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Review

A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases

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ABSTRACT

Aim: To evaluate the role of radiofrequency ablation (RFA) as treatment of colorectal cancer liver metastases (CLMs).

Method: A PubMed literature search for original articles published until August 2008 was performed. Studies with ⩾40 patients, ⩾18 month median follow-up and reported ⩾3 year overall survival (OS) rates after RFA of CLM were selected for analysis.

Results: Thirteen clinical series and 8 non-randomised comparative studies were analysed. Median progression free survival after RFA ranged between 6 and 13 months. Median and 5-year OS after RFA (RFA plus resection) ranged between 24–59 months and 18–40% (36–46 months and 27–30%). Comparative studies indicated significantly improved OS after RFA versus chemotherapy alone, RFA plus chemotherapy versus RFA alone and up-front RFA versus RFA following second-line chemotherapy.

Conclusion: Our findings support that RFA prolongs time without toxicity and survival as an adjunct to hepatectomy and/or chemotherapy in well-selected patients, but not as an alternative to resection.

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1. Introduction

The management of patients with metastatic colorectal cancer (mCRC) has been improved during the last decade. More effective systemic therapies including agents such as irinotecan, oxaliplatin, cetuximab and bevacizumab achieve response rates up to 50–80%, prolong survival in unresectable disease to 16–24 months, and appear to convert 5–15% of initially unresectable to resectable disease.[1–3] Resection offers the only curative option for patients with colorectal liver metastases (CLMs), with 5-year overall survival (OS) rates approaching 60%.[4–8] Expanded criteria for defining resectability and multimodality strategies increase the number of patients who can undergo potentially curative metastasectomy. However, the majority of patients with CLM are not surgical candidates because of extensive disease or comorbidity.

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Radiofrequency ablation (RFA) is the most widely used non-surgical technique for local therapy of CLM.[9] RFA of CLM has already permeated clinical practice, but its oncologic benefit remains uncertain.[9–11] The uncertainty results from a lack of phase III randomised trials comparing RFA with surgery and chemotherapy. Two attempts had little success in recruiting patients. The French-FFCD trial addressing the comparison to resection has been closed in 2004.[12] The EORTC-CLOCC trial addressing the comparison to chemotherapy had been downscaled to a phase II trial in 2006, and was closed early at 119 patients in 2007 because of poor recruitment.[16] Nevertheless, from clinical practice arises the increasing need to define patient groups who will benefit from RFA of CLM and those who may not.

The intent for performing RFA of CLM is to prolong OS and/or time without toxicity. Median and 5-year OS, and length of progression free survival (PFS) are usually taken as evidence to measure the oncologic outcome. This study reviews long-term OS and PFS data after RFA of CLM for updating of the evidence base and for identification of the clinical benefit. The aim of this study is to define the role of RFA in multimodality treatment of CLM based on actual outcome data.

2. Materials and methods

2.1. Data sources

A comprehensive MEDLINE (PubMed) search was performed by using the items 'colorectal neoplasms' [MeSH] AND 'liver neoplasms' [MeSH] AND 'radiofrequency ablation' [MeSH] AND 'survival' [MeSH] OR 'treatment outcome' [MeSH]. This list of articles was supplemented with cross-checking of the reference list of all retrieved articles. Original articles published up to August 2008 were considered for inclusion. Review articles, letters, comments and case reports were excluded.

2.2. Study selection

The inclusion criteria for study selection were as follows: (1) a study population including $\geqslant$40 patients with CLM, (2) a median follow-up after RFA of $\geqslant$18 month and (3) reported rates of $\geqslant$3 year OS after the RFA procedure. Exclusion criteria were as follows: (1) the data included liver tumours other than CLM and were not presented separately for CLM and (2) data were published twice (exclusion of the study with the fewest patients). Of 575 articles identified, 21 articles fulfilled the inclusion and exclusion criteria and were selected for data abstraction.

