REVIEW

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Rationale for ablation of oligometastatic disease and the role of stereotactic body radiation therapy for hepatic metastases

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Practice Points

- The term oligometastases refers to an intermediate, potentially curative state between the total absence of metastatic disease and widespread dissemination.
- Rationale for oligometastatic ablation may include the phenomenological justification, the patterns-of-failure concept, oligometastases as a potentially-curative state, the Norton–Simon hypothesis, the oligoprogressive state and immunomodulation.
- Hepatic resection for colorectal liver metastases is associated with dramatic survival improvements over historic controls.
- Approximately 80% of patients with colorectal liver metastases are considered unresectable due to technical and comorbid health considerations.
- Stereotactic body radiation therapy (SBRT) is a noninvasive approach for the precise delivery of ablative, high-dose radiation, typically given in one to five total treatments.
- Multiple prospective Phase I and II trials have evaluated the use of SBRT for hepatic metastases.
- Significant toxicity (grade 3 or higher) following SBRT is reported in <5% of patients.
- Local control rates following hepatic SBRT are 70–100% overall at 1–2 years, but may be consistently >90% with adequate radiation dosing.
- Randomized trials evaluating the ablation of colorectal liver metastases using SBRT and other local therapies are currently underway.

SUMMARY Management paradigms for metastatic solid tumors are evolving. Once regarded as uniformly incurable, today there is recognition of an intermediate oligometastatic state, where ablation of metastatic foci may improve disease control and prolong survival. In the setting of limited colorectal liver metastases, hepatic resection has resulted in favorable long-term outcomes, but is technically unsuitable for most patients. Stereotactic body radiation therapy represents an effective, noninvasive means of tumor ablation, supported by a large body of prospective evidence specific to hepatic metastases. This review examines

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the current rationale for ablation of oligometastatic disease, including various objectives beyond indefinite disease-free survival. The role of stereotactic body radiation therapy for ablation of hepatic metastases is then comprehensively reviewed.

Traditionally metastatic disease arising from solid tumors has been regarded as an incurable state where only systemic therapies and palliative interventions are considered appropriate. Not surprisingly, this paradigm has often engendered a sense of futility in the face of metastases among patients and physicians alike. More recently, there has been growing interest in identifying subgroups of patients where local therapies designed to ablate limited metastatic foci (via interventions such as surgery, radiotherapy and thermal ablation) may improve disease control and even prolong survival.

Early concepts regarding the nature of metastases were influenced by Halsted's description in 1907, wherein breast cancer was thought to proceed in a stepwise, temporal progression from primary site, to regional lymphatics and, ultimately, to disseminated disease [1]. This theory elevated the importance of the timely application of local therapy before the malignant horse had methodically made its way out of the gate. However, the conceptual futility of local interventions was quickly encountered at the first sign of distant disease, no matter how small a burden. More nihilistic views were later proffered in the form of a systemic theory, which suggested that malignancies destined to become disseminated will have done so prior to clinical presentation and irrespective of local interventions [2]. In the 1990s, a pair of enterprising radiation oncologists, Hellman and Weichselbaum, offered a third theory describing metastatic disease as a spectrum that included an intermediate state, termed oligometastases [3]. This theory suggested that oligometastatic patients, conventionally and perhaps arbitrarily harboring no more than five or six sites of distant disease, may even be cured if all foci were addressed with local ablation.

Hepatic resection for colorectal liver metastases

Whether pioneering, quixotic or heretical, the concept of oligometastatic ablation found early support within the burgeoning literature of hepatic resection for colorectal liver metastases (CLM) [4]. Overall, series of hepatic resection have demonstrated 5- and 10-year overall survival (OS) rates in the range of 30–60% and

20–25%, respectively, as compared with historic series of unresected CLM with 5-year OS rates of 0–5% (Table 1) [5]. Fong *et al.* characterized favorable prognostic factors for 1001 patients undergoing resection of CLM, including the absence of extrahepatic disease, metachronous presentations with extended disease-free intervals (DFIs) >12 months, single metastases <5 cm, early-stage primary tumors, low carcinoembryonic antigen, and negative hepatic surgical margins (R0) [6]. More recently, Tomlinson *et al.* reported a 99% long-term cancer-specific survival in 102 patients with CLM surviving ≥10 years after resection, suggesting the achievement of cure in this subset [7]. Today, the National Comprehensive Cancer Network guidelines recommend hepatic resection as a component of first-line therapy for patients with resectable, liver-confined, synchronous and metachronous CLM [101].

Despite widespread recognition of consistently favorable outcomes following hepatic resection of CLM, uniform application is limited by the surgical fitness of patient candidates and the paradigms of resectability, including planned R0 resections, preservation of at least two adjacent liver segments with vascular inflow/outflow and biliary drainage, and adequate postresection liver volumes [8]. Presently, it is estimated that 80% of patients with CLM are deemed unresectable at diagnosis and only 10–30% can be converted to a resectable state with chemotherapy [9,10]. As such, noninvasive alternatives are necessary for the treatment of patients who stand to benefit from locally ablative therapy, but for whom hepatic resection will never be possible.

