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REVIEW ARTICLE

Thermal Ablation versus SBRT in liver tumours: pros and cons

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Abstract
Non-surgical locally ablative treatments for primary liver cancer and liver metastases represent an effective therapeutic choice when surgery cannot be performed or is not indicated. Thermal ablative employing electric currents or electromagnetic fields have historically played an important role in this setting. Radiotherapy, in the last decades, due to a series of important technological development, has become an attractive option for the treatment of liver tumours, especially with the introduction of Stereotactic Body Radiotherapy. Published literature so far evidenced both for radiotherapy and thermal ablative techniques a benefit in terms of local control and other oncological outcomes; however, no direct prospective comparison between the two techniques have been published so far. The aim of this review is to summarize the technical and clinical implications of these treatment modalities and to identify criteria to allocate patients to one or another option in consideration of the expected efficacy. The main features and critical aspects of both thermoablative techniques and external beam radiation will also be covered in the present paper.

Keywords Primary liver cancer · Liver metastases · Stereotactic body radiotherapy · Thermal Ablation

Background

Surgical resection is a mainstay in the treatment of primary and metastatic liver tumours, yielding significant improvement in the outcome of patients. For example, in metastatic colorectal cancer, overall 5-year survival rate (OS) of patients receiving surgery raised to 50%, compared to approximately 15% in patients receiving exclusive systemic therapy [1]. Similarly, surgery is a fundamental component of curative treatments in patients affected by hepatocellular carcinoma (HCC) [2]. However, surgical resection is burdened by non-negligible morbidity rates, particularly, in case of suboptimal liver function due to cirrhosis or prolonged chemotherapy [3]. In these settings, there is a need to preserve the remaining functional reserve that may be reduced by the loss of resected hepatic parenchyma, and to reduce the risk of perioperative complications. For this reason, minimally invasive and non-invasive treatment options such as Thermal Ablation and Stereotactic Body Radiotherapy (SBRT) were developed to expand the indication of a metastases-directed approach to patients who are not eligible for a surgical treatment.

Technical considerations

Non-surgical locally ablative therapies have been developed for clinical use, exploiting different biophysical principles to induce tumour necrosis. Thermal ablative techniques rely on tissue heating through application of electrical currents (RFA) or an electromagnetic field (MWA), resulting in irreversible cell damage due to protein denaturation (beyond 60°) and ischemia secondarily to microvascular thrombosis (between 42° and 60°) [4]. In RFA, oscillating electrical current (450–500 kHz) is conveyed through a transcutaneous electrode directly implanted in the tumour bulk, generating resistive heating that irradiate from the core to the more peripheral regions through thermal conduction. However, since tumouricidal activity of RFA is contingent upon tissue impedance, heat exchange can be impaired by lower conductivity in the tissue in contact with the electrode due to instant charring and water vaporization, acting as an insulator that compromises thermal transmission and determines

