally treat tumors in most locations and sizes and produce a good response. Liver stereotactic ablative radiotherapy (SABR) is one such technique that may be able to overcome some of these limitations.

SABR FOR LIVER METASTASIS

The Canadian Association of Radiation Oncology has defined stereotactic body radiotherapy (SBRT) as the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses at least biologically equivalent to a radical course when given over a protracted conventionally (1.8-3.0 Gy/fraction) fractionated schedule[12]. SABR, stereotactic radiotherapy or radiosurgery are other terms used to describe this technique. Advanced radiation planning and delivery techniques have helped in conforming the ablative radiation doses tightly to the target with a surrounding sharp dose gradient, and have enabled greater confidence of intra-fraction tumour position with improved image guidance.

The initial experience with SABR for liver tumors was based on the principles of intracranial radiosurgery with a fixed body frame for rigid immobilisation. The earliest report was in 1995 in Stockholm, Sweden where investigators reported the results of 42 extracranially (solitary

Table 1 Prospective clinical trials in the literature studying stereotactic ablative radiotherapy in liver metastases and their results

Ref.	Design	No of patients	Tumor size	SABR dose	Toxicity	Outcomes
Scorsetti *et al*[15]	Phase Ⅱ (preliminary report)	61 (76 tumors)	1.8-134.3 cm^3 (mean 18.6 cm^3)	75 Gy in 3 fractions	No case of RILD. Twenty-six percent had grade 2 transaminase increase (normalised in 3 mo). Grade 2 fatigue in 65% patients, one grade 3 chest wall pain which regressed within 1 year.	1-yr LC94, 22-mo LC 90.6%
Goodman *et al*[16]	Phase Ⅰ (HCC and liver mets)	26 (19 liver mets)	0.8-146.6 mL (median, 32.6 mL)	Dose escalation, 18-30 Gy (1 fr)	No dose-limiting toxicity 4 cases of Grade 2 late toxicity (2 GI, 2 soft tissue/rib)	1-yr local failure, 3% 2-yr OS, 49% (mets only)
Ambrosino *et al*[17]	Prospective cohort	27	20-165 mL (median, 69 mL)	25-60 Gy (3 fr)	No serious toxicity	Crude LC rate 74%
Lee *et al*[18]	Phase Ⅰ-Ⅱ	68	1.2-3090 mL (median, 75.9 mL)	Individualized dose, 27.7-60 Gy (6 fr)	No RILD, 10% Grade 3/4 acute toxicity No Grade 3/4 late toxicity	1-yr LC, 71% Median survival, 17.6 mo
Rusthoven *et al*[19]	Phase Ⅰ-Ⅱ	47	0.75-97.98 mL (median, 14.93 mL)	Dose escalation, 36-60 Gy (3 fr)	No RILD, Late Grade ¾ < 2%	1-yr LC, 95% 2-yr LC, 92% Median survival, 20.5 mo
Høyer *et al*[10]	Phase Ⅱ (CRC oligomets)	64 (44 liver mets)	1-8.8 cm (median, 3.5 cm)	45 Gy (3 fr)	One liver failure, two severe late GI Toxicities	2-yr LC, 79% (by tumor) and 64% (by patient)
Méndez Romero *et al*[20]	Phase Ⅰ-Ⅱ (HCC and mets)	25 (17 liver mets)	1.1-322 mL (median, 22.2 mL)	30-37.5 Gy (3 fr)	Two Grade 3 liver toxicities	2-yr LC, 86% 2-yr OS, 62%
Herfarth *et al*[21]	Phase Ⅰ-Ⅱ	35	1-132 mL (median, 10 mL)	Dose escalation, 14-26 Gy (1 fr)	No significant toxicity reported	1-yr LC, 71% 18-mo LC, 67% 1-yr OS, 72%

SABR: Stereotactic ablative radiotherapy; RILD: Radiation induced liver disease; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; GI: Gastrointestinal; LC: Local control.

tumors in lung, liver or retroperitoneal space) treated tumors in 31 patients. They reported a response rate of 43% for 14 liver metastases treated with 20-45 Gy in 1-4 fractions, with a prolonged time to maximum response (approximately 16 mo for a 13-cm liver metastasis). No liver toxicity was observed but 1 patient developed grade 4 hemorrhagic gastritis[13]. In a 1998 update, the local control rate was 95% with a mean survival of 17.8 mo after SABR for 21 patients with liver metastases[14]. However due to the highly mobile nature of liver tumors with respiration and also their capacity to deform with this motion relative to the external frame, improved image guidance techniques were required to ensure accurate delivery of the high radiation doses. Soon various groups embarked on liver SABR programs and presented their institutional data. Table 1 shows the various prospective clinical trials in the literature studying SABR in liver metastases[10,15-21].