Stereotactic body radiation therapy for noninvasive tumor ablation

Stereotactic body radiation therapy (SBRT), also termed stereotactic ablative radiotherapy or extracranial radiosurgery, has emerged as a highly effective, safe and entirely noninvasive means of tumor ablation supported by a large body of evidence specific to hepatic metastases. In contrast to conventionally fractionated radiation, which delivers daily low-dose fractions (1.5–3.0 Gy) to larger anatomic regions over 1 to several weeks, SBRT entails precise delivery of high-dose fractions (typically ≥8 Gy) with one

to five total treatments over an elapsed time of 1–2 weeks, and is intended for complete tumor ablation with maximal normal-tissue sparing [11,12]. Termed ‘stereotactic’, in reference to 3D target localization, in reality SBRT refers to an array of concepts including the radiobiologic advantage of high-dose fractions, conformal and compact dose distributions, image guidance, patient immobilization and rigorous motion control. Since the early applications of high-dose extracranial radiation in the mid-1990s, one of the greatest assets to the rapid clinical adoption of SBRT for liver metastases has been the multitude of prospectively designed Phase I and II clinical trials examining its use.

In this review, the authors examine the current rationale for the ablation of oligometastatic disease in the liver and other sites, with an intended clinical emphasis on CLM, including various paradigms beyond a strictly curative-intent approach. The history, outcomes and clinical considerations associated with the use of SBRT for hepatic metastases are then comprehensively reviewed.

Rationale for oligometastatic ablation with SBRT

■ Current paradigms

Today, SBRT is paradoxically applied to malignancies on opposing ends of the oncologic spectrum. Elegantly suited for the eradication of early-stage cancers devoid of regional lymphatic involvement, SBRT has resulted in local tumor control rates >97% in stage I non-small-cell lung cancer [13], establishing a new standard of care for medically inoperable patients [102]. Here, only modest justification is required in defending the attendant time, costs and potential risks of a curative-intent therapy. By contrast, the use of SBRT for oligometastatic ablation requires a more careful evaluation.

Kavanagh and Timmerman previously described four categories of potential justifications for SBRT in the setting of limited metastases, listed in order of increasing complexity, including the phenomenological justification; the patterns-of-failure concept; the theory of oligometastases as an intermediate and potentially-curative state; and the Norton–Simon hypothesis [14]. In the time since this report, emerging data have provided additional rationale for the use of SBRT, which we believe merit discussion, including the oligoprogressive state and the impact of immunomodulation. These

Table 1. Selected series of hepatic resection for colorectal liver metastases.

Study (year)	Patients (n)	Operative mortality (%)	Median OS (months)	5-year OS (%)	10-year OS (%)	Ref.
Fong <i>et al.</i> (1999)	1001	2.8	42	37	22	[6]
Pawlik <i>et al.</i> (2005)	557	0.9	74	58	NR	[83]
Wei <i>et al.</i> (2006)	423	1.6	53	47	28	[84]
Shah <i>et al.</i> (2007)	841	3	48	43	NR	[85]
Malik <i>et al.</i> (2007)	687	3	50	45	NR	[86]
Rees <i>et al.</i> (2008) [†]	929	1.5	25	36	23	[87]
Kanemitsu and Kato (2008)	578	NR	41	39	NR	[88]
de Jong <i>et al.</i> (2009)	1506	NR	36	47	NR	[89]
Nathan <i>et al.</i> (2010)	949	0.9	52	45	22	[90]
Farid <i>et al.</i> (2010)	705	3.5	NR	34	NR	[91]

[†]Reported a 5- and 10-year cancer-specific survival.
NR: Not reported; OS: Overall survival.

concepts, which may have considerable overlap, are briefly reviewed here and summarized in [Table 2](#).

The phenomenological justification is considered to be the most straightforward rationale. To date, there is a body of level-one evidence indicating prolonged survival following ablation of solitary brain metastases [15,16]. While there are no reported randomized trials comparing resection of extracranial metastases with no resection, it has been consistently observed that patients undergoing hepatic resection for limited CLM can achieve dramatic survival improvements over historic controls. SBRT may be considered an attractive alternative to surgery with the potential for improved therapeutic ratio by demonstrating equivalent outcomes with inherently noninvasive techniques, as has been reported in the lung and further reviewed here in the setting of hepatic metastases [17].

The patterns-of-failure rationale draws parallels to established management strategies for aggressive lymphomas. For example, in early-stage Hodgkin lymphoma, several cycles of upfront chemotherapy are given, which may then be followed by consolidative radiation to the pre-chemotherapy involved nodal regions, as these

Table 2. Summary of current rationale for oligometastatic ablation using stereotactic body radiation therapy (with clinical emphasis on colorectal liver metastases).

Rationale	Summary	Ref.
Phenomenological rationale	Surgical ablation of CLM is associated with dramatic survival improvements over historic controls Noninvasive SBRT ablation may provide similar benefits with a potential for an improved therapeutic ratio and broader patient candidacy	[4,14,17]
Patterns-of-failure concept	Approximately two-thirds of initial failures following systemic therapy for advanced solid tumors will occur at sites of known metastatic disease. Consolidative local ablation to these sites might provide reliable improvements in PFS	[18–20]
Norton–Simon hypothesis	The Norton–Simon hypothesis suggests that tumor growth obeying Gompertzian kinetics will follow a sigmoid distribution from a starting point below detectable levels through a phase of exponential growth and on to a plateau of inevitable lethality. This hypothesis implies that ablation of metastatic foci may: 1) facilitate re-entry into a phase of exponential cellular division and, therefore, enhanced sensitivity to cytotoxic chemotherapy; or 2) provide a noninvasive means to prevent or delay the development of a lethal tumor burden	[24–26]
Curative-potential of oligometastases	The preferential hepatic spread of mCRC and ostensible cures following hepatic resection are well documented. It has been suggested that isolated CLM may, at times, represent an intermediate echelon occurring prior the acquisition of widespread metastatic potential	[7,22,23]
Oligoprogressive state	In the setting of limited disease progression, SBRT may be used as a component of a multidisciplinary strategy to delay the initiation of systemic therapy; bridge between changes in systemic therapies; or prolong access to systemic agents that are continuing to provide a clinical benefit	[30,31]
Immunomodulatory model	Tumor-directed radiation can promote CD8 ⁺ T-cell-dependent cytotoxicity at both the treated tumor, as well as untreated distant metastases, with the latter phenomenon termed the abscopal effect. High-dose radiation (SBRT), in particular, may lead to enhanced immune priming. Strategies to harness these systemic anti-tumor effects with coadministration of immunologic therapies are actively being investigated	[35–37]

