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Review

Stereotactic body radiation therapy and radiofrequency ablation for the treatment of liver metastases: How and when?

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ABSTRACT

Limited liver metastases represent a clinical challenge. Surgical approach is the most frequently reported treatment option, however, some patients are not eligible for surgical interventions. Relatively recent technologic advances have permitted the safe use of ablative techniques employed in the cure of hepatic metastases. Among these, radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) have emerged as valid treatments in a significant proportion of patients with intrahepatic oligometastatic disease. This review offers an up-to-date of current available literature on this issue focusing on the use and outcomes of RFA and SBRT, according to the PICO (Population, Intervention, Comparison and Outcomes) criteria.

1. Introduction

Although the last decades have been characterized by increasing advances in clinical oncology, the management of patients with intrahepatic metastases is still a challenging problem.

Surgical resection represents the gold-standard for the treatment of intrahepatic oligometastatic disease; however, only a small proportion of patients are candidate for surgery due to inadequate functional hepatic reserve, lesion location, contiguity of tumor to vessels and medical comorbidities.[1,2] In order to overcome these issues, novel therapeutic approaches for curing intrahepatic oligometastases have been recently employed. In this regard, chemoembolization, radioembolization, radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) have emerged as promising treatments in a substantial proportion of patients.[3]

In particular, it has been prospectively demonstrated that both RFA and SBRT provide good local control.[4–7]

The randomized EORTC Intergroup phase II study EORTC 40004[8,9] investigated the potential benefits of systemic therapy with or without RFA in patients with non-resectable colorectal liver metastases, demonstrating a 3-year progression free survival (PFS) rate of 27.6% in the combined treatment group and 10.6% in the systemic treatment group, with a statistically significantly longer OS as compared with the patients in the systemic treatment arm (HR = 0.58, 95% CI = 0.38 to 0.88, $P = .01$), with three-, five-, and eight-year OS rates of 56.9%, 43.1%, and 35.9% in the combined modality arm and 55.2%, 30.3% and 8.9% in the systemic treatment arm, respectively.

Encouraging local control and overall survival have been also observed after SBRT for liver metastases, although interpreting survival results is not trivial considering the wide variety of patients and the inclusion of different primary tumors with peculiar intrinsic radioresistance features. On the other hand, it has been demonstrated that SBRT provides good local control with rates at 1 year ranging from 71 to 100%, and at 2 years, between 64% and 92%,[4,5,10–14] while being reasonably safe, with limited grade 3 gastrointestinal toxicities.[4–6,10–15]

The aim of the present paper is to offer an up-to-date review of current available literature on the rationale, feasibility, safety, and

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outcomes of nonsurgical approaches, in particular RFA and SBRT, for the treatment of patients with intrahepatic oligometastases.

2. Patients and methods

The PubMed/MEDLINE database was employed to look for articles on the treatment of liver oligometastases with RFA and SBRT according to the PICO (Population, Intervention, Comparison and Outcomes) criteria. We used a search string based on a combination of terms: (a) intrahepatic OR liver metastases AND radiotherapy or (b) intrahepatic OR liver metastases AND SBRT or (c) intrahepatic OR liver metastases AND RFA or (d) intrahepatic OR liver metastases AND stereotactic radiosurgery or (e) intrahepatic OR liver metastases AND radiofrequency ablation. The search was updated until November 2018 and was limited taking into account only original papers published in English and performed in humans. The references of the retrieved articles were also checked so as not to miss important clinical studies. Original articles not in the field of interest of this review, editorials, commentaries, review articles, case reports and studies involving less than 5 patients were excluded. Animal studies were also excluded. Two researchers (A.C., S.P.) independently reviewed the titles and the abstracts of the retrieved literature, selecting relevant articles.

2.1. Clinical outcomes and toxicities

Retrospective studies have documented favorable rates of long-term progression free and OS in selected patients with limited hepatic metastases from colorectal cancer following surgical resection. In a large series from Memorial Sloan-Kettering Cancer Center, Fong et al. (1999) reported 5- and 10-year survival rates of 37% and 22%, respectively, in 1001 patients with limited hepatic metastases from colorectal cancer treated with surgical resection.[16] Statistical analysis revealed that the most favorable group of patients had negative surgical margins, solitary metastases, tumor size <5 cm, carcinoembryonic antigen (CEA) <200 ng/mL, disease-free interval >12 months, node-negative primary tumor and no evidence of extra-hepatic metastases. Among this selected group, the 5-year survival rate was 60%.[16] Similarly, Aloia et al. (2006) compared rates of local control, disease-free survival, and overall survival in 180 patients with solitary liver metastases from colorectal cancer treated with RFA (n = 30) versus hepatic resection (n = 105).[17] 5-year local recurrence-free survival and OS were higher in the group treated with hepatic resection (92% and 71% versus 60% and 27%, respectively), while no differences were observed between the two groups for distant hepatic recurrence or systemic recurrence.[17] These findings suggest that effective local therapy is essential to achieve long-term disease-free and OS for patients with hepatic oligometastases from colorectal cancer.