From various prospective and retrospective trials, SABR for liver metastases shows a local control rates ranging from 70%-100% at 1 year and 60%-90% at 2 years. Median overall survival after SABR ranges from 10 to 34 mo, with 2-year overall survival rates ranging from 30% to 83%, with occasional long-term survivors[10].

PATIENT SELECTION

There is no consensus regarding the selection criteria for patients for liver SABR. Even though tumors of most histopathologies are selected, the most common are CRCLM. Table 2 demonstrates the most commonly accepted criteria for selecting patients for SABR for liver metastasis. In general, patients with 1-3 liver metastasis with maximum tumor diameter < 6 cm, liver confined disease, good performance status with pre-treatment Child-Pugh status A are the best candidates for SABR. Patients with underlying hepatic conditions (*e.g.*, chronic hepatitis or cirrhosis) may not be good candidates but this is mainly an issue in SABR for hepatocellular cancers and not with metastases.

In our centre, generally select patients with 1-3 oligometastatic liver metastases with pre-treatment Child-Pugh status A/B and tumor size ⩽ 6 cm are selected for SABR treatment. In addition tumors unsuitable for RFA treatment due to their size criteria or location close to vessels or gastrointestinal structures are also selected for treatment.

SABR PLATFORMS AND TECHNICAL CONSIDERATIONS

There are various platforms for delivering SABR therapy for patients with liver tumors. The most common is using a modern linear accelerator equipped with some form of image guidance system to deliver SABR. SABR specific units such as the Vero® (Mitsubishi Heavy Industries Ltd., Tokyo, Japan and BrainLAB AG, Feldkirchen, Germany) and CyberKnife® (Accuray Inc., Sunnyvale, CA, United States) are also on the market. All these modalities report comparable outcomes with their techniques. The CyberKnife® is a robotic SABR platform where a miniaturised linear accelerator is mounted on a robotic arm possessing 6 axis of freedom and aligns accurately to the

Table 2 Organ at risk constraints in various prospective trials depending on their fractionation schemes[10,15,19,21,28-29,31]

Normal Liver (Liver- CTV-RFA cavities)	D30% = 6-12 Gy, D50% = 4-7 Gy	V_{15} Gy < 700 mL	30% < 21 Gy, 50% < 15 Gy	V_{15} Gy < 700 mL	V_{15} Gy < 700 mL	V_5 Gy ⩽ 700 mL, Dmean < 15 Gy	V_{15} Gy < 700 mL	V_{21} Gy < 700 mL
Stomach	Dmax ⩽ 12 Gy	NA	$D_{5\,mL}$ < 21 Gy	Dmax ⩽ 30 Gy	$D_{1\,mL}$ < 21 Gy	Dmax < 30 Gy; D5 mL < 22.5 Gy	$V_{21\,Gy}$ < 1%	Dmax ⩽ 32 Gy , $D_{10\,mL}$ < 28 Gy
Bowel	Small bowel Dmax ⩽ 35 Gy	D < 5% volume < 20 Gy	$D_{5\,mL}$ < 21 Gy	Dmax ⩽ 30 Gy	$D_{1\,mL}$ < 21 Gy	Dmax < 30 Gy	Duodenum, small bowel $V_{21\,Gy}$ < 1%	Duodenum: Dmax ⩽ 32 Gy; $D_{5\,mL}$< 18 Gy Jejunum/ileum: Dmax ⩽ 35 Gy, $D_{5\,mL}$ ⩽ 19.5 Gy Colon: ⩽ 38 Gy, $D_{20\,mL}$ ⩽ 25 Gy
Esophagus	Dmax ⩽ 14 Gy	NA	$D_{5\,mL}$ < 21 Gy	NA	$D_{1\,mL}$ < 21 Gy	NA	$V_{21\,Gy}$ < 1%	Dmax ⩽ 35 Gy, $D_{5\,mL}$ < 27.5 Gy
Kidney	NA	75% volume of each kidney < 5 Gy	NA	Total kidney D35% < 15 Gy	Total kidney D35% < 15 Gy	NA	$V_{15\,Gy}$ < 35% for both kidneys	Renal hilum/vascular trunk < 2/3 ⩽ 23 Gy Renal cortex (right and left): 200 mL < 17.5 Gy (3.5 Gy/fraction)
Spinal cord	NA	Dmax < 12 Gy	NA	Dmax ⩽ 18 Gy	Dmax < 18 Gy	Dmax ⩽ 20 Gy	$D_{0.1\,cm^3}$ < 18 Gy	Dmax ⩽ 30 Gy, $D_{0.25\,mL}$ < 22.5 Gy
Heart/ pericardium	NA	NA	$D_{5\,mL}$ < 21 Gy	NA	$D_{1\,mL}$ < 30 Gy	NA	$V_{30\,Gy}$ < 1%	Dmax ⩽ 38 Gy, $D_{15\,mL}$ < 32 Gy
Skin	NA	NA	NA	NA	NA	NA	NA	Dmax ⩽ 32 Gy, $D_{10\,mL}$ < 30 Gy
Great vessels	NA	NA	NA	NA	NA	NA	NA	Dmax ⩽ 53 Gy, $D_{10\,mL}$ < 47 Gy
Chest wall	NA	NA	NA	NA	NA	NA	$D_{30\,cm^3}$ < 30 Gy	NA