CLM: Colorectal liver metastases; mCRC: Metastatic colorectal cancer; PFS: Progression-free survival; SBRT: Stereotactic body radiation therapy.

areas represent the greatest risk for persistent or recurrent disease [103]. In the setting of metastatic non-small-cell lung cancer, patterns-of-failure analyses have demonstrated that sites of disease identified prior to chemotherapy administration will constitute approximately two-thirds of initial recurrences [18,19]. Similarly, Benoist *et al.* reported a 74% local recurrence rate at 1 year for unresected CLM following an initial radiographic complete response to chemotherapy [20]. Locally ablative techniques, including SBRT, would be expected to provide reliable improvements in progression-free survival (PFS) if metastatic foci were consolidated following effective systemic therapy.

The term oligometastases denotes an intermediate, potentially curative state between the total absence of metastases and widespread dissemination. Arguably, the most empirical evidence for this theory is found in the vast literature of ostensible cures of metastatic colorectal cancer (mCRC), albeit in a minority of patients, following local ablation of hepatic metastases [7]. Both clinical and autopsy studies have extensively characterized the preferential hepatic spread of mCRC, where approximately 25% of patients will present with synchronous hepatic metastases at diagnosis and an additional 50%

may ultimately develop metachronous liver disease [21]. Conversely, isolated nonliver metastases are observed in only 15–30% of mCRC patients [22]. This phenomenon is explained in part by the drainage of the portal circulation and extensions of the ‘seed and soil’ theory of organ-specific metastatic potential [23]. It has been suggested that isolated CLM may, at times, represent an intermediary metastatic echelon occurring prior to the acquisition of widespread metastatic potential [22,23]. If this were the case, then ablation of the primary tumor and all hepatic metastases in appropriately selected patients may indeed be curative.

The Norton–Simon hypothesis suggests that tumor growth obeys Gompertzian kinetics, whereby the total burden of cancer over time will follow a sigmoid distribution from a starting point beneath detectable levels, through a phase of exponential cellular division and on toward a plateau level that is invariably lethal to the host [24]. In this scenario, tumor cells will have the highest mitotic activity and, therefore, greatest sensitivity to chemotherapy during exponential regrowth immediately following SBRT or any other means of tumor ‘debulking’. This theory has notably served as rationale for the successes of adjuvant dose–dense chemotherapy in breast

cancer [25]. Similarly, although more controversial, this reasoning would also suggest that not all sites of identifiable disease would require local ablation to improve subsequent chemosensitivity. A second and distinct application of the Norton–Simon hypothesis is the recognition of SBRT as a noninvasive therapy, capable of eradicating large volumes of gross disease, with the ability to prevent or delay the development of a lethal tumor burden [26].

The term oligoprogression implies the emergence of limited metastatic foci after some period of disease control. Local ablation of oligoprogressive disease may represent an attractive multidisciplinary strategy to delay the initiation of systemic therapy, to bridge patients between changes in systemic agents or to allow extended access to well-tolerated systemic agents that are continuing to provide clinical benefit. The latter concept has recently been evaluated in the setting of metastatic non-small-cell lung cancer, where tumors molecularly driven by *EGFR* mutations, and *ALK* gene rearrangements may exhibit excellent responses to well-tolerated oral tyrosine kinase inhibitors [27,28]. Invariably, however, foci of acquired treatment resistance will emerge even in the setting of otherwise well-controlled systemic disease [29]. In a study evaluating the impact of local ablation for treatment-resistant foci, investigators from the University of Colorado (CO, USA) reported a median PFS extension of 6.2 months following ablative therapy and continuation of tyrosine kinase inhibitor treatment [30]. Similarly, Yu *et al.* reported a median PFS extension of 10 months following local ablation and a median time to subsequent change in systemic therapy of 22 months [31]. As more effective targeted therapies for mCRC emerge, comparable applications of local ablation in the liver and other sites may allow extended access to well-tolerated agents in the setting of oligoprogression [32,33].