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smaller ablation volumes [5]. Another known limitation is represented by the 'heat sink' effect, where blood perfusion from a close (< 1 cm) large (> 3 cm) vessel results in heat dissipation, thereby reducing the ablation volume [6]. In MWA, local hyperthermia up to 150° is induced by propagating high-frequency electromagnetic fields (915 MHz to 2.45 GHz), thus inducing dielectric hysteresis, a phenomenon in which polar molecules, namely water, are continuously realigned with the oscillating electric field, thus releasing kinetic energy. This mechanism of action implies more efficient heat transmission in high impedance tissues, shorter time to ablation and possibly, lower susceptibility to the heat sink effect [7]. RFA and MWA are well tolerated, apart from peri-procedure pain and nausea. However, owing to intrinsically invasive nature of both techniques, haemorrhage, sepsis, intrahepatic bile leakage, and pleural effusion may occur in 5–10% of cases [8]; skin burns due to the presence of grounding pods (RFA) or heat transmission through the entry site (MWA) have also been reported [9, 10]. A non-invasive hyperthermia-based approach uses high-intensity focused ultrasounds (HIFU) from multiple sources to a deep focal target point, inducing kinetic energy release and Thermal Ablation through cavitation; however, stringent requirements of immobilization and treatment duration limit the access to this treatment option [11]. For the purpose of this review, the latter and other Thermal Ablation techniques such as cryoablation or percutaneous laser ablation wil not be addressed [12]. Radiotherapy, on the other hand, mainly exerts its tumouricidal action through oxidative DNA damage induced by reactive oxygen species (ROS) released during water radiolysis [13]. Radiation therapy traditionally held a minor role in the treatment of liver tumours due to exquisite radiosensitivity of this organ, with historical reports of fatal Radiation-Induced Liver Disease (RILD) in patients receiving whole liver irradiation at doses as low as 37 Gy. RILD is a syndrome characterized by an acute transient (classical RILD) or a permanent decline in liver function (non-classical RILD) [14]. However, due to technical evolution, limited volumes of liver can be now safely treated up to effective dose if significant amounts of healthy tissue are spared [15]. In the last decades, SBRT emerged as a valuable option for the treatment of liver tumours, precisely delivering ablative radiation doses with a steep dose gradient that allows to minimize the exposure of critical organs [16]. SBRT is a non-invasive, painless and effective treatment modality with short treatment duration (< 1 h). To improve precision and reduce the impact of respiratory motion, real-time tumour tracking is usually performed after minimally invasive placement of 3–6 fiducial marker. However, fiducial marker placement is not a strict requirement for management of tumour motion: technical advances in Image-Guided Radiotherapy (IGRT) allow for fiducial-less radiation delivery using non-invasive methods (abdominal compression, breathing control, tumour motion registration) [17, 18]. Future implementation of high-resolution imaging (MRI-Linac) may further reduce the need for invasive marker placement by using enhanced soft-tissue contrast compared to plain kV or MV image guidance [19]. A typical SBRT course consists of three to six daily fractions. The choice of radiation dose and fractionation regimen is generally dependent on pre-treatment liver function and tolerance of neighbouring critical structures: the prescribed dose is in general the highest dose deliverable without critical violations of normal tissue constraints [20]. There is no formal restriction in the number of lesions that can be simultaneously treated, the limiting factor being the volume of residual liver to be spared from unintended irradiation; for example, in a 3 fraction schedule, at least 700 cc of healthy liver should be spared from radiation doses > 15 Gy to prevent onset of RILD [21]. There is concern about over-irradiation of surrounding organs at risk, in particular hollow organs (stomach, duodenum, bowels, biliary tract) that may expose patients to risk of serious adverse events such as perforation, bleeding and stenosis as a consequence of radiation damage [22]. Use of IGRT is mandatory to limit unintended dose delivery to these structures, and resort to risk adapted dose schedules has been frequent in complex cases where proximity of a critical organ jeopardizes the safety of the procedure [16]. However, this might potentially come at the price of treatment de-intensification and inferior results [23].

An interesting feature of SBRT is the possibility to elicit an anti-tumour immune reaction based on antigene release "encrypted" in an immune-stimulating chemical sequence (Immunogenic Cell Death) [24] that enhances adaptive immune response, a process that may possibly act synergistically with immune checkpoint inhibitors (CKI) [25]. In recent times, it has been proposed that Thermal Ablation may share this valuable feature, deserving further evaluation [26, 27].

Primary liver tumours

Hepatocellular carcinoma (HCC) is the most frequent primary liver tumour and represents an important source of cancer-related mortality [28]. Clinical management of HCC is based on tumour burden and liver function according to the Barcelona Clinic Liver Cancer (BCLC) staging system [29]. Curative treatment, consisting of surgery and liver transplant, is possible in early-stage patients with low disease burden and adequate liver function and yields 5-year survival rates up to 75% [30, 31]; however, less than 30% of candidate patients are eligible for this aggressive management [32]. Non-surgical ablative therapies can be offered to patients unfit for surgery as definitive treatment or bridging (i.e. removal of the tumour bulk therapies to prevent

