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Radiofrequency Ablation versus Resection for Resectable Colorectal Liver Metastases: Time for a Randomized Trial?

An Update

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Key Words

Colorectal liver metastases · Radiofrequency · Resection · Review · Randomized trial

Abstract

Background: A recent proposal of a randomized trial comparing resection and radiofrequency ablation (RFA) in a selected subgroup of patients with small resectable colorectal liver metastases (CRLM) has initiated a debate on this issue. Meanwhile, new data have been published. The aim of the study was to update and critically review the oncological evidence in favor of and against the use of RFA for resectable CRLM in general and in favor of and against conducting a randomized trial in a selected subgroup of patients. ***Methods:*** An exhaustive review was carried out of papers and abstracts on RFA of colorectal metastases published before July 15, 2008. ***Results:*** Local recurrence rate after resection of CRLM is 1.2–10.4%. Local recurrence rate after RFA of CRLM is between 1.7 and 66.7%. For tumors <3 cm, local control after open RFA is equivalent to resection. Local recurrence rates, however, are higher for larger tumors and for the percutaneous and laparoscopic route. Accumulating evidence suggests that RFA and resection induce profoundly different biological effects, which may influence survival. ***Conclusions:*** Local recurrence rate after open RFA for CRLM <3 cm seems to be equivalent to resection. A randomized trial under strict conditions would be justified in this subgroup of patients. A randomized trial is currently not justified for larger tumors or for percutaneous or laparoscopic RFA, since local recurrence rates in these groups are too high to be acceptable for resectable tumors.

Introduction

Surgical resection currently is the gold standard in the treatment of resectable colorectal liver metastases (CRLM) [1]. Evidence for the superiority of surgical resection over no treatment comes from several retrospective studies comparing the survival of patients with potentially resectable metastases. In these studies, 5-year survival was 27, 25, 25 and 31% in resected patients versus 0, 0, 1 and 0% for untreated, but otherwise comparable patients [2–5].

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Table 1. Survival after resection of CRLM

Reference No.	Patients	Mortality %	5-year survival %	10-year survival %	Remarks
6	423	2	47	28	
7	297	1	28	17	
8	585	NA	33	NA	
9	557	NA	58	NA	
10	410	NA	50	NA	
11	235	4	36	NA	
12	208	0	28	NA	
13	168	5	23	NA	
14	190	NA	58	NA	
15	133	0	58	NA	
16	102	3	29	NA	
17	100	1	58	NA	
18	150	NA	71	60	solitary
19	116	0	66	NA	solitary

NA = Data not available.

Five-year survival after resection of CRLM in series published since 2000 reporting their experience since 1990 is 23–58% [6–19], and 10-year survival is 17–28% [6, 7] (table 1). Five-year survivals of 66–71% have recently been reported after resection of solitary CRLM [18, 19]. In a review of high-quality papers on hepatectomy for CRLM published since 1990, 30-day postoperative mortality ranged from 0 to 6.6% (median 2.8%), with a mortality near to 1% in the most recent papers [20].

Very recently, however, hepatectomy is being challenged by a number of interstitial tissue 'ablation' techniques. These techniques were initially developed for the palliative treatment of unresectable liver tumors. Applied to unresectable CRLM, they achieve 5-year survival rates of 29% for microwave ablation [21], 33% for laser ablation [22] and 26% for cryoablation [13]. Radiofrequency ablation (RFA), the subject of this article, allows a 14–55% 5-year survival rate [18, 23–30, 192, 193] and a 28% 7-year survival rate [26] in these patients (table 2a).

Enthusiasm about these at first sight promising results in the 'palliative' (see further) setting has led an increasing number of interventional radiologists to suggest [31] or to apply and defend [23, 25, 32–37] (percutaneous) radiofrequency ablation for the treatment of resectable CRLM too, even though there is no evidence yet from randomized trials to support this. Even some surgeons are suggesting that RFA may replace resection, especially in certain circumstances such as new hepatic metastases after a first liver resection [38–44], limited central disease that technically would require a hemihepatectomy [42, 45, 46], small metastases [42, 45, 47–49] and solitary metastases [50].

Undoubtedly, the recently shown equivalent survival after percutaneous RFA and surgical resection for hepatocellular carcinomas (HCC) <5 cm in two randomized clinical trials [51, 52] will encourage the use of RFA for resectable CRLM.

The advantages of minimal invasiveness for RFA, combined with claims of equivalent local control [42, 45, 48] and equivalent survival [32, 36, 38, 50, 53], have already influenced our everyday practice. A survey from Germany reported that 25.9% of hospitals performed RFA for resectable tumors [54]. The practice of performing RFA for resectable CRLM has also been noted in the USA [55, 56].

Three recent papers that proposed a randomized trial comparing resection and radiofrequency ablation for resectable colorectal liver metastases [53, 57, 192] have initiated a lively debate on this issue [58–63, 192, 194]. Meanwhile, new data have emerged. The aim of this study is to update and critically review the oncological evidence in favor of and against the use of RFA for resectable CRLM in general and in favor of and against conducting a randomized trial in a selected subgroup of patients.

