External Radiation for Unresectable CRLM

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Introduction

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 [1]. The term "oligometastasis," introduced by Hellmann and Weichselbaum [2] in 1995, describes an intermediate stage of cancer, between localized and metastatic cancer, that is suitable for local treatment. The benefits of adopting a radical treatment approach in patients with oligometastatic liver disease are now well established.

The introduction of novel treatments, mainly consisting of chemotherapy agents and targeted therapy, has improved the overall survival (OS) of patients with CRLM (colorectal liver metastasis) [3, 4]. Combination of hepatic resection and systemic chemotherapy has improved 5-year survival rates to 50–60% [5]. However, only a minority of patients will be appropriate for surgery (about 25–30%) due to unfavorable disease distribution within the liver, comorbidities precluding surgery, or the presence of extrahepatic disease [6, 7].

Historically, the use of external beam radiation therapy (RT) in treatment of liver tumors has been limited due to the overall low tolerance of liver tissue to radiation [8]. Although radiation can achieve excellent tumor control when delivered to ablative doses [9], dose is limited due to this low tolerance of the surrounding normal liver tissue and adjacent organs. Radiation-induced liver disease (RILD) is a feared complication of treatment, classically manifesting as a triad of anicteric hepatomegaly, ascites, and elevation of alkaline phosphatase. Histopathologically, venous occlusion is the most predominant chance in pathological specimens [10, 11]. Other

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common adverse effects include nausea, vomiting, fever, chills, loss of appetite, and gastritis [12].

With the emergence of more sophisticated treatment planning software and methods of image guidance in the past two decades, more tightly focused treatment fields are now possible, allowing for delivery of higher doses in fewer fractions to discrete individual liver lesions, while minimizing exposure to surrounding normal liver [13–18]. Imaging techniques have also improved, allowing for precise delineation of hepatic tumors [10]. Breathing motion control and image guidance, both before and during treatment delivery, permit tumor-directed treatment with accurate localization, reducing treatment uncertainty, and decreasing the margin of error. Treatment planning techniques and machines have also improved, allowing highly conformal treatment delivery. With increased conformality, comes the potential to deliver higher doses of radiation and thereby increase local control without increasing toxicity [19, 20].

Over the past decade, multiple retrospective and prospective series [10–16] have been published on the use of conformal radiation treatment for hepatic malignancies, and results have been favorable with high rates of local control [9, 21–27]. Though many of these studies were small, and many were retrospective, they have provided ample background data to establish current prospective studies and randomized trials [10].

External beam radiation can be delivered using standard conformal (3D or intensity-modulated RT) or recently developed stereotactic (SBRT) techniques. Stereotactic body radiotherapy (SBRT), alternatively known as stereotactic ablative body radiotherapy (SABR), is a minimally invasive technique for delivering highly focused ionizing radiation with extreme precision. This technique was initially developed in neurosurgical practice and then applied to extracranial lesions. The utility of SBRT as a treatment for unresectable liver tumors was first reported in 1995 by Blomgren and colleagues [28]. Since then, there have been several additional series reporting excellent local control outcomes demonstrating low toxicity, feasibility, and efficacy [29–31].

SBRT delivers large doses of radiation in few fractions, compared with conventional fractionation, where many small doses are generally delivered in a period of weeks. Conformal RT delivers radiation from multiple planar angles, and compared with SBRT, the dose gradient is less steep and the treatment is less conformal, with a greater amount of healthy liver exposed to radiation. In contrast, SBRT can create a rapid radiation dose fall off by using multiple, noncoplanar beams or arcs, and with a coordinate system for localization targets the tumor with millimeter precision, allowing ablative radiation doses to be delivered to gross tumors while sparing adjacent tissue [10].

While SBRT is more costly and requires more intensive planning than conventional RT, this modality combines the local control benefit of dose-escalated fractionated RT with the convenience of short-course RT and an acceptable toxicity profile.

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 image (MRI) linac enables detailed evaluation of target and organ at risk motion and is able to track tumor motion. The ability to acquire real-time high resolution imaging, including functional MRI series, improves 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 [7].

As a result, SBRT has emerged as the primary technique of delivering radiation to liver tumors.