2.3. Data extraction

The following data were extracted for each article: (1) author and year of publication, (2) number of patients and CLM, (3) selection criteria for the RFA procedure, (4) approach and electrode type used, (5) size and number of ablated CLM, (6) length of follow-up (7), rate for and time to local tumour progression (RFA-site), (8) rate for and time to systemic disease progression (new metastases), (9) median length and rate (at $\geqslant$3 years) of OS after RFA treatment, (10) median length and rate (at 2 years) of PFS after RFA treatment, (11) prognostic factors if evaluated, (12) information on chemotherapy before and/or after RFA treatment and (13) complication rates.

3. Results

3.1. Study design

Twenty one non-randomised studies with different designs were identified. Nine of 13 clinical series evaluated RFA as single therapy,[14–22] and four series assessed RFA combined with resection.[28–31] Four of 7 non-randomised comparative trials compared RFA with resection,[22–27] and 3 studies evaluated RFA either combined with or compared to resection and/or chemotherapy.[32–34] The heterogeneity becomes even more complex considering different staging procedures (clinical staging: 10 studies,[14–16,18,20–27,34] by laparoscopy: 2 studies,[17,19] and by laparotomy: 5 studies[28–34]). To facilitate organisation of the data, the studies are grouped into three categories: studies evaluating RFA as single therapy (Table 1), studies comparing RFA with resection (Table 2) and studies evaluating RFA plus or versus other therapies (Table 3).

3.2. Patient selection

All patients underwent RFA for 'unresectable' CLM. The criteria for unresectability differed between studies and were not exactly defined. Reasons for exclusion of surgery in studies performing percutaneous and/or laparoscopic RFA (Tables 1 and 2) were as follows: comorbidity (36–73%), prior hepatectomy (14–50%), unresectable CLM at imaging (9–36%) or patients refusal (2–18%).[14–16,18–23,25–27] In studies selecting patients during laparotomy (Table 3), indication for open RFA was based on the local surgeons decision that CLM were not completely resectable (due to size, number, distribution and vessel contiguity) relative to the remaining liver volume, and that use of RFA would potentially allow complete tumour eradication.[28–33] Ten studies included a small subgroup of patients (proportion 11–28% of reported cases) with extrahepatic disease.[14–16,18,19,21,22,29,31,34]

3.3. Tumour characteristics

The maximum size and number of metastases reported as limiting inclusion criteria for RFA treatment ranged from $\leqslant$4 to $\leqslant$12 cm and from 1 to $\leqslant$5, respectively. The mean size and number of metastases treated by RFA per patient varied between 1.8–3.9 cm (range 0.2–13.5 cm) and 1–4.1 (range 1–12).

3.4. Technical approach

The access routes were as follows: percutaneous,[14–16,22–27] laparoscopic,[19] mixed percutaneous, laparoscopic and open,[17,18,20,21,24,34] or open.[28–33] The electrode types used were as follows: expandable,[16–19,24,28,30–34] internally cooled,[14,15,23,26] internally cooled and expandable,[20–22,25,27] and internally cooled, expandable and perfused electrodes.[29]

3.5. Local tumour progression

RFA-site recurrence rates after percutaneous and open RFA were 9–42% [14,16–18,20–27] and 5–14%,[28–33] respectively. Isolated first RFA-site recurrence occurred in 8.2–36% of treated patients.[21,25,26,33] Median time to local tumour progression var-

Table 1 – Studies evaluating radiofrequency ablation as single therapy for unresectable liver metastases of colorectal cancer.