If such potential situations can be identified after a well-balanced analysis, a proposal for a randomized trial for these selected indications may be formulated. In this article, we try to evaluate whether indeed the time has come to consider such a randomized trial.

Materials and Methods

A literature review was carried out according to recent guidelines [64], looking for potential oncological advantages and disadvantages of RFA versus resection for resectable colorectal liver metastases.

A potential oncological advantage or disadvantage was defined as a factor that might influence 5-year survival in a positive or negative way, respectively.

A comprehensive PubMed search of the world literature was performed using the key words [radiofrequency *or* radio-frequency *or* radio frequency] *and* [liver *or* hepatic *or* hepatocellular], without language restriction, from January 1, 1990, to July 15, 2008. Additional papers and book-chapters were identified by a cross-reference search. To include as much 'grey literature' [64] as possible, all conference supplements from the same period published in *American Journal of Radiology, Journal of Vascular*

Table 2. Five-year survival of RFA for unresectable CRLM

a Five-year survival of RFA for unresectable CRLM, all sizes[1]

Reference No.	Patients	Tumors/patient	Diameter of tumors cm	Approach	Mortality %	5-year survival %	7-year survival %
23	423	1.5	2.7 ± 0.9 (0.5–5)	P	NA	24	NA
24	177	2.2	2.2 (0.4–8)	P	NA	55	NA
25	167	4.1	3.9 (1–12)	P	0	14	NA
26	121	2.6	2.1 ± 0.9 (0.9–4)	P	0	35	28
27	234	2.8	3.9 (1.1–10.2)[a]	L	NA	18	NA
28	50	3.2	4.2	O	0	32	NA
29	122	1.6	2.9	P, O	0	22	NA
30	100	5.1	3 ± 1.6 (0.3–17.4)	P, L, O	1	31	NA
193	68	1	3.7 ± 0.2[b]	L	0	30	NA

b Five-year survival of RFA for subgroups of patients with unresectable CRLM ≤4 cm[2]

Reference No.	Patients total series	Patients subgroup	Tumors/patient	Diameter of tumors cm	Approach	5-year survival %	7-year survival %
191	291	40	1	≤4	P	40	NA
26	121	121	2.6	≤4	P	35	28
27	234	NA	2.8[c]	≤3	L	18	NA
29	122	NA[d]	1.6[c]	≤3	P, O	34	NA
18	>57[e]	30	1	≤3	O	18	NA
23	423	NA	1	≤2.5	P	56	NA

[1] Only independent series with ≥50 patients and data on 5-year survival calculated from the time of RFA were retained. [2] Only subgroups from series with a total of ≥50 patients and data on 5-year survival calculated from the time of RFA were retained.

[a] Diameter of dominant tumor. [b] Standard error of the mean (instead of standard error of the other series). [c] In total series. [d] 64% of tumors were ≤3 cm. [e] Based on reference 14.

P = Percutaneous; L = laparoscopic; O = laparotomy; NA = data not available.

and Interventional Radiology, European Radiology, Surgical Endoscopy, European Journal of Surgical Oncology and *Acta Chirurgica Belgica* were screened manually for abstracts on hepatic radiofrequency ablation, as well as all the proceedings of the annual meetings of the *RSNA*. The proceedings of the annual general and GI meetings of the *ASCO* [http://www.asco.org/] and of the 2007 and 2008 annual meetings of the *AHPBA* [http://www.ahpba.org/resources/prior_program_abstracts.asp] were screened electronically.

Both positive and negative studies were included. Papers or abstracts were excluded if they described clinical series that were partially or completely contained in publications at a later date. In case of overlap, only the most recent and complete report was retained. Evidence was ranked according to recent guidelines [64].

Survival after RFA

There are no 5-year survival data available yet after RFA for resectable CRLM. Five-year survival after RFA for unresectable CRLM varies between 14 and 55% [23–30, 193] (table 2a). Subgroups of patients with metastases ≤2.5–4 cm have a better prognosis [18, 23, 26, 27, 29, 191] (table 2b).

Eight nonrandomized studies have compared survival after RFA for unresectable CRLM versus after resection for resectable CRLM [14, 18, 19, 50, 65, 66, 192, 193]. Six studies found a better overall and/or disease-free survival after resection [14, 18, 19, 65, 66, 192], while two studies found no statistically significant difference [50, 193]. In-

Table 3. Oncological arguments pro and contra RFA for resectable CRLM

a Oncological arguments with direct evidence pro and contra RFA for resectable CRLM

Arguments with direct evidence	Level of evidence	Type of evidence
In favor of resection		
Better local control (except for tumors ≤3 cm using RFA via an open approach)	V	Meta-analysis of case series
Better staging: resection allows better intraoperative staging and hence an optimized treatment strategy in 40% of patients (vs. percutaneous RFA; not vs. surgical RFA)	V	Case series
No electrode track seeding (0–1.4% risk after percutaneous RFA)	V	Case series
In favor of RFA		
–		
Balance between resection and RFA unknown		
–		

b Oncological arguments with indirect evidence pro and contra RFA for resectable CRLM