CTV: Clinical target volume; Dx%: Dose to x%; Dx mL/cm^3: Dose to x mL/cm^3; RFA: Radiofrequency ablation; NA: Not available.

tumor and delivers the radiation in forms of hundreds of beamlets which allows optimisation of tumor dose and spares nearby normal tissues. The CyberKnife Synchrony® Respiratory Tracking System utilizes real time imaging of chest position and correlates that with tumor position *via* two orthogonally mounted X-ray units. Implanted fiducials are tracked in real time and used as a surrogate for tumour position. During treatment the system adjusts the position of the delivered beam during respiration so that the dose is delivered consistently to the moving tumor. The different SABR platforms perform image guidance using various imaging modalities such as megavoltage (MV) orthogonal imaging, fluoroscopy, ultrasound, or MV/kV cone beam CT for checking the tumor location prior to treatment.

The various SABR systems rely on imaging of some form of surrogate for the tumor(s) such as the liver itself, implanted fiducials, air-diaphragm interface or air-rib interfaces to help ensure that dose is delivered accurately[10]. Modern linac-based radiation delivery techniques such as volume modulated arc therapy have made the radiation delivery much faster and hence lessen the amount of uncertainties during treatment.

FIDUCIAL IMPLANTATION, TREATMENT SIMULATION AND PLANNING

For those centres that use fiducials to help identify tumour position within the liver, implantation is usually performed at least one week prior to simulation. For the purpose of image guidance, gold based fiducials are commonly used. There is some evidence that platinum fiducials are better as they are better visualized on the same treatment planning magnetic resonance imaging (MRI) sequences that gives the best tumor definition and hence a fiducial to fiducial based image registration while treatment planning is possible[22]. The location of implanted fiducials is also important. Seppenwoolde *et al*[23] showed that for liver treatment a close arrangement of fiducials to the tumour is recommended. An ideal implantation would surround the tumor (Figure 2), where the tumor centre is closer to the fiducial centroid[10]. The fiducials are usually implanted transcutaneously or through endoscopic ultrasound guidance depending on where they are located in the liver. For robotic SABR using the CyberKnife system, identifying fiducials as distinct entities on orthogonal X-rays acquired on the unit is required. Optimal conditions for this include a minimum of 2 cm distance between any two fiducials and a minimum of 15° degree angle within any three fiducials. Fiducials should not be placed in the same plane in such a way that they form about a 45-degree angle with the horizon. No fiducial should be greater than 5 to 6 cm away from the lesion. To track rotational movement, a minimum of three fiducials placed in three different orthogonal planes is necessary.