First author (year)	No. of patients (tumours)	Mean tumour size (cm) [range]	Route of access	Follow up (month) [range]	Local tumour progress	Systemic disease progress	Overall survival		Patient selection		
							Median (month)	Years (y)	Inclusion criteria for RFA	Exclusion of surgery (reasons)	Chemotherapy
Solbiati et al.[14]	117 (179)	2.8 [0.7–9.6]	Perc: all	18 [6–52]	39%	66%	36[c]	3y: 36%[c]	LM < 4 < 10 cm Limited EHD	Comorbidity, patients refusal, prior hepatectomy, EHD	17% Before RFA 72% Parallel to RFA (response NR)
Gillams and Lees[15]	73 (174)	3.9 [1.0–12]	Perc: all	32	NR	89%	31[c] 38[b]	5y: 25%[c] 5y: 30%[b]	LM < 5 < 5 cm Non-active EHD	Comorbidity, distribution of LM	80% Before RFA 47% Failure CT
Jakobs et al.[16]	68 (183)	2.3 [0.5–5]	Perc: all	21 [8–38]	18%	NR	NR	3y: 68%[c]	LM < 5 < 5 cm Limited EHD	Multidisciplinary decision (reasons not specified)	78% Parallel to/after RFA (response NR)
Amersi et al.[17]	74[a] (213)	3.4 [0.8–13.5]	Perc: 19 Lap: 14 Open: 41	33 [12–91]	24%	43%	30[c]	5y: 30%[c]	Small bilobular LM No EHD	Multidisciplinary decision and Lap diagnosis: R0 impossible	~80% Failure of CT before RFA
Abitabile et al.[18]	47 (174)	2.4 [0.3–12]	Perc: 23 Open: 47	21 [2–78]	9%	62%	39[b]	5y: 21%[b]	Limited extent of LM (80% < 3 cm) Resectable EHD	Comorbidity, patients refusal, R0 impossible, too small remnant LV	No CT before RFA, CT after recurrence after RFA
Siperstein et al.[19]	234 (665)	3.9 [1.1–10.2]	Lap: all	24 [1–94]	NR	82%	24[c]	5y: 18.4%[c]	LM < 20% of LV LM < 8(–12) cm Limited EHD	Comorbidity, R0 impossible, EHD	80% Failure of CT before RFA
Sorensen et al.[20]	100 (332)	2.2 [0.6–6.5]	Perc: 86 Open: 14	23 [1–92]	11%	NR	32[c] 52[b]	4y: 26%[c] 5y: 44%[b]	LM < 4 < 4 cm No EHD	Comorbidity, patients refusal, prior hepatectomy	25% Neoadjuvant before RFA (down-seizing, response)
Veltri et al.[21]	122 (199)	2.9 [0.5–8]	Perc: 108 Open: 14	19 [1–86]	26%	74%	31[c] 38[b]	5y: 22%[c] 5y: 33%[b]	LM < 5 < 5 cm LM < 20% of LV Limited EHD	Comorbidity, R0 impossible, EHD	71 % Before RFA 80% Parallel to RFA (response NR)
Gillams and Lees[22]	40 (40)	2.3 [0.8–4]	Perc: 40	38 [6–132]	42%	68%	59[c] 63[b]	5y: 40%[c] 5y: 54%[b]	Solitary LM < 4 cm Non-active EHD	Comorbidity, vessel contiguity, prior hepatectomy, poor biology	80% Failure of CT before RFA

CT, chemotherapy; EHD, extrahepatic disease; LM, liver metastases; LV, liver volume; NR, not reported; Perc, percutaneous; Lap, laparoscopy; RFA, radiofrequency ablation; and R0, complete tumour eradication.

a Additional 107 patients with non-colorectal LM were not included into analysis.

b Calculated from time of diagnosis of LM.

c Calculated after RFA treatment of LM.

Table 2 – Non-randomized studies comparing radiofrequency ablation for unresectable liver metastatses of colorectal cancer with resection.