Arguments with indirect evidence	Level of evidence	Type of evidence
In favor of resection		
Risk of post-RFA intrahepatic seeding	VII	level V evidence for increased seeding post-RFA in HCC
Risk of increased local and distant spread through post-RFA increased matrix metalloproteinase (MMP) activity	VII	level II evidence for increased MMP activity post-RFA; level V evidence for worse prognosis in patients with increased MMP activity
In favor of RFA		
(Resection) techniques with more parenchymal sparing allow a higher reintervention rate for new metastases and a better survival	VII	level V evidence for resection
Less immune suppression through less blood loss Post-RFA vs. postresection	VII	level V evidence for less blood loss post-RFA; level V evidence for relation between perioperative transfusion and survival
Stronger stimulation of cellular immunity post-RFA vs. postresection	VII	level II evidence from animal RCT#
Balance between resection and RFA unknown		
Stimulation of growth of residual tumor cells post-RFA vs. postresection	VII	level II evidence from animal RCT# for increased stimulation in one study and decreased stimulation in a second study
Risk of hematogenous metastases through increased presence of tumor cells in peripheral blood, both post-RFA and post-resection	VII	level V evidence for increased presence of tumor cells in peripheral blood both post-RFA and post-resection; relation to hematogenous metastases unknown
Post-RFA increased heat shock protein expression (HSP), with both beneficial and detrimental effects	VII	level II evidence for increased HSP expression post-RFA; level II evidence for beneficial effects of increased HSP expression; level V evidence of detrimental effects of increased HSP expression

Levels of evidence according to [64]. HCC = Hepatocellular carcinoma; RCT = randomized controlled trial.

terestingly, one of these studies analyzed 5-year survival in solitary CRLM according to tumor size. Survival was much worse after RFA when all tumors were considered (26% after RFA vs. 50% after resection), but equivalent for the subgroup of tumors <3 cm (55% after RFA vs. 56% after resection) [192].

Unfortunately, these studies do not allow answering the question whether RFA could become an acceptable alternative to resection for resectable CRLM. Resectable colorectal metastases may have a more favorable location and a different biological behavior than unresectable CRLM [42, 67].

Table 4. Local recurrence rate after RFA of CRLM

Main size, approach	Tumors	Mean diameter of tumors, cm	Approach (%)	Median follow-up months	Local recurrence rate, %
Small, open		<3	O (67) P (33)		
[45]	118			33	1.7
Small, laparoscopically					
[75]	308	<3	L	12	26.3
Small, percutaneously					
[26]	295	<3	P	41*	14.9
[29]	120	<3	P (89) O (11)	19	33.3
[34]	134	2.1 (0.6–4.0)	P	28	39.8#
Small, mixed approach					
[77]	76	1.7	L (40) O (38) P (21)	20	6.6
Mixed size, open					
[78]	130	3.6 (0.5–18.0)	O (53) L (7) P (40)	21*	9.2
[14]	57[1]	NA	O	21	9#
Large, open					
[45]	29	>3	O (67) P (33)	33	37.9
Large, laparoscopically					
[75]	130	3–5	L	12	43.3
[75]	42	>5	L	12	59.5
Large, percutaneously					
[26]	25	>3	P	41*	40
[29]	66	>3	P (89) O (11)	19	66.7

Only independent single-center series with ≥50 tumors in the total series and a median follow-up of ≥12 months were included.
Local recurrence rate = n local recurrences/n CRLM. NA = Data not available; P = percutaneous; L = laparoscopic; O = laparotomy.
* Mean follow-up (months). # Patient-based local recurrence rate = n local recurrences/n patients. [1] Number of patients.

Oncological Arguments with Direct Evidence Pro and Contra RFA for Resectable CRLM (table 3a)

Local Control

Local Recurrence after RFA for Unresectable CRLM (table 4)

The rate of local recurrence at the site of the ablation after RFA for CRLM varies widely between 1.7 and 66.7% [14, 18, 19, 26, 29, 34, 45, 50, 66, 68–78]. In a recent meta-analysis of 763 RFA-treated CRLM with a minimum follow-up of 6 months, mean local recurrence rate based on imaging and/or histology was 14.7% [79].

The most studied factors influencing local recurrence rate after RFA include tumor size and type of approach. There is overwhelming evidence that local recurrence rate after RFA of CRLM is smaller for tumors <3 cm than for tumors 3–5 cm, which in turn have a lower recurrence rate than tumors >5 cm [18, 26, 29, 45, 71, 79, 74–76, 80].

Table 5. Local recurrence rate after resection of CRLM

Reference No.	Tumors	Diameter of tumors, cm	Median follow-up months	Local recurrence rate, %
88	199	4.3 (0.7–18.0)	29	10.4
18	150	3.5 (0.5–17.0)	31	5.3
19	116	3.3 (0.5–18.0)	48	6.9
65	109	3.1	49*	1.2
193	90	3.8 ± 0.2#	33	2

Only series with ≥50 tumors were included.
Local recurrence rate = n local recurrences/n CRLM.
* Mean follow-up (months). # Standard error of the mean (instead of standard error for the other series).