Radiobiology of External Beam Radiation

Radiation produces tumor cell kill by depositing energy within atoms, causing transformation into free radicals. This results in direct DNA damage, as well as indirect and cellular damage through generation of reactive oxygen species. Ultimately, generation of DNA double strand breaks leads to tumor cell death [10].

Conventional radiotherapy (i.e., 1.8–2.0 Gy per fraction) results in a tumoricidal effect by means of mitotic death of cancer cells, allowing recovery of late sublethal damage of normal tissues. In contrast, SBRT may provide a novel mechanism of radiation-induced damage: data with higher doses per fraction (i.e., 10–20 Gy per fraction) suggest that, in addition to direct cytotoxicity, a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill [32, 33]. Endothelial apoptosis results in microvascular disruption and death of the tissue supplied by that vasculature [34].

There is a dose–response relationship for radiation and local control outcomes. Nevertheless, as with any other medical procedure, prescription of a course of radiotherapy must represent a balance between risks and benefits. The relative position and shape of the dose–response curves for tumor control and a given radiotherapy complication determine the possibility of delivering a sufficient dose with an acceptable level of side effects.

Major developments in radiotherapy fractionation have taken place during the past three decades and these have grown out of understanding in radiation biology. The relationships between total dose and dose per fraction for late-responding tissues, acutely responding tissues, and tumors provide the basic information required to optimize radiotherapy according to the dose per fraction and number of fractions.

Historically, normal tissue effects are more greatly impacted by fraction sizes than acute effects are, which is why 1.8–2.0 Gy fractionation is considered the standard for conventional radiotherapy, resulting in longer treatment times. In fact, small doses per fraction result in a tumoricidal effect by means of mitotic death of cancer cells, allowing recovery of late sublethal damage of normal tissues at the same time. SBRT may add a novel mechanism of radiation-induced damage: at higher doses per fraction, emerging data suggest that, in addition to direct cytotoxicity, a different mechanism involving microvascular damage begins to have a substantial effect on the tumor cell kill [32, 33]. Endothelial apoptosis results in microvascular disruption and death of the tissue supplied by that vasculature [32].

Thus, even if hypofractionated irradiation may heighten the risks of late toxicity from a radiobiologic point of view, SBRT techniques substantially counteract this concern, reducing the volume of normal tissue exposed to high doses as a result of their precision [35].

As for hepatocellular carcinoma, SBRT is expected to play a role in the treatment of oligometastases from colorectal cancer (CRC). However, negative factors also exist: for example, CRC metastases contain larger proportions of hypoxic cells compared to other tumor types, and hypoxia leads to decrease in radiosensitivity; another is that microscopic extension of oligometastases from CRC may compromise local control. In fact, the local control rates of SBRT in CRC oligometastases are significantly worse than those of oligometastases from other cancers, including NSCLC. Thus, dose escalation should be considered to achieve better local control [36].

It has been proposed that one of the causative mechanisms of local failure are regions of hypoxia, particularly within large regions [37]. In colorectal cancer, tumor hypoxia has been shown to be present heterogeneously throughout resected specimens [38]. 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 [7].

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 no to cause functional compromise [39, 40]. 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 [9, 41]. 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 [7].

Patient Selection

Good selection criteria for patients with liver metastases who are candidate for SBRT remain a controversial topic. A multidisciplinary tumor board discussion is recommended before each qualification. For discussion purposes, candidates for SBRT can be divided into three categories: suitable, cautionary, and unsuitable patients [42, 43]. Selection criteria may be based on the lesion number, the lesion diameter, the distance from the organs at risk (OAR), the liver function, and the patient's conditions [44].

In general, indications for SBRT are the same as those for metastasectomy, but without the limits regarding feasibility in patients unfit for surgery. In several reports, the eligibility criteria for SBRT for oligometastatic cancer were defined as follows: a limited number of metastases (one to five), a limited tumor diameter (<4 cm), a locally controlled primary tumor, and no other metastatic sites [45]. Other specific and recently proposed selection criteria to offer SBRT to patients with various

oligometastatic tumors include: a controlled primary, favorable histology, limited metastatic disease, the metachronous appearance of metastases, young age, and a good performance status of the patient. In clinical practice, patients eligible for SBRT are essentially those for whom surgery is not feasible because of their age or performance status and because of previous treatment with multiple lines of systemic therapy, when the toxicity of local treatments should be minimized [35].