First author (year)	No. of patients and technique	Mean tumour size [range] (cm)	Follow up median [range] (month)	Local tumour progress (%)	Systemic disease progress	Overall survival		Patient selection		
						Median (month)	Years (y)	Inclusion criteria RFA	Exclusion of surgery (reasons)	Chemotherapy
Oshowo et al.[23]	25 Perc RFA 20 Resection	3 [1–10] 4 [2–7]	18	12 0	>44% NR	37[a] 41[a]	3y: 53%[a] 3y: 55%[a]	Solitary LM	Comorbidity, EHD, vessel contiguity of LM	88% Before RFA 85% Before resection (response NR)
Aloia et al.[24]	30 Perc/open RFA 150 Resection	3 [1–7]	31.3 [4–138]	37 5	47% 39%	NR NR	5y: 27%[b] 5y: 71%[b]	Solitary LM	Comorbidity, liver disease, too small LV remnant	NR
White et al.[25]	22 Perc RFA 30 Resection	2.4 [1–5] 2.7 [1–5]	17 68	36 0	41% 60%	31[b] 80[b]	3y: 28%[b] 5y: 65%[b]	Solitary LM	Comorbidity, too small LV remnant, R0 impossible, prior hepatectomy	66% After resection 80% Before RFA 50% After RFA (response NR)
Park et al.[26]	30 Perc RFA 59 Resection	2.0 [0.6–4] 3.1 [0.5–8]	49 [10–149]	23 1.7	60% 55%	36[b] 56[b]	5y: 19%[b] 5y: 48%[b]	1–3 LM 1–5 LM	Comorbidity, patient refusal, too small remnant LV	73% After RFA 81% After OP (response NR)
Hur et al.[27]	25 Perc/open RFA 42 Resection	2.5 [0.8–3.6] 2.8 [0.6–8]	42 [13–120]	28 9.5	72% 47%	41[b] 60[b]	5y: 25%[b] 5y: 50%[b]	Solitary LM	Comorbidity, patient refusal, too small LV remnant, vessel contiguity of LM	NR

CT, chemotherapy; EHD, extrahepatic disease; LM, liver metastases; LV, liver volume; NR, not reported; perc, percutaneous; RFA, radiofrequency ablation; and R0, complete tumour eradication.
a Calculated from time of diagnosis of LM.
b Calculated after RFA treatment of LM.

Table 3 – Studies evaluating radiofrequency for unresectable liver metastases of colorectal cancer in multimodal and comparative concepts.

First author (year)	No. of patients	Median tumour size (cm) [range]	Follow up (month) [range]	Route of access	Surgical decision[a] of R0 resectability and treatment (no. of treated patients)	Local tumour progress	Systemic disease progress	Overall survival		Patient selection	
								Median (month)	Years (y)	Inclusion criteria for single or adjunct RFA	Chemotherapy
Pawlik et al.[28]	124[c]	1.8 [0.2–12]	21	Open: all	No: resection + RFA (124)	6%	57%	37[b]	5y: 30%[b]	Bilobular LM, R0 only feasible + RFA No EHD	NR
Elias et al.[29]	63	1.3 [0.4–10]	27 [15–74]	Open: all	No: resection + RFA (63)	7%	71%	36[b]	3y: 47%[b]	<3 cm deep located LM, R0 only feasible + RFA resectable EHD (27%)	90% Before RFA 70% after RFA (response NR)
Kornprat et al.[30]	665	2 [1–6]	21 [1–71]	Open: all	No: resection + RFA (39[d])	14%	78%	Mean 45[b]	3y: 50%[b]	Bilobular LM ± liver disease R0 only feasible + RFA	85% Neoadjuvant prior RFA (response) 100% after RFA
Ogata et al.[31]	105	2.1 [1.2–4]	47 [2–134]	Open: all	No: RFA ± resection (50[e])	5%	78%	43[b]	5y: 32%[b]	<4 cm deep located LM, R0 feasible with RFA Limited EHD (22%)	RFA: NR CT when RFA impossible
Abdalla et al.[32]	418	2.5	21 [4–112]	Open: all	Yes: resection (190)	2%	52%	NR	5y: 58%[b]	Extensive LM, R0 + suficient remnant LV only feasible with RFA	RFA ± resection: NR CT- group: systemic ± intraarterial CT
					No: RFA + resection (101)	5%	64%		4y: 36%[b]	No EHD	
					No: RFA alone (57)	9%	84%		4y: 22%[b]		
					No: chemotherapy (70)	–	–		4y: 9% [e]		
Ruers et al.[33]	201	3 [1-12]	61	Open: All	Yes: resection (117)	0.9%	68%	61[b]	5y: 51%[b]	Extensive LM, R0 + >30% preserved LV only feasible with RFA	RFA: no CT until disease progression
					No: RFA ± resection (45[f])	11%	89%	31[b]	5y: 27%[b]	No EHD	CT-group: 5-FU ± new agents
					No: chemotherapy (39)	–	–	26[b]	5y: 15%[b]		
Machi et al.[34]	100	3 [0.9–17.4]	24 [2–84]	Open: 62	No: RFA (100)	6.7%	87%	28[b]	5y: 30%[b]	LM < 40% of LV	RFA before 1st line CT versus RFA after 2nd line CT
				Lap: 23 Perc: 61	No: RFA → 1st line CT (55) No: 2nd line CT → RFA(45)	NR NR	NR NR	48[b] 22[b]	5y: 45%[b] 5y: 15%[b]	Unresectable EHD 19%	