The treatment planning simulation is usually done after a week of fiducial implantation to allow for development of fibroblastic reaction around the fiducials, making it more fixed to the implanted tissue[24]. Depending on the SABR platform used, the patient is simulated in the treatment planning position. Use of a body frame with reference fiducial markers or equivalent customized external vacuum-type or synthetic body mould is used in most linac based system to reduce both the patient and respiratory liver motion. Respiratory control is usually achieved by

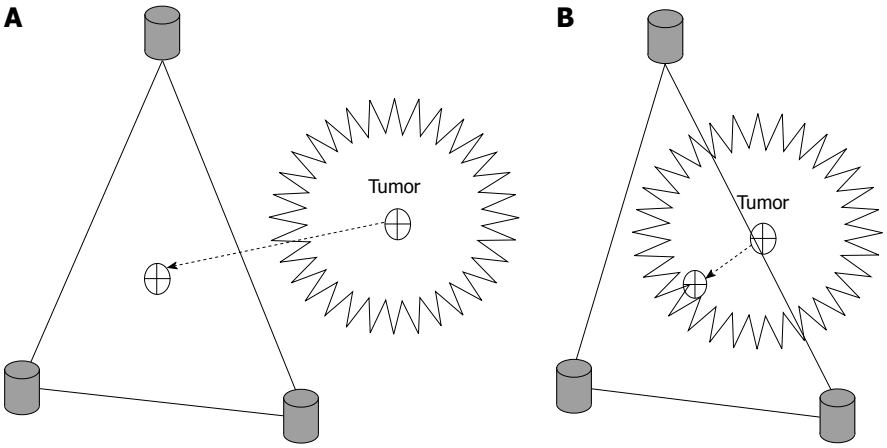

Figure 2 Diagram showing ideal post implantation distribution of the fiducials around the tumor (Adapted from Seppenwoolde *et al*[23]). Ideally the fiducial arrangement should be centred around the tumor, bracketing the lesion (B) and not lateralized to one side (A). At least 3 fiducials should be implanted.

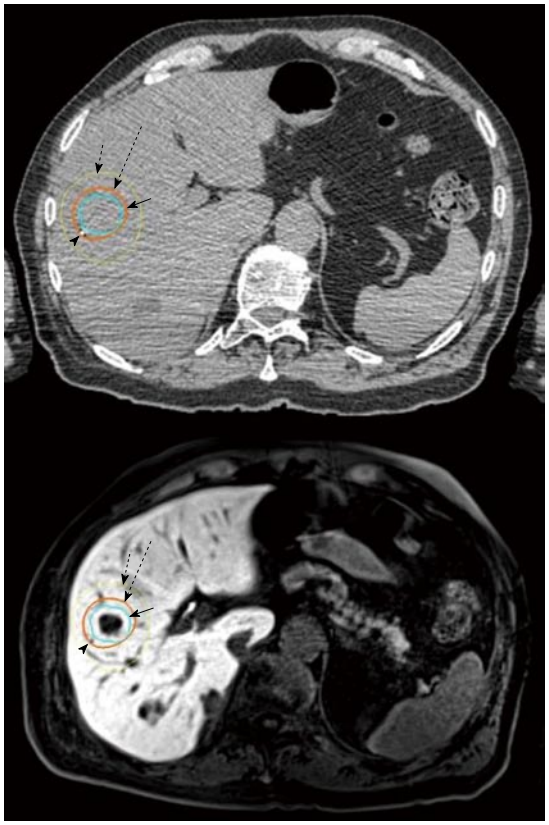

Figure 3 Demonstrating the tight prescription isodose (long broken arrow) around the planning target volume (solid arrow). The steep dose fall gradient is demonstrated by the 50% isodose curve (short broken arrow) around the prescription isodose. Platinum fiducials showed as arrow head as seen in both computed tomography and magnetic resonance imaging.

gating, active breath control or simply using an abdominal compression plate[25]. Robotic SABR system that perform real time tracking do not require patients to be in any rigid or semi-rigid immobilisation as the system will track the fiducials with breathing. A non-contrast CT scan, contrast enhanced CT scan and ideally a contrast enhanced MRI is used for treatment planning purposes, usually acquired in the same phase of respiration to facilitate easy fusion. A 4D-CT scan is also of benefit for assessing liver tumor motion and creating larger margins to account for tumor motion. The planning CT and MRI images are registered in the treatment planning system. Some centres use planning PET-CT scans for target delineation[26].

A gross tumour volume (GTV) is defined as all tumor appreciated on clinical and radiological studies. The clinical target volume (CTV) is generally the same as the GTV for SABR treatments. Centres using 4D-CT to account for respiratory motion may use the minimum intensity projection or maximum intensity projection or a combination to contour the internal target volume (ITV), alternatively they may fuse the 4D-CT images at end-inspiration and end-expiration and contour the tumor in each image and sum of the two would generate the ITV[27]. The CTV to planning target volume (PTV) margin varies depending on the SABR technique and platform. Most centres use a 5 mm radial margin and a 10 mm cranio-caudal margin to create a PTV. Centres that use fiducial based guidance may use a symmetrical 5 mm margin or less.