In addition to classically described mechanisms of DNA damage, radiotherapy promotes immune-mediated anti-tumor effects through highly dynamic processes involving the upregulation of proinflammatory cytokines, release of damage-associated molecular patterns, dendritic cell maturation, enhanced antigen presentation and phenotypic alterations in tumor cell surface antigens [34]. Overall, these processes are felt to converge on cytotoxic T-cell-dependent immune recognition and tumor destruction. High-dose radiation, in particular, may promote enhanced

priming and cytotoxicity of CD8⁺ T cells at both the treated tumor, as well as untreated distant metastases [35,36], with the latter phenomenon being termed the abscopal effect. The clinical implications of the abscopal effect (historically described in cases of melanoma, lymphoma, renal cell carcinoma, hepatocellular carcinoma and some adenocarcinomas) are far ranging, although therapeutically significant results are rarely achieved with the use of radiation alone [35]. As such, there is increasing interest in harnessing the immune-priming effects of radiation with coadministration of immunomodulatory therapies [35,37]. Applications of SBRT in this capacity represent an evolving frontier in the field of immuno-oncology.

■ Oligometastases: a spectrum within a spectrum

Even among patients with the most limited burden of discernible metastatic foci, there remains considerable heterogeneity in the domains of subclinical disease burden and prognoses. Christoduoleas and Marks suggested that oligometastases may be appropriately divided into three separate entities, including patients with first, *de novo* (synchronous) oligometastases identified at the time of diagnosis; second, recurrent (metachronous) oligometastases following local treatment of the primary tumor; and third, induced oligometastases in patients initially presenting with disseminated disease who then achieve a significant response to systemic therapy [38]. Improved outcomes among patients with metachronous disease and prolonged DFI are well documented in the setting of local ablation [6]. Using mathematical modeling, Withers and Lee hypothesized that a prolonged DFI may correspond to the probability of a truly oligometastatic distribution, whereas those with synchronous lesions are far more likely to harbor subclinical metastases, only requiring further doubling times to become apparent [39]. A state of induced oligometastases represents a double-edged sword for the consideration of local ablation, indicating advanced metastatic potential and a greater likelihood for subclinical disease, while in the favorable setting of treatment-responsive tumor biology.

Role of SBRT for hepatic metastases

■ Evolution of liver irradiation

For over half a century, whole-liver radiation therapy has been used for the palliation

of diffuse symptomatic liver metastases [40]. Prospective studies dating back to the 1970s found whole-liver radiation therapy useful in alleviating pain from capsular irritation and other sequela of metastatic hepatomegaly [41]. However, durable tumor control was limited by the sensitivity of the liver to whole-organ radiotherapy. Ingold *et al.* characterized the dose-limiting toxicity, today known as radiation-induced liver disease (RILD), involving hepatomegaly, anicteric ascites, weight gain and elevations in alkaline phosphatase occurring between 2 weeks and 3 months following treatment [42]. With the advent of 3D conformal radiation allowing for partial liver therapy, investigators from the University of Michigan (MI, USA) performed a number of tumor-directed dose-escalation studies, with the simultaneous goals of improving normal tissue sparing and disease control. Dawson *et al.* safely escalated peak tumor doses as high as 70–90 Gy in conventional fraction and observed no incidences of RILD on sequential dose-escalation studies when the mean liver doses were kept below 31 Gy [43,44]. Despite improvements in tolerance, disease control and even survival, in-field progression rates remained suboptimal at >50% at 1–2 years. Ultimately, new strategies would be required if sustained control of hepatic metastases were to be achieved using radiotherapy.

■ High-dose per fraction SBRT

Clinical investigation into the use of high-dose per fraction radiation to extracranial targets (today known as SBRT) had begun by the mid-1990s [45,46]. High-dose fractions were radiobiologically attractive for their ability to provide significantly enhanced tumor cell kill when compared with the same total dose delivered in smaller consecutive treatments. Interestingly, high-dose radiation to intracranial targets, termed stereotactic radiosurgery, had been introduced in the 1950s [47]. The fore-running stereotactic radiosurgery had been possible much earlier due to the relative ease of cranial immobilization, near-absence of internal organ motion and patient tolerance for ablation of noneloquent parenchyma (akin to traditional neurosurgery). For the safe application of extracranial SBRT, dramatic technical improvements were necessary to ensure reproducible patient positioning; rigorous internal motion control; stereotactic target registration; minimization of normal tissue exposure; and ablative

dose-fraction delivery with subcentimeter accuracy [48]. Similar to the concepts of liver and lung resection, tolerance of SBRT would rely heavily on the parallel architecture of these target organs, where multiple functional subunits could be ablated without compromise of global organ function (as opposed to serially-arranged organs e.g., the spinal cord or gastrointestinal ([GI] tract) [49]. Practice guidelines defining current standards for SBRT delivery and comprehensive reviews regarding the nuanced radiobiology of high-dose fractions have been reported [12,50]. Although it is beyond the scope of this discussion, targeted radiotherapy strategies outside of SBRT, such as selective internal radiation therapy and image-guided brachytherapy, have also been reviewed previously [51,52].

In 1995, investigators from Stockholm published the earliest clinical experience using SBRT for the treatment of liver tumors [45]. Although the number of patients treated with SBRT to hepatic metastases since that time is relatively modest in comparison to the vast literature of hepatic resection, a much larger percentage of reported experiences with SBRT have involved prospective Phase I and II trials [53–60]. The clinical implications of this point are substantial, as prospective designs offer pre-specified patient selection, uniform treatment delivery, strict ongoing follow-up, targeted end point evaluation, peer-reviewed scrutiny, and a higher likelihood of publication, whether experiences are considered positive or negative. As such, the clinical knowledge imparted by these efforts has allowed considerable application even in the setting of relatively smaller patient numbers.