CT, chemotherapy; EHD, extrahepatic disease; LM, liver metastases; LV, liver volume; NR, not reported; Lap, laparoscopy; RFA, radiofrequency ablation; and R0, complete tumour eradication.

a Intraoperative decision of the local surgeon.

b Calculated after RFA treatment of LM.

c Additional 38 patients with non-colorectal LM were not included into analysis.

d Including 20 patients undergoing cryosurgical ablation.

e Including 25 patients undergoing microwave ablation.

f Including 18 patients undergoing cryosurgical ablation.

ied between 3.5 and 9 months (range1.5-39 months).[14,19,21,26–28,33]

3.6. Systemic disease progression

Rates of new hepatic and/or extrahepatic metastases ranged between 41% and 99%.[14,15,17–19,21,25–30,32–34] Recurrence isolated to the liver occurred in 24–70% of patients.[15,21,25–27,32,33] Median time to systemic progression varied between 6 and 13 months.[14,19–21,25–27,30,33]

3.7. Survival

Median and 5-year OS varied between 24–59 months and 18–40%, when calculation begins after the time of RFA treatment,[14,15,17,19–22,24–27,34] and 37–63 months and 21–54%, when calculation begins from the time of diagnosis of CLM.[15,18,20–23] Median and 5-year OS ranged between 36–45 months and 27–30%, when calculated after RFA combined with resection,[29–33] and 41–80 months and 48–71%, when calculated after resection alone.[24–27,32,33] Median and 2-year PFS after RFA alone ranged between 6–13 months and 17–55%.[19,25,29,33,34]

3.8. Complications

Overall (major) complication rates ranged between 13–27% (3.5–13%) after open RFA,[28–33] and 1.8–13% (0.9–7%) after percutaneous RFA.[14–16,20–27] The mortality rates were 0–3.7% after open RFA,[28–33] and 0% after percutaneous RFA.[14–16,20–27]

3.9. Chemotherapy

There were no detailed data on specific schedules. The insufficient data about pre- and post-RFA chemotherapy treatment can be grouped as follows: no information about chemotherapy,[24,27,28,31,32] no chemotherapy until disease progression after RFA;[18,33] concomitant chemotherapy (72–100% of patients) with unclear response,[14,16,21,23,25,26,29] failure of chemotherapy (⩾80% of patients) before RFA[15,17,19,22] and response to chemotherapy (downsizing of 25–85% of CLM) before RFA.[20,30] Comparative studies showed significantly improved OS in favour of RFA when comparing RFA plus chemotherapy versus RFA alone,[19] RFA versus chemotherapy alone[29,30] and RFA as part of a first-line treatment versus RFA following second-line chemotherapy.[34]

4. Discussion

4.1. Limitations of the review

The role of RFA in multimodality treatment of CLM could be at best defined from phase III randomised trials comparing RFA with standards in CLM treatment such as surgery and chemotherapy. However, such trials had little success in recruiting patients.[12,13] The difficulty may reflect that any therapy in the complex group of stage IV CRC patients is highly individualised. Particularly any local therapy of CLM requires an individual decision based on the specific characteristics of the patient, the tumour, the course of disease and the individual aims of oncologic care. The ongoing advances of surgical[4–8] and systemic[1–3] treatment may additionally complicate the recruitment for randomised trials evaluating an interventional technique.