Similarly, there is much evidence that local recurrence rate is lowest for the open surgical approach, highest for the percutaneous approach, and probably intermediate with the laparoscopic approach. Six studies found superior local control rates for the open surgical approach compared to the percutaneous approach [79, 81–85]. Data on local recurrence rate after the less frequently used laparoscopic approach are harder to find. A retrospective study found a higher local recurrence rate for a laparoscopic approach when compared to an open approach [84]. A very recent study found a 26.3% local recurrence rate after laparoscopic RFA of CRLM <3 cm [75, size-related data kindly provided by Berber], which is higher than the 1.7% local recurrence rate in small CRLM treated by (mainly) open approach [45] (table 4).

Based on the above-mentioned data, authors publishing clinical results after RFA (local recurrence rates as well as survival) are strongly encouraged to analyze and report data separately for each approach (percutaneous, laparoscopic and open) and for each size category: small (≤3 cm), medium (3–5 cm), and large (>5 cm). Mixing up results after RFA through different approaches for a mixture of tumors of different sizes renders a correct interpretation, let alone a sound comparison with surgery, nearly impossible [79, 195] (table 4).

Other factors influencing local recurrence rate include proximity of large vessels, normal or interrupted blood flow, intentional ablation margin, and physician experience.

The local recurrence rate after RFA for tumors closer than 5 mm to a vessel of at least 3 mm in diameter is 36.5 versus 6.3% for tumors away from these vessels, in the absence of a Pringle maneuver [79, 86]. Interruption of blood flow neutralizes the increased risk of recurrence for tumors near blood vessels [80].

The local recurrence rates after RFA for tumors treated with an intentional ablation margin of 0, 0.5 and 1 cm are 14.5, 16.4 and 6.5%, respectively [79]. A very recent study found that local recurrence rate was identical for ablation margins between 1–2 and >2 cm, but significantly increased (hazard ratio 1.67) for an ablation margin <1 cm [75].

Four recent studies [76, 79, 81, 83] demonstrated that authors who treated large numbers of tumors had less local recurrences than authors who treated fewer tumors. Significant improvement occurs after 40–50 cases [81, 83], although the plateau phase in the learning curve is reached only at 100 procedures [79].

Local recurrence also seems to be lower when using newer-generation electrodes [45, 87].

Local Recurrence after RFA for Resectable CRLM

In a series of 88 patients with resectable CRLM treated with percutaneous RFA, patient-based local recurrence rate after a median follow-up of 33 months was 39.8% [34].

In a series of 47 patients with resectable recurrent liver tumors after a first hepatectomy (62% with CRLM) treated with percutaneous RFA, lesion-based local recurrence rate after a follow-up of 18 months was 10.3% [38].

Local Recurrence after Resection for Resectable Liver Metastases

Local recurrence rate posthepatectomy in series >50 CRLM is 1.2–10.4% [18, 19, 65, 88, 193] (table 5).

It is clear that RFA should at least equal this low local recurrence rate for resectable CRLM in order to be accepted as an alternative for resection.

Nine nonrandomized studies have compared local recurrence rates after RFA versus after resection for CRLM [9, 14, 18, 19, 65, 66, 73, 192, 193]. Local recurrence rate was found to be higher after RFA than after resection in eight [9, 14, 18, 19, 65, 66, 192, 193], and equivalent in one study [73, CRLM-related data kindly provided by Feliberti and Wagman]. Unfortunately, all nine studies have compared resection for resectable metastases versus RFA for unresectable metastases, so that no definite conclusions can be drawn on the outcome of RFA for resectable CRLM [42, 67].

Staging

A surgical approach (hepatectomy or open/laparoscopic RFA) allows a better staging than a percutaneous approach (percutaneous RFA) [79]. In about 30% of patients, additional hepatic tumors are found by intraop-

erative ultrasound during laparoscopy [69] or laparotomy [89] compared with state-of-the art preoperative imaging. They can be treated with curative intent during the same procedure [89]. These findings are a theoretical argument against the use of percutaneous RF ablation instead of hepatic resection for resectable CRLM, because it represents undertreatment in 30% of patients, which will lead to inferior disease-free survival in these patients. Whether this temporary undertreatment also results in a worse overall survival [89] remains to be seen. The missed tumors can often be treated with a new percutaneous approach as soon as they appear.

In about another 10% of patients, surgical exploration allows the detection of peritoneal metastases [89] or lymph node invasion of the hepatic hilum [89]. The presence of peritoneal metastases [90] or (extensive) hepatic hilum lymph node metastases [91, 92] seriously decreases the chances of 5-year survival so that most authors refrain from liver resection [93, 94]. One author advocates the combined surgical treatment of liver metastases and peritoneal or lymph node disease in selected cases [92, 95]. Whether such a combined treatment is worthwhile or not has to be analyzed by more studies. However, it is hard to believe that percutaneous RF ablation in these patients could have any impact on survival, because undiagnosed and untreated tumor is left behind.

In conclusion, a surgical approach allows better intraoperative staging and hence an optimized treatment strategy in 40% of patients, which may, at least in theory, lead to a better oncological outcome.