progression before transplant), resulting in slightly inferior survival outcome in the range of 40–50% survival rate at 5 years for RFA as compared to surgery, despite lower incidence of toxicity [33]. Since SBRT is a versatile, effective, well tolerated and non-invasive tool, it recently emerged in a wide range of clinical conditions spanning from early-stage disease in patients unfit for surgery to rescue therapy in intermediate stage patients after failure of other treatment modalities [34]; a role in palliation for advanced disease has also been reported [35]. As a bridging therapy, SBRT showed promising local control rates with minimal toxicity [36–38]. Sapisochin et al. reported that, in terms of pathologic response after liver explant, SBRT yielded a 13% pathologic complete response rate, a figure that compared favourably with results from other techniques although inferior to RFA (49%) [39]; however, no difference in disease control and survival were observed according to treatment modality. Recently, a phase II trial by Mirabel et al. evaluating a 45 Gy/3 fractions SBRT as bridging or definitive therapy in patients unfit for any local treatment, reported excellent 18-month rates in local control and survival (98% and 72%, respectively) [40]. In patients who are not candidate for transplant, SBRT confers 1-year local control rates superior to 80% [34, 41–47]. However, there is concern about potential risk of RILD: grade ≥ 3 toxicities were observed in up to one-third of patients in one of the largest prospective studies [45]. This may explain inferior results in term of local control and survival in patients with larger tumours and Child–Pugh (CP) $\geq$ B patients, which may be explained to lower tumour dose delivered in order to decrease the risk of RILD. Based on these considerations, dose regimens are adapted according to tumour size and CP category. Scorsetti et al. proposed in a recent review the following regimens: 3×15–25 Gy for patients with tumour size < 3 cm and adequate liver reserve (CP-A score 5), 5×10–12 Gy for patients with tumour sizes between 3 and 5 cm or inadequate liver reserve (CP-A score 6), and 10×5–5.5 Gy for patients with tumour size > 5 cm or CP-B score [48]. Using a risk-based approach, recent prospective series showed that high local control rates were obtained while less than 10% experienced a decline in CP category despite high prevalence of patients with suboptimal liver function [47]. Moreover, delivery of dose-intensive schedules seems effective even in the presence of larger than 10 cm [49, 50]. At present, no prospective comparison of SBRT vs RFA has been undertaken in HCC, only indirect evidences are available. However, when comparing independent cohorts of SBRT and Thermal Ablation, in particular RFA, it should be noted that SBRT was frequently applied in situations at high risk of treatment failure following RFA, including subcapsular or dome localization, proximity to large vessels and, most notably, tumour size. Local control rates following RFA dwindle from over 75% in 3–5 cm tumours to less than 40% in tumours larger than 5 cm [51]. In the report by Wahl et al. comparing RFA to SBRT in a retrospective cohort, 1-year local control was similar (respectively, 83.6% and 97.4%, $p =$ non-significant) between the 2 groups, though RFA was significantly less effective than SBRT in tumours > 2 cm (HR: 3.35) [52]. In a propensity score-matched analysis from the National Cancer Database [53], superior 5-year OS was reported in patients with HCC receiving RFA as compared to SBRT. However, multiple biases have been highlighted in this study, in particular, lack of information concerning CP category and BCLC status and higher prevalence of older patients and larger tumours in the SBRT group. A recent meta-analysis [54] addressed the benefit of different ablative modalities for liver tumours, including 8 studies on HCC. No significant difference in local control was found between SBRT and RFA in HCC studies (84.5 vs. 79.5% $p = 0.431$), but an advantage in overall survival (OR: 1.43) was shown in favour of RFA. Once again, possible selection bias related to allocation of patients unfit for RFA to SBRT cannot be ruled out. Most interestingly, incidence of severe complications was $< 5\%$ in both arms among the included studies, and no difference in terms of toxicity were highlighted. Table 1 summarizes the main features of the studies included in the Lee metanalysis. Of note, SBRT has been applied even in the presence of Portal Vein Thrombosis (PVT), a feature associated with advanced disease that represents a relative contraindication to local treatments. Late recanalization has been observed, suggesting that SBRT may possibly downstage disease in this population and improve outcomes [55, 56]. A sub-analysis in the ongoing RTOG 1112 will address this setting. However, caution is advised in this fragile population, since PVT may represent a risk factor for portal hypertension, cirrhotic decompensation and liver failure. Recently, successful association of SBRT with CKI has been reported, yielding excellent response rated with a benign toxicity profile [57].