SBRT Technique

Liver SBRT can be safely and effectively delivered using either a linear accelerator (linac) or a 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 noncoplanar nonisocentric beams used and respiratory tracking of the mandatory fiducial markers [7].

Fiducial markers are utilized in many institutions to reduce uncertainty from breathing motion and allow tumor tracking [10]. At least two or more gold fiducials should be placed in the vicinity (within 6 cm) of the tumor in a non-colinear fashion by the interventional radiology team, approximately 1 week before treatment planning computer tomography (CT) [36]. Markers are placed percutaneously with image guidance under local anesthesia; it is an outpatient procedure with standard risks from introducing a needle into the liver (bleeding, infection, seeding, pain) and small risk of fiducial migration [10].

Patients are typically simulated with a custom immobilization device (i.e., Alpha Cradle). 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 concerning inter and intrafraction motion.

Intrafraction motion occurs due to the effects of respiration. The motion degree can be significant, with intrafraction liver excursion of up to 39.5 mm being reported [46]. Tumor motion is usually predominantly in a craniocaudal direction due to diaphragmatic movement. Strategies to mitigate for intrafraction motion depend on the delivery platform used. A variety of motion management techniques can be used, including abdominal compression [47], gating [48], and breath-hold techniques [49], or alternatively accounted for by the use of four-dimensional computed tomography planning. For respiratory gating or tracking, between three and five fiducial markers are inserted around the tumor to enable intrafraction tracking of tumor motion using kV–kV (kilo Voltage) imaging during treatment [7].

Daily radiotherapy patient set-up is made difficult by the fact that the position of liver tumors relative to bony anatomy has been shown to change between fractions by up to 1 cm [50]. In addition, liver tumors are often of similar density with respect to adjacent normal liver tissue, therefore making daily localization of the tumor 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 tumor position [51]. The use of fiducial markers to aid localization is an alternative solution and has been shown to improve confidence in daily tumor visualization before treatment [52].

The liver may also undergo deformation between fractions of radiotherapy. This may be due to temporal 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 tumor and normal tissues compared with that expected from treatment planning, despite using daily cone beam computed tomography for patient set-up [53]. These uncertainties in the delivered dose distribution are particularly relevant when considering dose-escalation strategies for liver tumors, as the normal tissue dose volume histograms calculates at planning may not reflect the delivered dose [7].

After fiducial placement, a pretreatment CT is obtained from radiation planning purposes; this is ideally performed with multiphasic IV contrast in exhale or inhale breath-hold position. A diagnostic MRI or CT is also utilized to define the tumor volume.

The gross volume (GTV) is contoured by the radiation oncologist in each slice of the pretreatment CT. A clinical target volume (CTV) can be added to account for microscopic extension; in many cases, there will be no CTV expansion necessary. Finally, a planning target volume (PTV) expansion is added to the GTV to account for daily setup error and internal organ motion. The size and number of lesions that can be targeted, and dose radiation that can be delivered, is dependent primarily on normal liver reserve and estimated risk of liver complication. Depending on the location, multiple tumors can be treated at the same time. Patients with poor liver function may require dose reduction to reduce the likelihood of complication [24]. Childs Pugh class is one measure of estimating normal liver function; for Childs Pugh category B, reduction in radiation dose may be a consideration. Childs Pugh C is less commonly treated to ablative doses, given poor functional reserve and high risk of toxicity.

The dose prescribed depends on baseline function and normal tissue constraints. In general, the highest allowable dose to the tumor that respects normal tissue constraints is selected.

A useful method of estimating normal liver function is the measurement of the liver effective volume (V_{eff}). In this scheme, the value of V_{eff} for each dose volume histogram is independent of dose units (Gy, %). V_{eff} is utilized as an aid in dose prescription, along with standard metrics such as the mean liver dose. For example, for a five-fraction treatment, the prescribed total dose ranges from 27.5 to 50 Gy depending on the effective liver volume [54]. At least 700 cm^3 of normal liver should receive less than 15 Gy in order to maintain a <5% risk of RILD [10].