Awaiting data from randomised trials, this systematic analysis may come as close as one can currently get to define the role of RFA in multimodality treatment of CLM. As for its main strength, we found a sizable body of 13 larger clinical series and 8 comparative studies now demonstrating long-term OS after RFA treatment in a total of 1.578 patients with 3.655 RFA-treated CLM.[14–34] As for its main weakness, the figures relating to OS after RFA are difficult to be interpreted since the studies are heterogenous in study design, patient selection, tumour characteristics, data collection, route of access, electrode types used and periinterventional systemic treatment. However, the reported RFA associated OS data are relatively consistent. The two key questions are whether RFA is equal to resection in resectable CLM, and what additional benefit does RFA have over chemotherapy for unresectable CLM. The nature of the analysed studies precluded a meaningful meta-analysis. We conducted a systematic analysis following the idea of evidence-based practice techniques.[11] We recognise the limitations of this less formal analysis and, therefore, our answers and conclusions should be viewed with some cautions.

4.2. Local recurrence rates

Local recurrence rates of RFA-treated CLM varied widely, between 5% and 42%.[14,16–18,20–33] The dominant factor influencing local failure rates is the size of CLM,[35–37] with a dramatic increase in relapse rate for ⩾3 cm in diameter RFA-treated CLM.[9,19,21,27–29,32] Ahmed et al. obtained fewer local recurrences comparing more effective second-generation versus first-generation RFA probes (5% versus 17%).[38] However, RFA cannot achieve a similar degree of local control as resection, with margin recurrences of 0.9–5% for resected CLM.[24,26,32,33] Most RFA-site recurrences occurred at the rim of the ablated CLM within 6 months (range 1.5–39 months).[14,19,21,26–28,33,34] New RFA technologies can achieve ablation volumes of 5–6 cm in diameter.[4,9,38] RFA treatment of CLM, however, should intend a safety margin surrounding the macroscopic tumour edge because peritumoural micrometastases are found in 31–50% of resected CLM.[39] Overall, current data and RFA-techniques limit its use to small CLM (⩽3–4 cm), whereas hepatectomy is limited to preserve >30% of functional liver parenchyma.[4,6]

4.3. Systemic recurrence rates

Most RFA-treated patients (range 41–99%) developed new hepatic and/or extrahepatic metastases,[14,15,17–19,21,25–30,32–34] predominantly within 9–13 months, and in about 40–50% confined to the liver.[15,21,25,26,32,33] Two groups compared surgically staged patients undergoing open RFA for unresectable or resection for resectable CLM; Ruers et al. showed a significantly lower median PFS in the RFA-group (9 months versus 18 months after resection),[33] and Abdallah et al. reported a significantly higher intrahepatic recurrence rate in the RFA-group (44% versus 11% after resection).[32] Park et al.[26] reported similar finding following ablated versus resected patients (median PFS 11 months versus 24 months; intrahepatic recurrence 43%

versus 16%). As a consequence, patients who received RFA in published series were probably at a higher risk of developing new metastases for two reasons. First, they had more advanced disease, as RFA was performed in unresectable CLM. Second, hepatectomy may reduce unrecognised parenchymal micrometastases who are at a risk for future CLM.

4.4. *Comparison of RFA with resection*

The 5-year OS after resection of resectable CLM is 23–58%, with contemporary rates approaching 51–58%.[4–8,32,33,39] When applied to unresectable CLM, the 5-year OS after RFA is 18–40%.[14,15,17,19–22,24–27,34] These rates correlate to those observed after other non-surgical local techniques as microwave ablation (29%), laser ablation (33%) or cryoablation (26%), but they remain below those observed with resection.[4,39] However, resection was applied to 'resectable' and RFA to 'unresectable' CLM.

Factors that determine resectability include comorbidity, disease extent, response to chemotherapy and hepatic reserve.[3–9] The definition of what constitutes resectability varies largely between analysed studies and depends on the opinion and experience of the centre (Tables 1–3).[14–34] Nevertheless, patients undergoing RFA generally have a less favourable prognosis as poor performance status, extrahepatic disease and failure of chemotherapy are generally considered as a contraindication for hepatectomy.[4–8,39] In fact, the patients recruited in the RFA study reporting the lowest 5-year OS rate (18.4%) fall into a poor prognostic group, as they were deemed inoperable, had extrahepatic disease (23.5%) and/or failed prior chemotherapy (80%).[19]