Berber et al. (2008) investigated the survival of patients with solitary colorectal intrahepatic metastasis undergoing resection versus laparoscopic RFA, demonstrating that the 5-year OS was 30% for the RFA group and 40% for the surgical resection group[18] Median Kaplan–Meier actuarial survival after diagnosis of liver metastasis was 33 months for RFA with extrahepatic disease (n = 26), 40 months for RFA without extrahepatic disease (n = 42), and 59 months for resection (n = 90; p = 0.005). After excluding RFA patients with extrahepatic disease, the actuarial median disease-free survival was 9 months for the RFA group and 30 months for the resection group (p < 0.0001).[18] However, Hur et al. (2009) comparing 42 patients treated with resection demonstrated that RFA and resection achieved similar results both for the 5-year OS (55.4% vs. 56.1%) and recurrence-free interval (85.6% vs. 95.7%), concluding that RFA may be considered as an alternative option in patients with lesions smaller than 3 cm and unfit for surgical resection.[19]

Reuter et al. (2009) compared RFA vs. hepatic resection in patients which shared similar Fong Clinical Risk Score [16] for colorectal cancer recurrence, presence of extrahepatic disease, and number of hepatic lesions.[20] This study obtained a lower chance of recurrence for hepatic resection vs. RFA (2% vs. 17%), while providing similar 5-year survival rates (45% vs. 49%).[20] Otto et al. (2010) used different inclusion criteria in assigning patients to RFA or resection. In particular they opted to perform RFA in patients who presented metastases 1 year after colorectal resection and to perform resection in patients who were not suitable for RFA due to diameter, location and number of metastases, founding similar 5-year survival rates both for RFA and hepatic resection (48% vs. 51%. respectively).

Kim et al. (2011) compared patients undergoing resection, RFA or combined therapy, achieving similar results in 5=year disease-free survival. In patients with a single metastatic tumor <3 cm, 5-year OS rates were 51.1% and 51.2% for RFA and hepatic resection, with disease-free survival it was 33.6% and 31.6%, for RFA and hepatic resection, respectively. On the other hand, in patients with solitary metastatic tumor >3 cm, disease-free survival was significantly lower in the RFA group (23.1% vs.36.6%, P = 0.01).[21]

Finally, the first randomized controlled trial on the efficacy of RFA, published in 2012, compared systemic chemotherapy or systemic chemotherapy plus RFA for the treatment of unresectable liver metastases from primary colorectal cancer. This phase II study obtained a 30-month OS of 57.6% for systemic treatment alone and 61.7% for systemic treatment plus RFA. The Median OS was 45.3 for the combined treatment and 40.5 months for the systemic treatment (P = 0.22). The 3-year PFS rate for the combined treatment was 27.6% compared with 10.6% for systemic treatment only (HR = 0.63, 95% CI 0.42-0.95, P = 0.025). Median PFS was 16.8 months (95% CI 11.7–22.1) and 9.9 months (95% CI 9.3–13.7), respectively.[8]

The favorable outcomes observed in these studies on metastatic patients have encouraged the evaluation of nonsurgical treatments, such as RFA and SBRT.