The goal of SABR treatment planning for liver metastasis is to produce highly conformal dose distributions with multiple beams using either coplanar or non-coplanar geometries (Figure 3). The prescription dose is generally prescribed to the planning isodose covering the PTV (generally the 80%-90% isodose line). Intensity modulation radiotherapy can be more beneficial around concave targets compared to spherical targets in liver SABR[28]. In contrast to conventionally fractionated radiotherapy; dose heterogeneities with the target are generally acceptable in the form of a higher dose within the primary tumor, as long as there is no overlap with an organ at risk. Radiobiologically this distribution may also be desirable because as the tumor centre is considered to be relatively hypoxic and hence relatively radioresistant[29].

TUMOR AND ORGAN AT RISK DOSE VOLUME CONSTRAINTS

Due to lack of clear evidence, various dose fractionation

schemes are used by various centres depending on the technique available and also based on the clinical scenario such as size or location of the tumor. In a phase I trial led by the group at the University of Colorado, it was shown that it is safe to treat up to 3 liver metastases to 60 Gy in 3 fractions as long as a minimum of 700 mL of normal liver receives < 15 Gy total dose in 3 fractions[19]. Another phase I dose escalation trial from UTSW did not reach maximal tolerated dose but reached the predefined maximal dose of 60 Gy in 5 fractions. In this trial at least 700 mL of normal liver had to receive < 21 Gy[30]. Goodman *et al*[16] reported a phase I trial of single session SABR to the liver where doses where safely escalated from 18 Gy to 30 Gy in 1 fraction for liver tumors (both metastases and hepatocellular carcinomas). There was no dose limiting toxicity. Lee *et al*[18] reported the results of a phase I trial which gave individualised tumor prescriptions in 6 fractions guided by NTCP calculations using the Lyman model of normal tissue complication probability. Using this model, the calculated risk of hepatic toxicity was escalated from 5% to 20%. However due to the lack of any RILD noted in none of the 68 patients in the study, there is criticisms that even though this model may be a useful tool for guiding dose selection, it may not predict the actual risk of liver toxicity[9]. As fractionations beyond the above mentioned are considered to be less ablative and higher total doses may increase liver toxicity, that has been attempted less.

It may be logical to say that for tumor abutting luminal GI structures, a more protracted dose fractionation may be reasonable. Also due to the lesser experience with SABR for larger tumors (> 6 cm in maximal diameter), a more individualised approach similar to the University of Toronto approach or use of a less ablative dose per fraction may be reasonable[9].

The existence of a dose-response ratio with liver SABR has also been studied. A pooled analysis of 47 CRCLM patients demonstrated that total dose, dose per fraction and biological effective dose (BED) were significant for local control on multivariate analysis. The estimated dose of 46-54 Gy in 3 fractions or a BED of 117 Gy_{10} (EQD2 = 98 Gy) would be required for a 1-year local control rate of > 90%[31]. Vautravers-Dewas *et al*[32] in their series of 42 patients could not demonstrate a clear dose response, however their dose prescription was limited to 40 Gy in 4 fractions and 45 Gy in 3 fractions (BED 80-113 Gy_{10}, EQD2 = 66-94 Gy). The similarity in the BED between the regimens may have contributed to the results. Lanciano *et al*[11] in a retrospective series treating a cohort of patients mixed histopathologies with higher SABR doses with time also demonstrated that a dose response relationship is possible. An increase local control was noticed for a BED > 100 Gy_{10} (EQD2 = 90 Gy). All three studies mentioned above did not show tumor size to be a predictor of outcome, counter to traditional beliefs.

Severe (grade 3 or above) toxicity due to SABR to the liver is uncommonly reported. Currently there is no consensus regarding the organ at risk (OAR) dose volume constraints due to the different fractionation schemes and techniques that each centre uses. The Quantitative Analyses of Normal Tissue Effects in the Clinic recommends a mean liver dose of < 15 Gy in three fractions and < 20 Gy in 6 fractions and ≥ 700 mL of normal liver receives ≤ 15 Gy in three to five fractions for a < 5% risk of RILD[34]. Pre-existing liver dysfunction, as measured by the Child-Pugh score, should be recorded, as well as any change in status of Child-Pugh score after treatment[9].