It could be argued that lead time and selection bias may be responsible for the improved OS associated with resected CLM. However, there are several lines of evidence in favour of hepatectomy. First, technical advancements as portal vein embolisation and multi-stage approaches now enable resection of up to 70% of liver parenchyma,[4,6] whereas RFA is ineffective for CLM >4–5 cm in size.[4,9,37] Second, even for small (⩽3 cm) CLM, local failure is more common after RFA than after resection, and incompletely RFA-treated CLM progressing to incurability has been described.[35,41] Third, it seems unlikely that the differences in local control and intrahepatic recurrence do not translate into the differences in outcome. Fourth, RFA to date is palliative, whereas resection has a documented potential for attaining cure based on at least 17% and potentially 25% 10-year survivors.[5]

The overwhelming evidence in favour of metastectomy does not support RFA as an alternative to resection of resectable CLM. Some authors propose a new effort to run a randomised trial comparing RFA and resection for resectable CLM.[40] However, in accordance with other groups,[32,41,42] we do not think that it is time for such a trial yet.

4.5. *Comparison of RFA with chemotherapy*

Chemotherapy for unresectable CRC disease is rarely, if ever, associated with long-term OS beyond 5 years.[1–3] Use of 5-FU plus irinotecan, oxaliplatin, bevacizumab and cetuximab now results in median OS of 16–24 months, whereas non-responders and patients receiving fluorouracil-based salvage chemotherapy survive 6–12 months.[1–3,19] Median and 5-year OS after RFA of CML is, respectively, 24–59 months and 18–40%, when calculated from the time of intervention,[14,15,17,19–22,24–27,34] with an increase to, respectively, 37–63 months and 21–54%, when calculated for RFA from the time of diagnosis of CLM.[15,18,20–23] Based on these data, the use of RFA in a subgroup of CRC patients with unresectable CLM seems justified.

Following surgically staged patients with newly diagnosed liver-only CLM and comparable prognostic factors, Ruers et al. observed an improved OS of 5 months after RFA without chemotherapy until progression (31 months) versus up-front chemotherapy alone (26 months).[33] Some authors calculated an additional OS benefit from RFA of 24–30 months, given that 80% of their RFA-treated patients failed prior chemotherapy.[19,43] Machi et al. showed an improved OS of 26 months for RFA as part of first-line treatment (48 months) versus RFA following second-line chemotherapy (22 months).[33] Siperstein et al. showed an improved OS of 28 months versus 19 months for those who received chemotherapy after RFA.[19] Two surgical groups demonstrate improved OS rates after RFA of liver-only CLM versus chemotherapy alone at 4 years (22% versus 9%)[32] and at 5 years (27% versus 15%).[33]

The insufficient detailed information about pre- and post-RFA chemotherapy makes it difficult to evaluate an independent effect achieved by RFA. However, there is some evidence supporting an additional benefit from RFA adjunct to chemotherapy. First, without subsequent chemotherapy, RFA can obtain median PFS of 6–13 months, which may provide time without toxicity[19,25,26,30] with good quality of life.[33] Second, in the RFA-collective, RFA of CLM has the potential for attaining 5-year OS rates of 18% (calculated from the time of RFA after the failure of chemotherapy) [19] up to 44–54% (calculated from the time of diagnosis of CLM).[22,33] Although one cannot definitively exclude that these results are due to the selection of patients, it seems unlikely that these OS rates would have been obtained without RFA.

Based on the pooled and individual study RFA OS data, RFA appears to confer an OS benefit over chemotherapy alone of 5 to potentially 30 months and in terms of 10–15% improved 5-year survivors, particularly when it is offered as a part of first-line treatment.[19,30–34,43] However, RFA OS data are extracted from the studies recruiting their patients from 1995 to 2007, and we cannot exclude that RFA OS data of our analysis are in part a reflection of improved systemic therapy resulting in longer OS despite recurrence. The interim results of the randomised phase II EORTC-CLOCC trial comparing RFA and chemotherapy versus chemotherapy alone in unresectable liver-confined CLM showed an improved PFS (median 16.8 versus 10 months; 60% versus 39% at 1 year) in favour of the combination; the primary end-point; however, the OS at 30 months is not reached yet.[13]

4.6. *Prognostic factors*

Prognostic factors in the analysed RFA-studies parallel those of liver resection studies.[44,45] As a common finding, significant factors for better OS are ⩽3 CLM, lesion size ⩽3 cm and carcinoembryonic antigen level ⩽200 ng/mL,[19,21,27–33] which reflects that a limited amount of liver tumour burden is the dominant factor for determining OS after RFA of liver-only CLM.