Liver metastases

According to the oligometastatic model, patients with a limited tumour burden may be eligible for aggressive local therapies in order to obtain durable disease remission [58]. This paradigm, extrapolated from observation of improved outcomes following surgical resection of colorectal [59] and sarcoma metastases [60], has been successfully translated in other settings [61]. Liver is one of the main sites of metastatic dissemination from different primary cancers, and use of minimally or non-invasive metastases-directed therapies may increase access to local treatment in cancer patients. In a case-matched analysis, addition of local treatments to chemotherapy in patients affected by liver metastases of breast cancer resulted in a 3-year OS of 81% versus 32%

Table 1 Selected studies comparing SBRT and RFA in Hepatocellular Carcinoma (HCC)

Author (year)	Population	No. of patients (SBRT)	SBRT dose	LC 1 year (SBRT)	OS 1 year (SBRT)	Toxicity SBRT	No. Patients (RFA)	LC 1 year (RFA)	OS 1 year (RFA)	Toxicity (RFA)
Shiozawa et al. (2016) [54]	SBRT:single HCC ≤ 5 cm RFA:solitary HCC ≤ 3 cm inoperable	35	60 Gy/3–5 fx	97.1%	95.2%	≥ G3 late 11.4%	38	97.4%	100%	N/A
Wahl (2016) [52]	Localized HCC	63 (tumours: 83)	27–60 Gy/3–5 fx	97.4%	74.1%	≥ G3 early 5% ≥ G3 late 3.3% − 8.3%	161 (tumours: 249)	83.6%	69.6%	≥ G3 acute 11% ≥ G3 late 6%–6.4%
Parikh et al. (2018) [54]	Age > 65 years, HCC T1-2 N0	78	N/A	N/A	78.1	N/A	78	N/A	79.4	N/A
Rajyaguru et al. (2018) [53]	HCC T1-2 N0	296	N/A	N/A	76.5	N/A	521	N/A	85.5%	N/A
Hara et al. (2019) [54]	Localized HCC ≤ 3 cm, in number ≤ 3	143 (tumours: 220)	N/A	94.7% (4 years)	56.9% (4 years)	N/A	231 (tumours: 474)	77.1% (4 years)	61.8% (4 years)	N/A
Kim et al. (2019) [54]	Localized HCC ≤ 3 in number, maximum diameter < 5 cm	95	60 or 52 Gy/4 fx	83.7%	86.9%	No acute/ late ≥ G3	95	76.1%	87.1%	≥ G3 acute < 2% No ≥ G3

OS overall survival, *LC* local control

in case of exclusive chemotherapy [62]. Thermal therapies have been largely used in patients unfit for surgical resection, yielding excellent local control rates. As example, the randomized trial EORTC 40004 [63] reported a significant benefit of RFA to liver metastases, in terms of Progression-Free Survival (PFS), in unresectable colorectal cancer patients allocated to exclusive systemic therapy, and an impact on OS was demonstrated [64]. In a recent propensity-matched population data-base, after adjusting for factors known to affect treatment choice, no significant difference in OS was shown after MWA versus resection. Ongoing prospective studies are confirming the efficacy and cost-effectiveness of Thermal Ablation as compared to surgical resection [65, 66]. According to literature, there is no significant difference between RFA and MWA in terms of OS, local failure and complication rates in patients with liver metastases. MWA may be superior to RFA for lesions close to the vessels, whereas RFA may be safer in case of proximity to the biliary tract because of slower heat transmission [67]. In the last decade, a growing number of prospective trials on stereotactic treatment of liver metastases was published, reporting encouraging results in terms of outcome and toxicity [68]. Higher SBRT doses and smaller tumour size are associated with improved LC and OS [69, 70]. Most interestingly, response to SBRT is not simply based on a mechanistic dose–response relation but suggests an interesting interplay with tumour biology and patient-related characteristics. Klement et al. [71] evaluated the influence of tumour histotype and prior chemotherapy, showing that a 90% Tumour Control Probability at 2 years could be achieved with lower cumulative doses in chemotherapy-naïve versus heavily pretreated patients, as well as in breast cancer metastases as compared to colorectal cancer metastases. Further research in this field allowed to develop a radiosensitivity index based on a 10-gene panel, predicting a 100% 2-year local control in non-colorectal metastases versus 59% in colorectal metastases [72]. Concerning the immune modulating effects of radiotherapy, a recent phase I trial associating SBRT to metastases in solid tumours to anti-CTLA4 ipilimumab provided initial promising results in term of systemic disease control [73]. Most interestingly, SBRT to liver metastases was associated to increased immune activation (measured as a function of peripheral T-cell activation) as compared to irradiation of other metastatic sites, a feature that may be associated to greater clinical benefit in patients receiving the SBRT and CKI combination. This is a major argument in favour of SBRT, since immune stimulation from Thermal Ablation according to recent studies may be insufficient to generate significant antitumour activation [27], though further evaluation is needed.