2.2. RFA for patients with liver metastases

RFA is a promising non-surgical technique for ablation of non-operable liver metastases, or after bilobar metastases resection, although its employment is restricted to a selected group of patients. The feasibility of RFA in treating liver metastases follows the same therapeutic algorithm as that applied in treating hepatocellular carcinoma (HCC): RFA is recommended for patients with no more than three hepatic lesions with a maximum diameter of 3 cm who are contraindicated for surgical treatment.[22,23] The liver metastases diameter of 3 cm is one of the most commonly reported major factors affecting the RFA outcomes,[24,25] and this threshold is driven by the maximum diameter of the ablation zone guaranteed by the most common ablative probes, that is approximately 4 cm. For this reason, there is an increased risk for insufficient treatment margins in metastases larger than 3 cm.[26]

However, RFA yields sub-optimal results when metastases are located nearby major blood vessels, main bile duct and gallbladder or beneath the diaphragm. In particular lesions should be not more distant than 1 cm from the glissonian capsule and with a distance from the large hepatic veins equal or major to 2 cm.[27]

Moreover, a recent study proposed four selection criteria to establish which patients treated with systemic therapy could benefit from RFA: i) responsiveness to systemic therapy; ii) less than three metastases; iii) each one smaller than 3 cm; iv) circulating CEA < 100 ng/mL. Indeed, the presence of four criteria identified a subgroup of 23 patients with significantly higher probabilities for OS and RFS at 5 years (39% and 22%, respectively) compared with patients with any or less than 4 criteria (0-27% and 0-9%, p < 0.001, respectively).[28]

Table 1
Summary of most important Radiofrequency Ablation series. Survival outcomes, local recurrence rate and complications are reported.

Author	Year	N. Pts with Colorectal mts	Median N. mts	Mts diameter (cm)	median FU (months)	Median OS (months)	1y OS (%)	2y OS (%)	LRR (%)	Major complications (%)	Minor complications (%)
Aloia	2006	27		3	50	–	100	57 (3y)	37	–	–
Berber	2005	135		4.1	–	28.9	~80	~60	53	–	–
Abitabile	2007	47	3.1	2	33	39	88	80	8.8 overall/ 1.6 mts<3 cm	7	–
Gillams and Lee	2004	167	4.1	3.9	17	32	91	40 (3y)	14	4	6
Hildebrand	2006	56	3.5	3.5	21.2	28	92	67	17	3.4	5.6
Iannitti	2002	52	2.7	5.2	20	–	87	67	–	7	–
Machi	2006	100	3.5	3	24.5	28	90	42 (3y)	6.7	4.8	12.3
Knudsen	2009	36	–	2.1	27	39	–	34 (5y)	–	11	–
Solbiati	2001	117	1.6	2.6	–	36	92	69	39.1	1	0
Solbiati	2012	99	2.1	2.3	72	53.2	98	69 (3y)	11.9	1.3	–
Abdalla	2004	158	1	2.5	–	–	92.5	60	90	–	–
Wong	2001	31	–	3.1	9.5	–	77.5 (9 m)	–	–	20	–
Schindera	2006	14	–	1.8	18	35	72	60	14.8	2.1	16.7
Jackson	2018	69	–	1.8	30.5	25.9	63.1	52.3	–	4	–

It has been reported that the local recurrence rate after RFA for intrahepatic metastases ranges from 8.8% to 40%.[17,20,29–35] The success of RFA in local control of metastases is mainly influenced by tumor dimensions, since the local tumor progression (LTP) corresponds to 30–33% when the tumor dimension does not exceed 20−30 mm and to 42–66% when exceeding such cut-off.[36–38]

In particular, it has been demonstrated that the tumor size is the main predictive factor for RFA failure (i.e. LTP),[17,22,36–42] which is defined as the development of tumor foci within 1 cm of an ablated zone as assessed by abdominal ultrasound, CT scan or MRI.[42,43] The exact cut-off allowing RFA to be performed has never been defined but is between 20 and 30 mm. The treatment of metastases with a diameter smaller than 20–30 mm at the time of the RFA procedure results in a risk of LTP of 3–33%.[17,22,36–42] It is generally accepted that metastases exceeding 25–30 mm in diameter at the time of the procedure are not good indications for RFA because of a high risk of LTP (42–66%).[17,22,36–42]

Local control and survival rates are also influenced by whether the treatment is performed by percutaneous rather than laparoscopic or surgical approach. The open surgical or laparoscopic approach would allow a better placement of RF needles, or repeated placements in multiple sites to ablate larger tumors.

Moreover, Berber et al. (2008) reported that the local recurrence rate after RFA (in 21.7% of tumors) also depends on the histology of tumors: colorectal metastases (34%), noncolorectal, nonneuroendocrine metastases (22%) and neuroendocrine metastases (6%).[44] For a comprehensive description of the series analyzed regarding RFA and liver metastases, see Table 1.