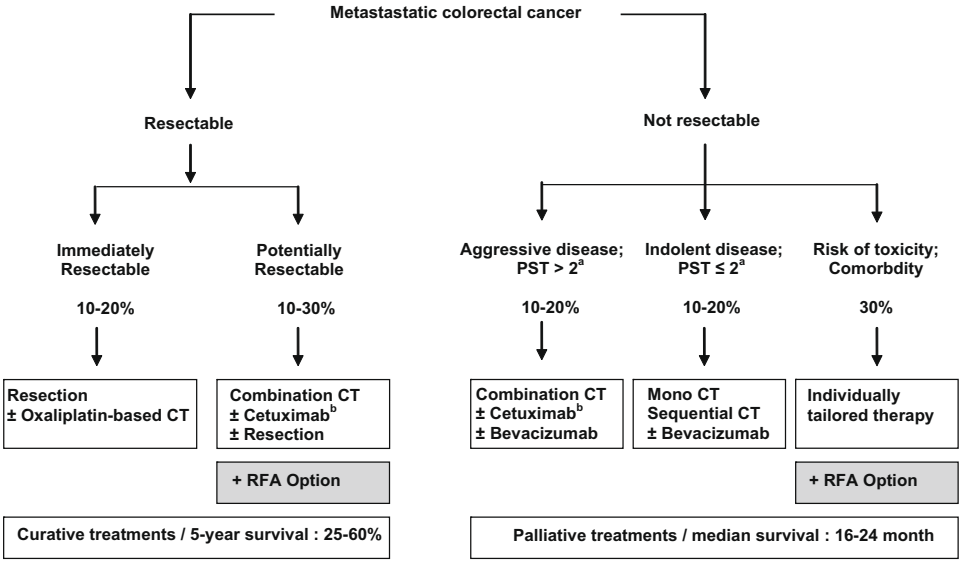

Fig. 1 – Options for liver-directed radiofrequency ablation in multimodality treatment of metastatic colorectal cancer.

4.7. *Extrahepatic disease*

Although generally believed as contraindication, 10 RFA-studies included small groups of patients (11–28%) with extrahepatic disease.[14–16,18,19,21,22,29,31,34] Siperstein et al.[19] found no effect on OS related to the presence of extrahepatic disease, whereas Machi et al.[34] observed a negative effect probably due to the extent of disease. However, limited amounts of extrahepatic disease do not appear to affect OS adversely.[43] RFA may be also useful as an adjunct to chemotherapy in those patients with liver-predominant CLM.

4.8. *Conclusions*

Multimodality treatment of CLM should begin with the consideration of surgery and chemotherapy. RFA offers a complementary option for local treatment of limited CLM (Fig. 1). There are no data to support RFA as an alternative in surgical candidates with resectable CLM. There are, however, data supporting that RFA is an useful adjunct to surgery and chemotherapy in well-selected patients with unresectable CLM. In surgical candidates with extensive liver-confined CLM, open RFA may extend the limits of resection and contribute to complete eradication of disease, particularly as part of a neoadjuvant approach, and ultimately to increase the number of patients treated with a curative intent. In non-surgical candidates with limited predominant or liver-only CLM, percutaneous RFA may eradicate measurable disease, particularly when remaining after downsizing following chemotherapy, and ultimately to prolong time without toxicity and potentially survival. Until the clinical benefits are verified in randomised studies, the use of RFA should be decided restrictively and within a multidisciplinary tumourboard.

Conflict of interest statement

All authors disclose any financial or personal relationships with other people or organisations that could have influenced their work.

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