Electrode Track Seeding

Several cases of electrode track seeding after RFA of CRLM have been reported [25, 29, 96–103]. The incidence of seeding after RFA of CRLM is 0–1.4 % in large series [25, 29, 97, 99, 101, 102, 104].

Several mechanisms may contribute to seeding [105]. Viable tumor cells may adhere to a biopsy needle [106] or to the electrode [107, 108] during its retraction. Tumor cells may also be carried into the track with a little bleeding. Furthermore, cells may be forced into the track by sudden intratumoral hyperpressure that is frequently encountered during RFA, audible as a popping sound. Finally, when using a wet electrode, cells may leak out the track together with the saline injected into the tumor [109–111].

Risk factors for the development of track seeding include preprocedural biopsies, multiple electrode placements and sessions, a direct approach to subcapsular tumors, no cauterization of the electrode track, and poor differentiation of the tumor [25, 99, 101, 105–107, 112].

Performing a biopsy of resectable CRLM before resection has been shown to be associated with needle track seeding and a deleterious effect on a patient's long-term survival [113]. Similarly, it is to be feared that seeding after RFA seriously jeopardizes a patient's chance of cure.

Oncological Arguments with Indirect Evidence Pro and Contra RFA for Resectable CRLM (table 3b)

Parenchymal Sparing

In a study of 374 patients who underwent a liver resection for CRLM between 1985 and 2004, clear differences were noted between the patients operated before and after 1999. In 1999, a parenchymal sparing strategy was adopted. Since that time, a lower percentage of anatomical resections and a higher percentage of atypical resections were performed, more patients with bilateral and multiple CRLM were operated upon, mortality decreased from 2.7 to 0%, re-resection rate in case of hepatic recurrence increased from 39.2 to 58.2% and 5-year survival increased from 24 to 49.2% [114]. The parenchymal sparing strategy thus was associated with resection of more patients with a higher number of metastases, with an increased re-resection rate in patients with liver recurrence and with a better 5-year survival [114]. For the same oncological reasons, a recent editorial cautiously wondered whether RFA should replace resection for small central lesions that would require large resections [42], while other authors have already applied this idea for several years [25, 39, 45, 115].

Intrahepatic Seeding

Thirty-nine cases of rapidly progressive scattered recurrences after RFA for a small HCC have recently been described [116–123]. The mean incidence of scattered recurrences after RFA of HCC in these series was 3% (range 0.8–8.0%) [118–123].

Scattered recurrences have some common characteristics [120]. First, recurrences occur rapidly following RFA, mostly within 6 months. Second, multiple recurrent tumors are almost equal in diameter. The recurrent tumors are either scattered around the ablated tumor or all over the liver. Finally, they often occur after radiologically complete tumor coagulation [116, 117, 119, 121, 122]. The most probable hypothesis is that they are caused by a too fast coagulation process [120]. Under these circumstances, intratumoral steam production and a steep build-up of

intratumoral pressure has been demonstrated [124]. The tumor then bursts with an audible popping sound, leading to an explosive intravascular spread of the tumor cells into the portal or arterial branches. In one study, scattered recurrences could be completely prevented by replacing the current RFA protocols by slower and more progressive treatment protocols [120], which increased intratumoral pressure much less [124]. Survival of patients with scattered recurrences is significantly worse [120].

After RFA of CRLM, an increase in intrahepatic viable tumor cells has been observed in a small study on 8 patients [125]. So far, however, scattered recurrences of CRLM have not yet been described. Time will tell whether this is due to biological differences between these two tumor types, structural differences between cirrhotic and non-cirrhotic liver, or simply the fact that this complication is not yet widely known and therefore not yet being recognized.

Hematogenous Seeding

There is concern that RFA may increase the release of neoplastic cells into the circulation during the treatment. In a study of 28 patients with HCC, tumor cells in peripheral blood were present in 39% of patients just before RFA and in 50% of patients 1 h after RFA [112]. In a study on 8 patients with CRLM, tumor cells in peripheral blood were present in 12.5% of patients just before RFA followed by resection and in 25% of patients after RFA and resection. In a similar group of 12 patients with CRLM, tumor cells in peripheral blood were present in 0% of patients just before resection and in 50% of patients after resection. The presence of tumor cells in peripheral blood was not related to cancer recurrence after a median follow-up of 3 years [125]. No definite conclusion can be drawn from this study because of small numbers and because of the combination of RFA and resection. It remains unclear whether RFA alone increases the number of tumor cells in peripheral blood in CRLM, whether any increase is more or less than after resection alone and whether this possible increase translates into increased hematogenous metastases.

Cellular and Humoral Factors Influencing Tumor Growth

Data on cellular and humoral factors influencing tumor growth after RFA, such as influence of blood transfusion, growth factors, cellular immunity, and heat shock proteins, are slowly coming in, but they are still scarce and fragmentary.