2.3. SBRT for patients with liver metastases

Similar to RFA, the main goal of SBRT is to achieve local control of oligometastatic sites, but the translation into clinical or survival benefit for patients depends on multiple aspects, such as age, performance status, comorbidities, prior therapies and histology of lesions. Hence, the selection of patients should be careful and strict. Ideally, candidates for SBRT might present the following characteristics: i) a limited number of metastases (one to five), ii) a limited tumor size (<6 cm), iii) favorable histology (i.e. colorectal and breast cancer), iv) good performance status, v) young age and vi) adequate pre-SBRT liver function.

The efficacy of SBRT for intrahepatic metastases can be measured by the rates of local control achieved and by the OS of patients.

Generally, local control rates range from 70%–100% at 1 year and from 60%–90% at 2 years.[15,45] The differences between published studies depend on the tumor volume and histopathology, prior therapy, SBRT doses and fractionation regimens.

Herfarth and colleagues (2001) evaluated single-fraction SBRT at a dose of 14–26 Gy for 55 liver metastases (mostly from colorectal cancer). The 18 months actuarial local control was 67%, and no high-grade toxicity was observed.[12] Hoyer and colleagues (2006) evaluated SBRT with a dose of 45 Gy/3 fx for 141 colorectal cancer metastases, including 44 hepatic metastases, showing a 2-year actuarial local control of 79%. One patient died of liver failure, one patient experienced colonic perforation, and two patients experienced duodenal ulceration.[10] In a phase II trial, Méndez-Romero and colleagues (2006) evaluated SBRT (mostly 37.5 Gy/3 fx) for 45 primary or metastatic hepatic lesions reporting a local control of 82%. Among metastatic patients, the 2-year local control was 86%, and only three grade 3 toxicities were observed.[11]

In a phase I/II trial, investigators from the University of Colorado demonstrated a high rate of local control with SBRT for patients with three or fewer liver metastases, each measuring less than 6 cm. In phase I, the dose of SBRT was safely escalated from 36 Gy to 60 Gy in three fractions without dose-limiting toxicity.[46] In phase II, the dose was 60 Gy in three fractions. In total, 13 patients received doses less than 60 Gy, and 36 patients received 60 Gy in three fractions. Only three in-field local failures occurred among 47 lesions evaluable for local control (patients with at least 6 months radiographic follow-up) after SBRT. The actuarial local control of all SBRT-treated lesions was 92% at 2 years[5] (Rusthoven et al. 2009b). It is worthy to note that when looking at lesions measuring <3 cm in the greatest dimension, the 2-year actuarial local control was 100%. Only one case of grade 3 toxicity was observed, and no patients experienced grade 4–5 toxicity. At last follow-up, 20 of 47 patients were alive, and the two-year actuarial survival after SBRT was 30%.

A few years later, the promising outcomes from the University of Colorado study were confirmed by Rule et al.[15] in a dose-escalation phase I clinical trial using SBRT for liver metastases. In particular, the investigators evaluated three dose cohorts: 30 Gy/3 fx, 50 Gy/5 fx, and 60 Gy/5 fx. No grade 4–5 toxicity was reported, and only one grade 3 event (asymptomatic grade 3 transaminitis) occurred in the 50 Gy group. The 2-year actuarial local control was 56%, 89%, and 100% for the 30 Gy, 50 Gy, and 60 Gy cohorts, respectively.

Lee et al. from the Princess Margaret Hospital conducted phase I/II trial using 6 fractions over 2 weeks of SBRT in 68 patients with liver metastases of varying sizes (up to 3090 mL) and different primary histology (colorectal, n = 40; breast, n = 12; other n = 16) to evaluate the safety of SBRT for larger liver metastases. Radiotherapeutic dose was individualized based on the liver volume irradiated in order to avoid Radiation-Induced Liver Disease (RILD) (range: 24–60 Gy). With a median follow-up of 11 months, the 1-year LC rate was 71% and the median survival rate was 18 months. There was no RILD, resulting in a low risk of serious liver toxicity (95%

Table 2
Summary of the most important Stereotactic Body Radio Therapy (SBRT) series. Survival outcomes, local recurrence rate and complications are reported.