■ Patient selection

Selection criteria on prospective trials of SBRT for hepatic metastasis have shared a number of commonalities. In a practical sense, pretreatment evaluations are useful in defining characteristics of patients who are technically eligible to be safely treated with liver-directed SBRT and are most likely to benefit from aggressive hepatic therapy. For eligibility, clinical trials have generally included patients with one to five liver metastases with individual lesions <6 cm [53,59,60]. In reality, the exact number and size of metastases are probably less important than the deliberate sparing of adequate normal liver parenchyma (discussed below), although these features are likely to be correlated in most patients. Cirrhotic

livers are known to be less tolerant of SBRT [61] and studies have generally excluded patients meeting Child–Pugh B and C classifications or their equivalents [53,57–60]. Fortunately, in contrast to hepatocellular carcinoma, the majority of patients with hepatic metastases do not have underlying cirrhosis [62]. While most lesions treated have been secondary to mCRC, experience with metastases from virtually all primary sites and histologies have been reported. Prior systemic therapy has been reported in 50–90% of patients on prospective trials and does not preclude eligibility, even among the most heavily pretreated candidates [55,56,58–60]. Patients with prior hepatic resections or other liver-directed therapies, reported in 15–45% of cases, may also receive SBRT, provided adequate normal liver volumes can be spared [55,56,58–60].

In the context of clinical trials, eligibility has primarily been restricted to patients with unresectable disease or those refusing surgery. As this may suggest, noninvasive SBRT is suitable for a larger cross-section of metastatic patients due to both technical and general health considerations. In contrast to hepatic resection and radiofrequency ablation (RFA), the safety and efficacy of SBRT are not limited by the regional architecture of the hepatic blood supply or conditions of multisegmental liver involvement [8,63]. Subcapsular tumors, lesions near the hepatic hilum, and those in proximity to the luminal GI tract require dosimetric consideration, but may also be safely treated when contemporary normal tissue constraints are observed (Figure 1) [64].

Overall, the characteristics of patients most likely to benefit from local ablation with SBRT closely approximate features reported in series of hepatic resection. These characteristics broadly include younger age, normal baseline liver function, good performance status, controlled primary tumors, absence of extrahepatic disease, metachronous presentations with prolonged DFI, limited prior therapies and small, solitary hepatic tumors.

■ Safety & tolerability

Significant toxicities following SBRT for hepatic metastases are uncommon with grade 3 or higher complications observed in <5%. The incidence of major events also appears to be declining across reports. Among 114 total patients treated with SBRT on three prospective trials specific to hepatic metastases since 2010, only one incidence of grade 3 toxicity (chest wall [CW] pain) has

been observed [53,58,60]. This fact is largely attributable to the improved understanding of normal-tissue constraints gained from the rigorous reporting of earlier SBRT experiences. Overall, the most relevant normal tissues at risk include the uninvolved normal liver parenchyma, the luminal GI tract, and the neighboring CW [62].

Isolated cases of RILD have been reported following SBRT for hepatic metastases, primarily within early clinical studies. In a Phase II study reported by Hoyer and colleagues, including 44 patients with CLM, one patient developed hepatic failure and death 7 weeks after treatment, although the exact cause was uncertain [55]. In separate Phase I/II trials, two cases of grade 3 nonclassic RILD were reported among 17 patients undergoing SBRT for hepatic metastases [57]. Following these initial reports, the now widely adopted ‘critical volume’ model for normal liver sparing was introduced by Schefter and colleagues, who safely escalated doses as high as 60 Gy in three fractions with no incidences of RILD [65]. Conceptually, these investigators extrapolated principles from the hepatic resection literature where it has been

Figure 1. Axial and coronal computed tomography images from a representative stereotactic body radiation therapy plan. Depicted is a nongated (free breathing) radiation planning computed tomography image, without intravenous contrast. The stereotactic body radiation therapy target is a large, inoperable hilar liver metastasis (4.2 × 4.1 × 3.8 cm) treated with stereotactic body radiation therapy to a total dose of 50 Gy delivered in five fractions (10 Gy per fraction). The central dark red contour corresponds to the 125% prescription isodose line (62.5 Gy) representing an intended radiation ‘hot spot’ within the tumor’s more resistant, hypoxic center. The middle light red contour corresponds to the 100% isodose line (50 Gy) and conforms tightly to the tumor planning target volume outlined in black. The outer yellow contour corresponds to the 60% isodose line (30 Gy) demonstrating rapid 3D dose attenuation. This stereotactic body radiation therapy plan was delivered using a volumetric modulated arc therapy technique. The axial path of the gantry head is represented by the purple arc and degree positions.

demonstrated that as much as 80% of the normal liver can be safely resected without inducing hepatic failure [66]. Assuming an average liver volume of 2000 ml, the deliberate sparing of a critical volume of 700 ml (below a threshold dose of 15 Gy in three fractions) would conservatively ensure the preservation of 35% uncompromised liver volume. Ensuing trials have adopted this approach with adjustments for total fraction number, and have similarly avoided any incidences of RILD [53,58,60]. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) has also advocated this model as well as the proposed mean liver-dose thresholds of 15 Gy in three fractions and 20 Gy in a six-fraction regimen [61].