Blood Transfusion

A large portion of patients undergoing liver resection for CRLM receive a blood transfusion: 46% in a recent study of more than a thousand patients [126]. After RFA, blood transfusion is very exceptional [105]. Blood transfusion is significantly associated with adverse perioperative and long-term survival [126]. Part of this effect is certainly due to a selection bias (worse cases have more perioperative blood loss and need more transfusions), but the known suppressive effects of blood transfusion at various levels of the immune system may also play a role [126]. A difference in amount of blood transfusion between hepatectomy and RFA may, at least in theory, translate into a different survival. This theoretical argument in favor of RFA may disappear with the advent of novel devices that enable near bloodless liver resections [127–132].

Growth Factors

Effect of Hepatectomy on Growth of Residual Tumor

Surgical resection in general stimulates cell division of tumors and facilitates recurrence and spread, in part due to the production and release of growth factors [133].

Hepatectomy in particular is known to stimulate growth of residual, both intra- and extrahepatic, tumor cells in animal experiments [134–138]. The stimulating effect is proportional to the extent of the resection [134, 138]. The stimulation is attributed to the production and release of growth factors for liver regeneration [134–136, 139], the intensity of which is also proportional to the extent of the liver resection [140]. For instance, hepatocyte growth factor, which strongly enhances liver regeneration after surgical resection or chemical damage, has also been found to increase colon cancer cell motility, growth and metastasis [135].

Effect of RFA on Growth of Residual Tumor

RFA of CRLM also induces the release of growth factors such as hepatocyte growth factor [141].

The results of two recent experimental studies on mice on the effect of RFA on the growth of residual tumor are conflicting [137, 139]. In a first study, RFA of CRLM promoted intrahepatic growth of residual neoplastic cells compared with a control group [137]. The stimulation of growth of residual tumor cells was found to be higher after RFA than after resection [137]. In a second and slightly different study partial hepatectomy, but not RFA, stimulated growth of residual neoplastic cells compared

with a control group [139]. The expression of hepatocyte growth factor and basic fibroblast growth factor was increased after hepatectomy, but decreased after RFA [139]. At present, it is unclear why these only slightly different experiments resulted in completely different outcomes. More experiments are needed to clarify this issue.

In a very recent clinical study, growth rate of new HCC nodules after percutaneous RFA was shown to be three times the growth rate of the originally treated HCC nodules [142].

Matrix Metalloproteinase Activity

Matrix metalloproteinases (MMPs) are a family of matrix-degrading endopeptidases that play an important role in the normal turnover of the extracellular matrix. The activity is enhanced in inflammation and in tissue repair [143]. Increased expression of MMPs is also noted in oncological processes such as tumor cell invasion, metastasis and angiogenesis. The MMP-2 and MMP-9 degrade the basement membrane, which allows tumors to spread locally and distally. MMP-2 and MMP-9, which contribute to colorectal cancer progression in experimental models [143], are overexpressed in patients with CRLM [144–146], and are associated with increased risk of tumor recurrence and decreased survival in patients with colorectal cancer [147]. In a pilot RFA experiment in healthy pig liver, a threefold MMP-2 and MMP-9 activity was found in the transition zone surrounding the coagulated hepatic parenchyma [148]. Increased MMP activity may therefore, at least in theory, facilitate local and distal spread of residual malignant cells. If this hypothesis is confirmed by more research, RFA should only be attempted when complete eradication of the tumor including a safety margin is possible.

Cellular Immunity

Surgery

Surgery in general has long been known to cause generalized immunosuppression, including depressed function of immune cells, such as lymphocytes, NK cells and Kupffer cells [133, 149]. This immunodepression in turn may enhance the growth of liver metastases [149].

Hepatectomy in particular is also an immunosuppressive event that results in significant Kupffer cell and T cell dysfunction [150].

RFA

RFA is followed by a marked local inflammatory response with a dense T-cell infiltrate in the liver of tumor-free domestic pig [151] and in the liver of rabbits implanted with a VX2 tumor [152]. Moreover, in several animal models [152–155] as well as in human primary [156–158] or secondary [156, 157] liver tumors, RFA can induce an antigen-specific T cell response. In a rabbit VX2 tumor model, RFA induced the presence of tumor-specific circulating T cells, as well as a dense peritumoral T cell infiltration [152]. T cells of untreated tumor-bearing rabbits showed no reaction and only sparse T cell infiltration. In a murine melanoma cell tumor model, RFA of a tumor nodule caused by tumor cell injection in the thigh induced a modest oncological protection of the surviving mice when exposed to a second tumor cell injection [153]. This protection was measurable as an increase in median and long-term survival, and was T cell mediated. In a murine H22 liver tumor model, RFA stimulated splenocyte activation and proliferation, and enhanced splenocyte cytotoxicity to the tumor cells [154].