Authors	Year	Type of study	Type of SBRT	N. Pts	N. Mts (%)	Lesion size (cm) (range)	Primary Site	Previous CT	Dose range (Gy/fxs)	BED10Gy	Median FU (months)	Median OS (months)	1y OS (%)	2 OS (%)	1y LC (%)	2y LC (%)	Toxicity (%)
Scorsetti	2015	Phase 2	VMAT	42	1 (81 %)	1.1–5.4	Colon (71%); rectum (29%)	–	75/3	262.5	24	29	–	65	95	91	G2 liver toxicity (25)
Stintzing	2013	Prospective series	Cyberknife	30	1 (86%)	0.7–5.3	–	–	24–26/1	81.6–93.6	23.3	34.4	–	–	85	80	Bleeding and rising bilirubin (3)
van de Voorde	2015	Retrospective	VMAT	17	–	–	–	–	EQ2 62–150/3-10	–	21	25	–	–	–	–	–
van der Pool	2010	Prospective series	LINAC	20	31 (total)	0.7–6.2	Colon (75%); rectum (25%)	–	37.5–45/3	93.6–112.5	26	34	100	83		74	G3 liver toxicity (10), G2 (90)
Vautravers-Dewas	2011	Retrospective	Not specified	30	62 (total)	0.7–10	–	–	40/4 45/3	80 112.5	14.3	–	–	58		86	–
Ahmed	2016	Retrospective	Not specified	22	2 (0–5)	2 (0.6–6.7)	Colorectal	2 lines	50–60/5	100–132	20.5	–	100	73	79	59	–
Ambrosino	2009	Prospective series	Cyberknife	11	1.8	–	Colorectal	–	25–60/3	45.83–180	13	–	–	–	–	–	G1-2 liver toxicity (36.4)
Berber	2013	Retrospective	Cyberknife	53	1.6	–	Colorecta	–	41/3	96.76	17	–	56	–	60	–	G1 fatigue and nausea (21); Death n = 1
Chang	2011	Retrospective cohort (pooled analysis)	Cyberknife	65	1–2 (80%)	–	Colorectal/	–	22–60/1-6	40.5–180	14	–	72	38	62	45	GI-G2 & G3 acute GI toxicity (17&3)
Mendez Romero	2016	Retrospective	LINAC & Cyberknife	40	1–2 (95%)	2.5 (0.7–6.2)	Colorectal	–	50.25/3	134.42	25	43	94	81	93	90	G1-2 liver toxicity (97.5), G3 liver toxicity (7.5)

Table 2 (*Continued*)

Authors	Year	Type of study	Type of SBRT	N. Pts	N. Mts (%)	Lesion size (cm) (range)	Primary Site	Previous CT	Dose range (Gy/fxs)	BED10Gy	Median FU (months)	Median OS (months)	1y OS (%)	2 OS (%)	1y LC (%)	2y LC (%)	Toxicity (%)
									37.5/3	84.38	26	35	95	69	96	74	–
Doi	2017	Retrospective	LINAC	24	1 (75%)	3.5 (7–11.6)	Colon (75%); rectum (25%)	Yes (87.5%)	45–72/8	71.7–115.5	16	45	82.3	67.1	67.2	35.9	G1-2 liver toxicity (16), duodenal ulcer (4)
Goodman	2016	Retrospective	LINAC	54	–	–	–	–	32–60/3–5	52.48–180	33	38	95	78	93	88	Death n = 1
Hoyer	2006	Phase 2	LINAC	44	–	3.5	Colon (59%); rectum (41)	Yes (52%)	45/3	112.5	52	19.2	–	38	–	78	G3 intestinal toxicity (5), liver failure (2), G1-2 nausea & diarrhea (34 & 23), G3 (3); Death n = 1
Joo	2017	Retrospective	LINAC	70	1–2 (86%)	2.9	–	0–2 lines (69%)	45–60/3-4	58–180	34.2	–	–	75	–	–	G1-2 nausea (34), G1-2 liver toxicity (15)
Kim	2009	Prospective series	Cyberknife	10	14	–	Colon (60%); rectum (40%)	>1line (100%)	36–51/3	79.2–137.7	12	25	53.00	40	80	60	G1 nausea and musculoskeletal discomfort (40)
Lee	2009	Phase 1	Not specified	40	2 (1–8)	–	–	>1 line (85%)	27.7–60/6	40.44–120	10.8	15	63	–	–	–	–
Liu	2013	Retrospective	Not specified	24	1–4	–	–	–	24–60/1-5	81.6–132	18	25.2	–	–	86	67	–
McPartlin	2017	Phase 1 & 2	Not specified	60	1 (1–6)	–	–	>1 line (82%)	22.7–62.1/6	31.28–126.37	28.1	16	63	26	50	32	G3 nausea (2)
Jackson	2018	Retrospective	Not specified	92	2	2.7 (0.0–9.2)	Colorectal (19.4%)	>1 line	50Gy/5	>80	20.2	24.5	75	50.2	96	88.2	Gastronitestinal bleeding and rising bilirubin (4)