Significant GI toxicities have also been reported in a limited number of cases and appear to be largely avoidable when consideration is given to modern dose constraints. In the trial reported by Hoyer *et al.*, one colonic perforation (requiring surgery) and two duodenal ulcers (treated conservatively) were reported, all in the context for luminal GI doses >30 Gy in three fractions [55]. Lee *et al.* reported two incidences of grade 3 gastritis/esophagitis among 68 patients treated on a Phase I dose-escalation trial [56]. Subsequently, four prospective trials with accordingly conservative GI dose constraints have been reported with no incidences of grade 3 or higher GI complications [53,58–60]. Milder grade 2 GI ulcers have also been reported infrequently with treatments near the hepatic hilum in the setting of radiobiologically aggressive dose fractions [53], underscoring the importance of conservative techniques when treating this region.

CW toxicities including pain, rib fracture and soft-tissue complications, are additional dose-dependent toxicities that may be seen in a minority of patients. In a Phase I/II trial totaling 47 patients, the only reported grade 3 toxicity involved a soft-tissue breakdown in the setting of >48 Gy in three fractions to the affected area [59]. Nontraumatic rib fractures were reported by Lee and colleagues in two patients (3%) at 6 and 23 months post-SBRT with CW doses of 52 and 66 Gy in six fractions, respectively [56]. Currently, the most widely reported metric for predicting CW toxicity assesses the volume of CW receiving >30 Gy (V30). In a multicenter pooled analysis, Dunlap *et al.* reported a 30% risk of significant pain or rib fracture when the V30 was >35 cm³,

and no incidences with a V30 less than 30 cm³ (median three fraction course, range: 3–5) [67]. In addition, a number of transient grade 1 and 2 toxicities have been reported with variable incidences, including fatigue (10–65%), nausea (15–40%), abdominal pain (5–40%), mild transaminitis (20–30%), diarrhea (0–25%) and skin erythema or ulceration (0–10%) [53,55,56,60]. These acute symptoms are generally self-limited and tend to resolve within days to weeks following treatment.

Outcomes

Herfarth *et al.* reported the first Phase I/II trial involving a dose escalation from 14 to 26 Gy in a single fraction [54]. A total of 37 patients were enrolled and 60 total lesions were treated, including four primary liver tumors and 56 metastases (30 mCRC, 14 breast, four lung and four sarcoma). At 18 months, the actuarial local control (LC) rate for the entire group was 67%. Their experience was particularly instructive regarding the SBRT dose–response relationship, as patients treated with >20 Gy achieved a LC rate of 81%. These same investigators went on to describe the time-dependent multiphasic liver computed tomography findings following SBRT, involving an enlarging hypodensity observed within the high-dose region that resolves several months after treatment [68].

Following the pilot experience by Herfarth and colleagues, a number of prospective clinical trials have been conducted (Table 3). Tumor control rates and toxicity profiles, though encouraging even among the earliest reports, have continued to improve in contemporary studies. Investigators from the University of Colorado reported on the first North American multi-institutional Phase I/II experience including 47 patients with 63 hepatic lesions. Patients were treated with doses starting at 36 Gy and escalated in 6-Gy increments to a predetermined maximum dose of 60 Gy in three fractions [59]. No incidences of RILD or dose-limiting toxicities were observed and the actuarial 1- and 2-year LC rates were 95 and 92%, respectively. Investigators from Stanford University (CA, USA) subsequently demonstrated the feasibility of a high-dose single fraction regimen by safely escalating doses from 18 to 30 Gy, and achieving a 1-year LC of 77% with no RILD or incidences of grade 3 or higher toxicity [53]. Researchers from the University of Texas Southwestern (TX, USA)

published their single institution Phase I trial of 27 patients, where doses were escalated from 30 Gy in three fractions, to 50 Gy in five fractions, and ultimately to 60 Gy in five fractions [58]. The 2-year LC rates for the 30 Gy, 50 Gy and 60 Gy dose levels were 56, 89 and 100%, respectively, with no incidences of RILD, dose-limiting toxicities or grade 3 toxicities observed. Most recently, an Italian group reported the results of a Phase II study involving 61 patients treated with 52.5–75 Gy in three fractions, prescribed as a mean dose to the planning target volume [60]. At 12 and 22 months the actuarial LC rates were 94 and 91%, respectively, with no incidences of RILD.

A variety of SBRT dose-fractionation schedules have been prospectively investigated, ranging from one to six total fractions, generally delivering 10–30 Gy per fraction, to total doses

of 18–75 Gy. Overall, the actuarial LC rates following hepatic SBRT range from 70 to 100% at 1–2 years. The best results have been achieved using contemporary three- and five-fraction regimens to total doses ≥ 50 Gy, where the actuarial 2-year LC rates have been 89–100% [58–60]. More protracted ablative fractionation schedules (technically beyond the one- to five-fraction SBRT parameters) have also been used, which may be described under the broader heading of hypofractionated, image-guided radiotherapy (HIGRT) [69]. Notably, investigators from the University of Rochester (NY, USA) prospectively reported encouraging 2-year actuarial LC rates of 74–87% primarily using a radiobiologically more conservative regimen of 50 Gy delivered in ten total fractions to tumors in liver, lung and mediastinum [70]. Their experience was also instructive in demonstrating that local

Table 3. Prospective Phase I and II studies of stereotactic body radiation therapy for hepatic metastases.