In a study with 20 patients with a HCC, RFA induced a tumor-specific T cell response [158]. RFA increased the number of patients responsive to their HCC antigens, the number of circulating tumor-specific T cells, and their degree of cytotoxic activation. RFA in 13 patients with liver metastases and 4 patients with HCC enhanced a T cell-mediated IFN-γ response towards tumor-specific antigens [159]. RFA in 20 patients with primary or secondary liver tumors was shown to induce tumor-antigen-specific CD8+ T lymphocytes in some patients from 3 months on after treatment [156]. In a study with 6 patients with HCC and 6 patients with CRLM, RFA induced a tumor-specific cytotoxic T cell stimulation with a dramatically increased tumor-specific cytolytic activity of CD8+ T cells [157]. Post-RFA necrotic tumor debris has been shown to stimulate the antigen-presenting dendritic cells, which play a pivotal role in the induction of immunity [160–162].

Taken together, these observations support the hypothesis that RFA induces a tumor-specific T cell reaction by facilitating the presentation and recognition of otherwise cryptic tumor antigens by enhanced release, and/or thermal alteration. In other words, the tumor debris left in the body after RFA tumor destruction seems to be a potential tumor antigen source able to activate the immune response. Whether this tumor-specific T cell reaction has any impact on patient survival is currently unknown.

Cellular Immunity after RFA versus Resection

Only one study compared cellular immunity after RFA versus resection. In a murine H22 liver tumor model, splenocyte activation and proliferation, and splenocyte cytotoxicity to the tumor cells were significantly

higher in the RFA group than in the surgical resection group [154].

Humoral Immunity

In patients with CRLM, increased numbers of circulating B cells were found post-RFA [159]. Similarly, an increased serum level of antibodies against colon cancer cells was found in patients after RFA of CRLM, while a decreased serum level was found after resection [163].

Heat Shock Protein Expression

An incomplete coagulation of a liver tumor by radiofrequency is a common event, especially by a percutaneous approach [79]. In the coagulation zone, the temperature between 60 and 100°C causes immediate cell death through protein coagulation and membrane fusing [109]. In the spared tumor tissue immediately adjacent to the coagulation zone, temperature is insufficient (37–60°C) for immediate cell death but causes a variable degree of sublethal damage. This hyperthermic damage stimulates the expression of heat shock proteins (HSP), as has been demonstrated in cell cultures [164], in animal experiments [133, 165, 166], and in patients [156, 166, 167]. Overexpression of HSP in the edge of an incompletely coagulated liver tumor may have beneficial but also detrimental effects from an oncological point of view.

Potential Beneficial Effects of HSP 70 Expression

HSP 70 is involved in tumor antigen presentation which then triggers a cellular immune response against the tumor cells [164, 165]. HSP 70 binds tumor peptides in malignant cells [168]. HSP 70-tumor peptide complexes appear at the cell surface, and are taken up by antigen-presenting dendritic cells. The dendritic cells present the antigens to T cells, which as a consequence may develop into cytotoxic T cells [169]. A clear correlation between hyperthermia-induced HSP 70 expression and an increased cellular immune response has been observed in preclinical models as well as in patients [164, 165].

Potential Detrimental Effects of HSP 70 Expression

HSP 70 is known to inhibit apoptosis and thereby increase the survival of cells exposed to a wide range of lethal, including thermal, stimuli [170]. HSP 70 has been shown to render cells resistant to several anticancer drugs, such as gemcitabine, topotecan, cisplatin, doxorubicin, and 5-fluorouracil [171–173]. Overexpression of HSP 70 has been linked to more malignant phenotypes in breast cancer [174]. Therefore, tumor cells that survive RFA with the induction of HSP 70 expression may alter their biological activities and become more malignant, as well as more resistant to chemotherapy. They also become more resistant to a second heat exposure [170]. This may in part explain the poor local control figures after repeat RFA of a local recurrence [79]. In conclusion, an incomplete RFA treatment of a liver tumor will not only lead to local recurrence, but these surviving tumor cells may have become more resistant to future locoregional or systemic treatments.

Discussion

Rationale for a Randomized Trial

RFA certainly has nononcological advantages over hepatic resection, such as shorter hospital stay [20, 36, 69] and a lower complication rate [6, 11, 13, 15, 20].

Most patients undergoing percutaneous RFA require an overnight stay; some can be discharged the same day, while elderly patients stay 2–3 days [36]. After laparoscopic and open RFA, mean hospital stay is 1–3 days [69] and 4–7 days [69], respectively. When compared to the mean hospital stay of 12.5 days after resection [20], there is certainly an advantage for RFA, whatever the approach.

In a review of 3,670 patients treated by RFA, morbidity of percutaneous, laparoscopic and simple open RFA was 7.2, 9.5 and 9.9%, respectively. Mortality was 0.5, 0 and 0% [105]. Mortality after hepatectomy ranges from 0 to 6.6% (median 2.8%), with a mortality near to 1% in the most recent papers [20]. Morbidity after resection remains significant between 17 and 37% [6, 11, 13, 15, 20].

In oncology, however, the goal is not minimal invasiveness, but cure [14, 175–177]. RFA as a less invasive technique can replace resection only when 5-year survival in a randomized trial is at least as good [79].

Survival

At present, there exist no comparative data, let alone randomized trials, on 5-year survival after RFA versus after resection for resectable CRLM.