CI, 0 to 5.3%). Grade 2 nontraumatic rib fractures occurred in two patients treated with the maximum doses to 51.8 Gy and 66.2 Gy in 6 fractions to 0.5 mL of the rib.[4]

Scorsetti et al. (2013) published a phase II trial of high-dose SBRT using 75 Gy in 3 fractions. A total of 61 patients with 76 lesions were treated. The median follow-up was 12 months, the in-field local response rate was 94%, the median survival rate was 19 months, and 1-year actuarial survival rate was 83.5%. No RILD was detected.[47] More recently, the final results of the phase II trial for SBRT for patients with inoperable liver metastases from colorectal cancer provided a 2-year local control rate of 91%. In particular, 52 lesions were treated over 3 fractions, with 75 Gy representing the mean dose delivered to the PTV.[6]

The same authors have recently showed that the 5-year results of the phase II trial confirmed the role of high-dose SBRT in the treatment of liver metastases with diameter >3 cm, which are often unsuitable for other effective local ablative therapy, such as RFA. The local control rates at 1, 3 and 5 years were 94 ± 3.1%, 78.0 ± 5.9% and 78.0 ± 5.9%, respectively, even though the median local control time was not achieved. The median OS was 27.6 months and the survival rates at 1, 3 and 5 years after SBRT were 85.2 ± 4.5%, 31.1 ± 5.9% and 18.0 ± 4.9%, respectively. The univariate analysis revealed that better survival was correlated with primary site (colorectal, breast and gynecological) of metastases (p = 0.001). As regard toxicity, one patient experienced G3 late chest wall pain, which resolved within 1 year from SBRT and no cases of RILD were reported.[48] Table 2 reports the details of the series analyzed regarding SBRT and liver metastases.

2.4. SBRT or RFA: are they equivalent approaches?

If on the one hand, several studies compared RFA with hepatic resection, on the other hand, direct evidence comparing SBRT and RFA is still lacking. Jackson et al. (2017) have recently retrospectively evaluated 161 patients most of them with limited (<5 cm) or stable extra hepatic disease. Sixty-nine patients were treated with RFA to 112 metastases and 92 patients were treated with SBRT to 170 metastases. When the metastases treated were less than 2 cm in diameter the outcomes were comparable both for SBRT and RFA providing excellent local control, while when lesions were larger than 2 cm SBRT led to improved local tumor control. In particular, 1 and 2-year rates of local control were 96% and 88.2% in patients treated with SBRT and 74.7% and 60.6% for those treated with RFA, although such a difference was not statistically significant (HR:2.66, 95% CI:0.97-7.25, p = 0.057). The local control rates after RFA or SBRT were not influenced by the tumor histology, and both treatments led to similar results in terms of OS while being reasonably safe, with limited grade 3 treatment related toxicities.[49]

Literature concerning comparative cost-efficiency between RFA and SBRT on liver metastases is currently lacking too. Kim et al. (2016) employed a Markov model to carry out a cost-effectiveness analysis of RFA and SBRT in patients with oligometastases from colorectal cancer.[50]

Assuming equal survival between the two non-invasive ablative techniques, SBRT has been shown to not be as cost-effective as RFA. However, assuming that improved local control may lead to even small gains in OS, then SBRT can be considered as a clearly cost-effective option as well. In addition, SBRT was found to be a cost-effective treatment in patients with intrahepatic metastases >4 cm.[50] However, these results come from a Markov model, therefore comparative clinical trials are needed to better guide the appropriate management and to provide more definitive evidence about the cost-effectiveness of these two ablative techniques.

Table 3
Summary of Radiofrequency Ablation (RFA) and Stereotactic Body Radio Therapy (SBRT) minor and major toxicities. Values are expressed as the median and range (min-max) of patients (in %) as reported in the studies explored.

	Minor/G1-G2	Major/G3-G4
RFA	4 (0–20)	0 (0–16.70)[a]
SBRT	0 (0–97.50)	0 (0–10)[b]

[a] i.e. Hepatic abscess, visceral perforation, infections, hemoperitoneum.
[b] i.e. Gastrointestinal bleeding, biliary stricture.