Study (year), type	Pts [†]	Histology by patient	Eligibility	Total dose (fractions)	Median (F/U)	Actuarial local control (%)	Toxicity	Ref.
Herfarth <i>et al.</i> (2001), Phase I/II	37	33 mets Four PHT	1–3 mets <6 cm	14–26 Gy (1 Fx) [‡]	6 mo	18 mo: 67 (overall) 18 mo: 81 (≥ 20 Gy)	No RILD No significant toxicity observed	[54]
Mendez Romero <i>et al.</i> (2006), Phase I/II	17 [§]	14 CRC Three other	1–3 mets <7 cm	30–37.5 Gy (3 Fx) [¶]	13 mo	12 mo: 100 24 mo: 86	Two grade 3 transaminitis (11%) One grade 3 asthenia (6%), one grade 3 melena (6%) No grade 4 or 5 toxicity	[57]
Hoyer <i>et al.</i> (2006), Phase II	44 [#]	CRC only	Any number <6 cm	45 Gy (3 Fx) [¶]	52 mo	24 mo: 79	Three gastrointestinal ulcers (all with intestinal max dose >30 Gy) One grade 5 HF (cause uncertain)	[55]
Rusthoven <i>et al.</i> (2009), Phase I/II	47	15 CRC 30 other Two PHT	1–3 mets <6 cm	36–60 Gy (3 Fx) [¶]	16 mo	12 mo: 95 24 mo: 92	No RILD One grade 3 soft tissue toxicity (2%) No grade 4 or 5 toxicity	[59]
Lee <i>et al.</i> (2009), Phase I	68	40 CRC 28 other	Any number Any size	27.7–60 Gy (6 Fx) [¶]	11 mo	12 mo: 71	No RILD Nine grade 3 toxicity (13%) One grade 4 thrombocytopenia (1%)	[56]
Goodman <i>et al.</i> (2010), Phase I	26	Six CRC 13 other Seven PHT	1–5 mets <5 cm	18–30 Gy (1e Fx) [¶]	17 mo	12 mo: 77	No RILD No grade 3, 4 or 5 toxicity	[53]
Rule <i>et al.</i> (2011), Phase I	27	12 CRC 15 other	1–5 mets Any size	30 Gy (3 Fx) [¶] 50 Gy (5 Fx) 60 Gy (5 Fx)	20 mo	24 mo: 56 24 mo: 89 24 mo: 100	No RILD No grade 3, 4 or 5 toxicity	[58]
Scorsetti <i>et al.</i> (2012), Phase II	61	29 CRC 32 other	1–3 mets <6 cm	52.5–75 Gy (3 Fx) ^{††}	12 mo	12 mo: 94 22 mo: 91	No RILD One grade 3 chest wall pain (2%) No grade 4 or 5 toxicity	[60]

[†]Pts may have one or multiple treated lesions.

[‡]Dose prescribed to a reference point.

[§]Mendez Romero *et al.* data presented in this table are limited to Pts with liver metastases (eight hepatocellular carcinoma excluded).

[#]Dose prescribed to an isodose line covering the entire planning target volume.

[¶]In the manuscript by Hoyer *et al.*, local control and toxicity data included all-comers with metastatic CRC including: 44 patients receiving stereotactic body radiation therapy to liver metastases, 12 lung, three lymph node, one adrenal and four multiorgan.

^{††}Prescription reported as a mean-dose covering the planning target volume.

CRC: Colorectal cancer; Fx: Fraction; HF: Hepatic failure; mets: Metastases; mo: Month; PHT: Primary hepatic tumor (hepatocellular carcinoma or intrahepatic cholangiocarcinoma); Pts: Patients; RILD: Radiation-induced liver disease.

failures, if they are to occur following ablative-dose radiation, are rare beyond 2 years following treatment.

■ Evaluating tumor control following nonresective interventions: RFA & SBRT

Similar to retrospective evaluations of hepatic resection versus SBRT, the comparison of observational outcomes between the most commonly used nonsurgical approaches, including SBRT and RFA, must be made with caution due to uncontrolled variations in patient selection and institutional practices. Timmerman *et al.* previously reviewed the patient candidacy, technical considerations and outcomes associated with ablative techniques, including surgery, SBRT, and RFA to metastatic lesions of the liver and lungs [4]. Overall, reported LC rates following RFA to CLM have ranged from 5 to 50% with a trend toward improvement in recent series, while significant toxicity rates generally range from 3 to 10% [4,71]. Stintzing *et al.* recently reported the outcomes of a small matched-pair analysis, including 30 patients prospectively managed with single-fraction SBRT to CLM matched to 30 patients treated with RFA during the same time interval [72]. Although survival outcomes were similar between groups, SBRT was associated with a significant improvement in local disease-free survival (34 vs 6 months; $p < 0.001$). A European randomized Phase III trial is currently underway to compare the outcomes of SBRT and RFA for patients with CLM, with a primary end point of local PFS [104].

■ Factors influencing LC

Radiation dose is the most consistent predictor for sustained LC and has been reported in multiple prospective investigations of hepatic SBRT [54,56,58]. Moreover, in a multi-institutional pooled analysis, Chang *et al.* evaluated prognostic factors for LC in 65 patients treated with SBRT to 102 liver lesions from mCRC [73]. On multivariate analysis, the total dose, dose per fraction and biologic equivalent dose (related to total dose and dose per fraction) were the only factors associated with LC. These investigators suggested that a sustained LC of 90% could be achieved using an SBRT regimen in the range of 46–52 Gy in three fractions. Similarly, in a series by Dewas *et al.* totaling 120 patients (72 with liver metastases, 48 with primary liver tumors), significantly

improved LC was observed with higher total dose (>45 Gy) and higher dose per fraction (>15 Gy) [74]. McCammon *et al.* reported a retrospective analysis of 241 metastatic lesions treated with SBRT (81 in liver, 165 in lung) and found improved LC with higher nominal radiation dose and equivalent uniform dose, and recommended a prescription of ≥ 54 Gy in three fractions to ensure durable tumor control [75].