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-estratified individualized prescription technique using a normal tissue complication probability model. This effectively allows individualization of tumor dose according to the modeled risk of RILD for each patient, a toxicity of particular concern when treating large lesions. The prescribed dose is dependent on the volume of normal liver exposed to radiation and has been previously described [40, 54]. Outcomes of using this approach in six to ten fraction regimens have reported 1 year local control rates varying from 65% to 71% [40, 55]. 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 [56].

Typically, in smaller lesions, treatment is delivered in three to six fractions, with minimum 1–3 days between each fraction. Depending on location, it is possible to target multiple tumors in a single fraction. The actual radiation treatment is less than 1 h in duration. Because it is a noninvasive and painless, no sedation or anesthesia is required [10].

Prognostic Factors Related to Local Control

Main factors to impact the local control are the target volume and the dose delivered. In most articles, a tumor volume appears as an independent factor predictive of the local control, and smaller volumes are reported to have better outcomes.

Notwithstanding, the dose delivered (and optimal fractionation) is the most important factor affecting local control. Prospective trials with dose escalation demonstrate this dose effect relation. There is a dose–response relationship for radiation and local control outcomes. A variety of dose regimens have been used, varying from single fractions of up to 30 Gy to six fraction regimens where dose is individualized according to the predicted risk of liver toxicity. Several studies have shown a dose–response, with local control improving with higher doses [25, 40, 57]. A meta-analysis concluded that a dose of 46–52 Gy in three fractions or higher is required to achieve 90% of local control at 1 year for the treatment of colorectal liver metastases, equivalent to a biologically equivalent dose ($BED_{10) >117\ Gy}$ [58]. Still, more recent studies have persuaded a dose-escalation strategy, using doses of up to 75 Gy in three fractions, reporting local control rates of 94% at 1 year [43]. It should be noted, however, that the mean gross tumor volume in this series was small at 18.7 cm^3 with 60% of lesions being ≤3 cm in size. The feasibility of delivering such high doses to larger lesions is unproven. In general, most series have included lesions up to a maximum size of 6 cm [7].

The size and number of lesions that can be targeted, and dose radiation that can be delivered, are dependent primarily on normal liver reserve and estimated risk of liver complications. For this reason, those with a longer disease-free interval and absence of chemotherapy, adenocarcinoma histology, and metachronous disease presentation seem to have better outcomes.

Clinical Outcomes

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 summarized in Table 40.1. The treatment indications are likely to expand as the evidence base for efficacy continues to grow. Interpretation of the reported survival rates is confounded by the significant variation in primary tumor histology, the volume of metastases treated with 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 [7].

Table 40.1 Summary of reported studies of stereotactic body radiotherapy for liver metastases

Study	Year	Type of study	$N°_{\text{patients}}$	Radiotherapy dose	LC	Toxicity grade ≥3
Blomgren et al. [28]	1995	R	14	8–66 Gy/1–4	80% (24 mos)	14%
Herfarth et al. [62]	2004	Phase I/II	56	14–16 Gy/1	67% (18 mos)	NMT
Schefter et al. [64]	2005	R	18	36–60 Gy/3	NR	NMT
Wulf et al. [63]	2006	R	44	30 Gy/3	61% (24 mos)	NMT
Kavanagh et al. [64]	2006	Phase I/II	36	36–6-Gy/3	93% (18 mos)	NMT
Mendez Romero et al. [24]	2006	Phase I/II	45	37.5 Gy/3	82% (24 mos)	11,8%
Hoyer et al. [39]	2006	Phase II	44	45 Gy/3	86% (24 mos)	6,6%
Katz et al. [64]	2007	R	69	30 Gy/7	57% (20 mos)	NMT
Milano et al. [56]	2008	R	293	50 Gy/5	67% (24 mos)	NMT
Rusthoven et al. [9]	2009	Phase I/II	63	60 Gy/3	92% (24 mos)	2%
Lee et al. [40]	2009	Phase I	68	28–60 Gy/3	71% (12 mos)	NMT
Ambrosino et al. [41]	2009	R	27	25–60 Gy/3	74% (12 mos)	NR
Van de Pool et al. [65]	2010	R	20	37.5–45/3	74% (24 mos)	NMT
Goodman et al. [66]	2010	Phase I	40	18–20 Gy/1	49.4% (24 mos)	NMT
Vautravers Dewas et al. [67]	2011	R	42	40 Gy/3	86% (12 mos)	NMT
Rule et al. [25]	2011	Phase I	37	30–60 Gy/3–5	89% (24 mos)	NMT
Scorsetti et al. [43]	2013	Phase II	61	52.5–75/3	94% (12 mos)	NMT
Yuan et al. [68]	2014	R	57	39–54 Gy/3–7	89.7% (24 mos)	NMT