3. Conclusive remarks

In an era of increasing advances in technology and increasing interest in individualized precision medicine,[51–55] surgical resection represents the gold-standard for the treatment of intrahepatic oligometastatic disease when feasible. However, some patients are not surgical candidates for potentially curative resection because of inadequate functional hepatic reserve, lesion location, contiguity of tumor to vessels and medical comorbidities. In these cases, there are several non-surgical approaches, and among these, systemic or regionally delivered chemotherapy and regional lesion ablation, such as RFA, microwave ablation and SBRT, have proved to be promising options in this setting of patients.

Although external beam radiotherapy for the treatment of liver metastases has been historically limited by low tolerance of liver parenchyma, SBRT has recently allowed to deliver high-dose radiation in a few fractions to the tumor with extreme accuracy, minimizing normal surrounding tissue toxicity (Table 3). Indeed, recent studies have investigated the use of SBRT for the treatment of limited liver metastases from a variety of primary tumors. Similar to the lung, the liver is an attractive organ for SBRT due to its parallel arrangement in functional subunits. Such organization permits to deliver safely ablative radiation doses to small volumes while an adequate proportion of the normaly functioning liver is successfully spared. In parallel, RFA is also widely used for focal liver therapy and it has prospectively been demonstrated to provide good local control, with local recurrence rates less than 20%,[44] while being reasonably safe (Table 3).

To the best of our knowledge, there are no randomized clinical trials to guide the decision between SBRT and RFA for patients with oligometastatic liver disease who are unfit for surgical resection.

There is little doubt that RFA is preferred for the treatment of no more than three hepatic lesions with a diameter $\leq$ 2 cm, far from major blood vessels, main bile duct and gallbladder or beneath the diaphragm, not more distant than 1 cm from the glissonian capsule and with a distance from the large hepatic veins equal or major to 2 cm. On the other hand, SBRT can provide an excellent local control when the metastases treated are one to five in number and $\leq$ 6 cm in diameter in patients with a good performance status and an adequate pre-SBRT liver function; in particular, SBRT should be preferred for lesions larger than 2 cm regardless of the tumor histology. Table 4 reports the pros and cons of RFA and SBRT in treating liver metastases.

These two ablative techniques seem to have a similar cost-effectiveness, but it is worth to outline that improved local control, regardless if obtained via RFA or SBRT, does not correspond to improved OS as intrahepatic progression outside the field of the treated lesions and extrahepatic progression, occurring approximately in 58% and 64% of patients, respectively, remain the major clinical problems for these patients.[49] On this issue, the novel systemic agents (i.e. immune checkpoint inhibitor) used concurrently with RFA and SBRT could ameliorate both local control and extrahepatic disease.[56–59]

Only 20% of patients with liver metastases die of isolated intrahepatic progression[60] supporting the concept that even if RFA and

Table 4
Pros and Cons of Radiofrequency Ablation (RFA) and Stereotactic Body Radio Therapy (SBRT).

	RFA	SBRT
PROS	• Minimally invasive • Preserve the surrounding liver tissue • Low rates of death and major complications • No radiation exposure • Safe	• Non-invasive • IGRT • Respiratory gating. breath-hold and active tracking • No need for sedation • Very conformal radiation dose to the lesion and a minimal radiation dose to surrounding critical tissues • Technically feasible in every hepatic parenchyma locations • Low rates of death and major complications • Safe
CONS	• Limited ablation volume (4–5 cm) • Local and conscious sedation • Micro-satellites lesions around the main metastasis may increase and spread • Technically infeasibility for lesions in peculiar locations • Heat sink effect • Needle track seeding • Intravascular spreading of metastases by increasing intralesional pressure during procedure • Operator dependent • Toxicity	• Limited ablation volume (4–5 cm) • Stringent immobilization • Long delivery times of more than 40 min. • Fiducial placement • Hepatic and organs at risk toxicity

SBRT lead to a high nonsurgical local control of individual lesions, much effort has still to be done in order to ameliorate the OS in this setting of patients.

As a conclusive advice, the available data suggest that liver metastases can be treated by SBRT with very low toxicity and excellent local control rates ranging from 70%–100% at 1–2 years; however, it is worth to note that the type of very high-dose stereotactic regime, which necessitates accurate delineation of tumor lesions including the use of four dimensional PET/TC[61] and respiratory-gated radiotherapy, should be carried out in appropriately qualified and experienced centers.

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Conflict of interest

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