There is a general lack of studies comparing SBRT versus Thermal Ablation in liver metastases. The question was addressed by a recent meta-analysis [54]. The meta-analysis by Lee et al. included 3 studies on liver metastases reporting pooled 2-year LC rates of 60.0% and 83.6% for Thermal Ablation and SBRT arms, respectively; OS could not be calculated due to insufficient report of outcome. Interestingly, one of the studies [74] found superior efficacy for SBRT compared to RFA in tumours larger than 2 cm, while this advantage was lost for smaller tumours. There was no difference in survival and in the incidence of overall and severe toxicity, the latter occurring in 4% (bleeding, biliary stricture) and 4% (abscess, haemoperitoneum, haemothorax) of patients in SBRT and RFA, respectively. Table 2 collects the patients and treatment characteristics analysed in the meta-analysis by Lee [54].

Concluding remarks

Both SBRT and thermal therapies are effective and safe options for the treatment of both primary and secondary liver tumours, and grant access to a local option in patients who are unsuitable for surgical resection. A certain number of clinical conditions already favour use of SBRT over thermal therapies: difficulty in percutaneous approach, tumour located in proximity of vessels, presence of portal vein thrombosis and large tumour size. Furthermore, since its use is limited only by the volume of irradiated healthy liver and need for fiducial markers can be overcome by modern tumour motion control techniques, SBRT allows for simultaneous treatment of multiple distant intrahepatic tumours, reducing the need for repeated invasive interventions. A synergistic effect in combination with immunomodulatory agents such as CKI has been also reported. On the other hand, thermal therapies, in particular RFA, have greater cumulated evidence and can be performed in a single intervention. Moreover, thermal treatments allow for collection of biopsies in the same operative time, an advantage in terms of availability of tumour tissue to track down emergence or loss of possible target mutations and adapt systemic treatment. Finally, as previously reported, response to SBRT can be restrained by intrinsic tumour biological features, such as primary tumour histotype and prior use of chemotherapy, that are linked to increased failure rate and need for higher doses to eradicate the metastatic foci. Thermal therapies could be used to overcome radio-resistance and decrease dose to critical structure in a cooperative strategy with SBRT. Therefore, further studies are advocated to identify the categories of patients that could draw higher benefit from each technique.

Table 2 Selected studies comparing SBRT and RFA in liver metastases

Author (year)	Population	Histology	No. of patients SBRT	SBRT dose	LC 1 year (SBRT)	OS 1 year (SBRT)	Toxicity	No. patients RFA	LC 1 year (RFA)	OS 1 year (RFA)	Toxicity
Stintzing et al. (2013) [54]	Liver metastases, inoperable	Colorectal cancer	30 (metastases:35)	24–26 Gy/1 fx	85%	Median 52.3 m	No ≥ G3	30 (metastases: 35)	65%	Median 34.4 ms	No ≥ G3
Viganò et al. (2018) [54]	Liver metastases	Colorectal cancer	8 (metastases: 17)	75 Gy/3 fx	70.8%	N/A	N/A	19 (metastases: 27)	63%	N/A	N/A
Jackson et al. (2018) [74]	Mostly limited (< 5 cm) or stable extrahepatic disease	Miscellaneous	92 (metastases: 170)	24–61 Gy/3–5 fx	96%	63.1%	≥ G3 4.3%	69 (metastases: 112)	74.7%	75%	≥ G3 4.3%

OS overall survival, *LC* local control

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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