Tumor size has also been associated with LC outcomes in a number of studies. In the Phase I/II trial reported by Rusthoven *et al.*, the actuarial 2-year LC was 100% for tumors ≤ 3 cm in greatest dimension and 77% in those >3 cm [59]. Lee *et al.* reported improved LC at 12 months for tumors volumes <75 ml [56]. In the pooled analyses by Dewas *et al.* and McCammon *et al.*, the only factors predicting for LC in addition to radiation dose were related to tumor diameter (<5 cm) and tumor volume [74,75]. However, tumor size has not been associated with LC in all series [54,55,60] and was not predictive for LC in a pooled analysis specific to liver metastases from mCRC [73].

The relationship of histology and LC has also been variable across reports. Although worse LC outcomes have been suggested among patients with mCRC owing to high rates of pretreatment and technically unresectable disease [4], an analysis of 141 patients with liver and lung metastases found no differences in tumor control for colorectal cancer (CRC) versus non-CRC histology [75]. Milano and colleagues found breast cancer primaries to be associated with improvements in all cancer-specific outcomes (including LC), although no significant differences between CRC and other nonbreast histologies were observed [70]. Scorsetti *et al.* found no differences in LC rates among tumors designated as radio-resistant (including melanoma, renal cell carcinoma, pancreatic and biliary adenocarcinomas) and nonradio-resistant histologies (including CRC, breast and gynecologic tumors) [60]. Additional factors, including age, gender and number of prior chemotherapy regimens, have been evaluated but have not been associated with LC in large series [73,75]. The latter point has significant clinical implications, as hepatic SBRT would be expected to offer excellent LC even in heavily pretreated patients, despite diminishing systemic response rates to successive lines of chemotherapy [76,77].

■ Factors influencing OS

The actuarial 2-year OS rates following SBRT to hepatic metastases range from 22 to 65%, with a median OS of 17–37 months in prospective reports. As most patients included on SBRT trials have been ineligible for other invasive local therapies, survival comparisons across modalities should be made with caution [11]. As with series of hepatic resection, metachronous metastatic presentations and the absence of active extrahepatic disease have been associated with improved OS [54,55]. A higher net burden of disease prior to SBRT has been correlated with diminished OS [78]. Milano *et al.* observed inferior OS among patients demonstrating radiographic disease progression in the setting of systemic therapy prior to SBRT, which may be more a reflection of aggressive tumor biology than treatment strategy [70]. History of prior chemotherapy has been associated with worse PFS as compared with outcomes in chemo-naïve patients [55], while a correlation between OS and number of prior systemic therapy regimens has not been demonstrated [55,73]. In the multi-institutional pooled analyses by Chang and colleagues, survival was also found to be closely associated with tumor control following SBRT [73].

■ Systemic therapy & SBRT

Even in the setting of optimal LC following ablation of hepatic metastases, the majority of patients will ultimately manifest out-of-field progression [59]. As such, there is strong rationale for the coordination of SBRT with systemic therapy. In the context of hepatic resection, perioperative chemotherapy has resulted in improved PFS in patients with limited CLM and no extrahepatic disease [79]. Although, given the substantial heterogeneity of patients undergoing hepatic SBRT, today these strategies are not well established. A number of clinical trials are ongoing to evaluate the prospective coordination of systemic therapy and SBRT for oligometastatic CRC [105–108].

Conclusion & future perspective

Liver metastases are a common problem in the setting of mCRC and many other primary malignancies. Despite favorable long-term outcomes and potential cures following metastasectomy, most patients are not candidates for hepatic resection. SBRT offers an entirely non-invasive means of tumor ablation suitable for a

wide cross-section of metastatic patients and is supported by a large body of prospective trials specific to hepatic metastases. Tumor control rates and safety profiles have improved dramatically since the introduction of SBRT owing to evolving technologies and enhanced understanding of both ablative dose fractionation and normal-tissue tolerances. Overall, hepatic metastases are controlled at rates of 70–100% in prospective reports, although sustained LC >90% may be achieved with modern SBRT delivery.

■ Beyond curative intent

Perhaps most notable about this appraisal of the current paradigms and outcomes for oligometastatic ablation in the liver and other sites, is the range of objectives beyond the achievement of indefinite disease-free survival (i.e., cure). While admiration for metastatic cure is well founded, an ‘all-or-nothing’ approach to the continuum of metastatic disease appears too insular. Included in this review are a number of evolving treatment strategies with dynamic involvement of systemic therapy, such as consolidative SBRT, ablation of treatment-resistant oligoprogressive foci and immunomodulation. Although today, for the majority of patients undergoing SBRT to oligometastatic sites, the most immediate goals entail optimal local disease control, delayed disease progression, and a potential delay in the need for further treatments [80]. Nevertheless, as seen in mCRC and other malignancies following effective noncurative therapies, consistent achievement of these goals with minimal collateral impairment has the capacity to prolong survival [81] and improve quality of life [82]. Ultimately, each of these objectives can only be truly evaluated in the context of a randomized clinical trial and several international efforts evaluating the ablation of CLM are currently underway [104,107,108].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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