R retrospective, *LC* local control, *mos* months, *NR* not reported, *OS* overall survival, *NMT* no major toxicity

Higher SBRT doses ($BED_{10} \geq 100$ Gy) and smaller tumor volumes ($\leq 40\ cm^3$) are associated with improved local control and overall survival [18].

Long-term results with SBRT have also shown low toxicity (grade 3 <5%) and long survivals (3 years OS 44%) [71]. Although most of the studies have treated limited number of liver metastases (one to three lesions), patients with multiple liver metastases could be treated safely and benefit from sequential SBRT with high LC (80.6% and 65% at 2 and 4 years) and prolonged survivals (5 year OS of 57.6%) [72].

A further exciting avenue for SBRT research is the discovery that delivering radiation doses within the ablative range seems to enhance antitumor 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 [59, 60]. This has stimulated research interest into the potential for combining SBRT with immunotherapy in oligometastatic disease, in order to therapeutically exploit this immune response [7, 61].

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, the 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 complementary information if the lesion cannot be reliably visualized on computed tomography. However, accurately determining the treatment response using a standard response evaluation criteria in solid tumors (RECIST) alone can be difficult. A phenomenon of pseudoprogression 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. 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 [7].

Toxicity

Respecting individual target volumes and dosing schemes, toxicity rates can be minimized, even for larger volumes. In contrast to primary liver cancer, liver metastases most commonly occur in noncirrhotic livers, and the most predominant toxicity to radiation will be RILD. However, adhering to established dose constraints of normal liver tissue, i.e., keeping below 30 Gy median liver dose in conventional

fractionation [62] or application of less than 15 Gy to 700 mL of healthy liver tissue, this may be securely avoided [62].

SBRT in liver metastases is a very well-tolerated treatment, with a low toxicity profile and severe toxicity is exceptional. Most series have reported low rates of treatment-related toxicity, with rates of common terminology criteria for adverse effects (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 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 of liver metastases treated with SBRT have reported rates of RILD <1% [63].

Conclusions

Historically, conventional radiation therapy has played a limited role in the treatment of liver metastases because of the risk of liver toxicity induced by high doses delivered to normal liver tissue. However, recent technological advances have contributed to the development of SBRT as a precise tightly focused radiation technique that allows the treatment of hepatic metastases with an ablative intent, in few fractions, while significantly limiting dose to the healthy liver and surrounding tissues.

Liver SBRT requires the integration of imaging, in order to properly define the metastases, highly conformed dosimetry to further minimize radiation dose in healthy tissues, and intrafraction control of the liver motion, with image guided systems, to deliver the dose to the metastases with accuracy.

The safety and effectiveness of SBRT has been evaluated with encouraging results in retrospective and prospective clinical studies. Reports of SBRT for primary and metastatic liver disease have been steadily increasing since 2006 and results have been associated with minimal toxicity and high local control rates, most in the range of 70–90% at 1–2 years. As a result of these advances, radiation is being re-explored as a treatment modality for both primary and metastatic liver tumors. SBRT offers an alternative, noninvasive approach, to the treatment of limited hepatic metastases in inoperable patients, or with unresectable metastases with fewest local therapeutic options, and the role of SBRT for the treatment of these patients should therefore be kept in mind in interdisciplinary treatment decisions.

Further clinical evaluation, preferentially in randomized settings comparing to surgery of other locally ablative techniques will further elucidate the full potential of SBRT in patients with liver metastases, especially in the subgroup of oligometastatic patients.

Considering the high propensity for distant progression in these patients, the combination of novel drugs and SBRT needs to be deeply explored with prospective trials in order to improve the overall survival of these patients.

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