Gastrointestinal toxicity is also less commonly reported even though it depends on the location of the tumor. Intestinal ulceration and perforations were reported in 3 patients with bowel doses greater than 30 Gy in 3 fractions[10]. Grade 3 subcutaneous toxicity has been reported in a single patient with skin doses of 48 Gy in 3 fractions[30]. Rib fractures has been reported in patients receiving maximum doses to 51.8 Gy and 66.2 Gy in 6 fractions to 0.5 cm^3 of rib[18]. The various prospective trials for liver metastases with their OAR dose volume constraints depending on their fractionation schemes are given in Table 2[10,15-16,19,21,30,33-34]. Many centres also follow the Rule *et al*[30] publication of dose volume constraints which even though unvalidated, provides some basic planning constraints for the planners to achieve. But in general, SABR treatments which spare at least 700 cc of liver is associated with almost no toxicity.

In our centre, we would treat with a risk adapted strategy based on the tumor size and capacity for liver sparing. For smaller tumors, we adopt an aggressive strategy with lesser number of fractions such as 54 Gy in 3 fractions and for larger tumors which are close to the intestine, we use protracted fractionation upto 5 fractions (48 Gy in 5 fractions). As fractions more than 5 are not generally classified as SBRT in the United States, the experience with higher doses with protracted fractions is limited.

POST TREATMENT RESPONSE EVALUATION

Post treatment response imaging is usually done by contrast enhanced CT scan or MRI scan at frequent intervals, generally starting 3 mo following treatment and then at least every 3 mo for a year. After a year, the follow-up protocol varies between centres[15-16,19,21,30,33-34]. Some centres also use PET-CT scan for the post SABR follow-up[15].

Herfarth *et al*[35] studied the CT changes of patients treated in a prospective phase I - II post SABR (single fraction) using non-enhanced and contrast enhanced scans acquired at different times after contrast injection. He described three different types of reaction based on time after imaging post SABR corresponding to the histological changes seen in veno-occlusive disease (VOD). Type I occurred up to 3 mo, type II occurred at 3 to 6 mo, and type III occurred more than 6 mo after SABR. The post treatment change is usually a hypodense area (liver metastasis are also typically hypodense) which reduces in size with time. This hypodense area may be

larger than the primary tumor size as the prescription isodose conforms around the PTV which is larger than actual tumor. However there may be a surrounding radiation reaction which may be initially enhancing (pseudo progression) and may undergo change with time.

There are concerns regarding the use of RECIST criteria for post SABR liver imaging. A recent retrospective study by Jarraya *et al*[36] also reports the use of changes in enhancement in addition to size criteria for response evaluation following SABR. They report that the post SABR VOD that was seen in early imaging as a hypodense area would become fibrotic, becoming smaller and denser on successive follow-ups. The "thin" rim enhancement radiation reaction seen early during the post SABR imaging is likely due to the presence of granulation tissue related to inflammatory response to the treatment. Usually there is a clear border between the target and normal parenchyma at the treatment margin especially with robotic SABR. The authors also described a thick lobular enhancement pattern which could be suggestive of local recurrence, which could present earlier than a size progression. In order to objectively identify necrosis, a objective definition of a difference of $\leqslant$ 10 Houndsfield units between the non-contrast and contrast-CT scans in the hypodense areas was used, even if there was an increase in size[36]. It is important for the treating physician and the radiologist to be aware of these treatment induced changes post SABR, and in case of any suspicion serial imaging may be required to assess these tumors closely and to distinguish between tumor recurrence and pseudo progression due to radiation reaction.

FUTURE CONSIDERATIONS

As with any other treatment, the role of liver SABR for metastatic disease needs to be evaluated by conducting randomised clinical trials comparing the various competing therapies. As out of field recurrences develop in a significant number of patients post SABR, there is a rationale in combining SABR with various systemic and targeted agents. So an optimum combination of various modalities needs to be studied further. Due to the difference in radiobiology, there is also a need to study the various histopathology-specific dose fractionation schemes in order to maximise tumor control and minimise toxicity by delivering lower doses for relatively radio responsive tumors. The role of functional imaging for both radiation planning and for post treatment response evaluation to rule out radiation induced change *vs* recurrence also needs to be elucidated.

CONCLUSION

Stereotactic ablative body radiotherapy is a well-tolerated and effective therapy for patients with liver metastasis who are not suitable candidates for resection. More prospective trial data is required to find the optimum fractionation schedules and to compare its efficacy and toxicity with other competing ablative therapies.

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