Several uncontrolled series and a meta-analysis provided some data on the factors influencing local control rate. Long-term survival, however, does not depend on local control alone. Fragmentary evidence is seeping in, indicating that both RFA and resection have a profound impact on the release of cellular and humoral factors that may stimulate or inhibit growth of residual tumor cells. As the different favorable and unfavorable effects of RFA and resection on blood transfusion, growth factors, cellular

immunity, and heat shock proteins only start to be investigated, the sum of these effects on survival is still unknown. Five-year survival after RFA and after resection may therefore be different, even when applied to a similar patient population with a similar local control rate.

Local Control

Nevertheless, complete local control of CRLM is a minimal requirement for there to be any chance of cure. If even a minimal amount of residual tumor remains after resection [5, 178] or after RFA [179], the treatment is futile, with no impact on survival and no perspective of cure. Retreatment of an established local recurrence by RFA is often impossible or is followed by a high failure rate [18, 71, 75, 79]. Of note, local recurrence rate after resection is not zero, but 1.2–10.4% [18, 19, 65, 88] (table 5).

Proposal for a Randomized Trial

The only way to find out whether RFA can ever replace resection for resectable CRLM is to perform a randomized trial in selected patients for whom the investigator is in a state of equipoise. Equipoise, or uncertainty, means that the investigator has no valid reason to believe that one of the two treatments is superior to the other [180]. At the present state of knowledge, it seems fair to say that situations in which local control rate and staging are at least as good for RFA as for resection represent a state of equipoise. A randomized trial of RFA versus resection for resectable CRLM seems to be justified in these cases. Table 6 proposes in general terms inclusion and exclusion criteria for such a trial.

The importance of these criteria cannot be overestimated. They should guarantee a good local control after RFA. A randomized trial between RFA and resection for CRLM for any size of tumor, for any approach and regardless of physician's experience is ethically unacceptable. These criteria are important, too, for the interpretation of the results of this trial in the future: the results will be valid only for the selected subgroup and cannot be extrapolated to e.g. larger size tumors or other approaches, a fear which has been rightfully expressed recently [58, 60].

A 2002 French attempt for a randomized phase III study (essai FFCD 2002-02) failed because few centers agreed to participate [181]. It is very likely that in 2002, time was not yet ripe. At that time, only short-term survival results were available from uncontrolled studies. The factors influencing local recurrence after RFA were less understood so that a correct selection of a subgroup of patients with a high likelihood of local control was not yet possible.

Table 6. Proposal of a randomized trial of RFA vs. resection for resectable CRLM

Inclusion criteria
– Resectable CRLM, defined as CRLM for which an experienced hepatobiliary surgeon judges that complete tumor resection is possible, obtaining negative resection margins (R0) and preserving adequate liver reserve.
– No contraindication for RFA
– Only small tumors (<3 cm)
– RFA only by open surgical approach, including full exploration for hepatic, peritoneal and regional lymph node metastases
– Only tumors away from large vessels unless a Pringle maneuver can be safely applied
– RFA only by experienced physicians (minimum >50 tumors)
– Intentional margin of 1 cm
– Only with electrodes that produce a well-documented, regular and predictable ablation zone
Exclusion criteria
– Past or present extrahepatic metastases
– Positive lymph nodes at the hepatic hilum
– Patients whose general or specific medical condition is judged not to allow a safe liver resection
– Tumors >3 cm
– Percutaneous and laparoscopic approach
– Tumors near large vessels if a Pringle maneuver cannot be safely applied
– Insufficient RFA experience (<50 tumors)

In the authors' view, the very recent arrival of data on long-term survival after RFA [18, 23–26, 28, 30, 45, 193], data on factors influencing local recurrence [79] and data on size and geometry of the ablation zone [176, 182] have paved the way for a more scientifically founded, more refined and more generally acceptable trial.

The primary end point of such a study should be survival; secondary end points can include disease-free survival, local recurrence rate, procedural morbidity and mortality, hospital stay, quality of life and costs.

In order to prove by a noninferiority trial that the difference in 5-year survival is less than 10% (based on an estimated 5-year survival in both groups of 45% [6–11, 13–15, 17, 18, 23–26, 28, 30, 45], a hypothesized exponential distribution, and α and β risks of 0.05 and 0.20), 380 patients per group would be necessary (StudySize 2.0, CreoStat, V. Frolunda, Sweden). The value of this 10% maximal difference has of course to be discussed, as well as the other parameters involved in the computation. About 48% of patients with resectable CRLM have lesions with a maximal diameter of 3 cm [8]. In other words, nearly half of the patients currently undergoing resection for CRLM can be included in this trial.

It is hoped that the current analysis and proposal strengthens the opinion of the proponents [19, 25, 30, 31, 36, 37, 42, 46, 48, 50, 53, 57, 61, 67, 86, 98, 125, 181, 183–187, 192, 193] of such a study and contributes to convince its opponents [18, 58, 59, 62, 188–190, 194]. We hope that, in the era of evidence-based medicine, the surgical community will support a renewed effort to run such a trial (for more information, please contact: t.ruers@nki.nl or stefaan.mulier@skynet.be). At the present state of knowledge, performing RFA for resectable CRLM outside a trial is not justified.

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