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

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Background: Surgical resection is the gold standard in the treatment of resectable colorectal liver metastases (CRLM). In several centers, resection is being replaced by radiofrequency ablation (RFA), even though there is no evidence yet from randomized trials to support this. The aim of this study was to critically review the oncological evidence for and against the use of RFA for resectable CRLM.

Methods: An exhaustive review of RFA of colorectal metastases was carried out.

Results: Five-year survival data after RFA for resectable CRLM are not available. Percutaneous RFA is associated with worse local control, worse staging, and a small risk of electrode track seeding when compared with resection (level V evidence). For tumors ≤3 cm, local control after surgical RFA is equivalent to resection, especially if applied by experienced physicians to nonperivascular tumors (level V evidence). There is indirect evidence for profoundly different biological effects of RFA and resection.

Conclusions: A subgroup of patients has been identified for whom local control after RFA might be equivalent to resection. Whether this is true, and whether this translates into equivalent survival, remains to be proven. The time has come for a randomized trial.

Key Words: Colorectal liver metastases—Radiofrequency—Resection—Review—Randomized trial.

Surgical resection is the gold standard in the treatment of resectable colorectal liver metastases (CRLM). Evidence for the superiority of surgical resection over no treatment comes from several retrospective comparative studies on 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%, respectively, for untreated but otherwise comparable patients.[1–4]

Five-year survival after resection of CRLM in series reported since 2000 reporting their experience since 1990 is 23%–58%,[5–15] and 10-year survival is 17%–28%[13,15] (Table 1). A 5-year survival of 71% has recently been reported after resection of solitary CRLM.[16] In a review of high-quality papers on hepatectomy for CRLM published since 1990, the 30-

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TABLE 1. *Published results of large series of resection of colorectal liver metastases since 2000*

Reference	No. of patients	Mortality (%)	5-Year survival (%)	10-Year survival (%)	Remarks
5	133	0	58	NA	
6	190	NA	58	NA	
7	100	1	58	NA	
8	235	4	36	NA	
9	585	NA	33	NA	
10	410	NA	50	NA	
11	102	3	29	NA	
12	168	5	23	NA	
13	297	1	28	17	
14	557	NA	58	NA	
15	423	2	47	28	
16	150	NA	71	60	Solitary

NA, data not available.

day postoperative mortality ranged from 0% to 6.6% (median 2.8%), with a mortality near to 1% in the most recent articles.[17]

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. When applied to unresectable CRLM, they achieve 5-year survival rates of 29% for microwave ablation,[18] 33% for laser ablation,[19] and 26% for cryoablation.[12] Radiofrequency ablation (RFA), the subject of this article, allows a 14%–55% five-year survival rate[16,20–26] and a 28% seven-year survival rate[23] in these patients.

Enthusiasm about these at first sight promising results in the palliative setting has led to an increasing number of interventional radiologists to suggest[27] or to apply and defend[20,22,28–33] percutaneous RFA 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,[34–40] limited central disease that technically would require a hemihepatectomy,[26,38,41] small metastases,[26,38,42–44] and solitary metastases.[45]

Undoubtedly, the recently shown equivalent survival after percutaneous RFA and surgical resection for hepatocellular carcinomas (HCC) < 5 cm in two randomized clinical trials[46,47] will encourage the use of RFA for resectable CRLM.

The advantages of minimal invasiveness for RFA, combined with claims of equivalent local control[26,38,43] and equivalent survival,[28,32,34,45,48] have already influenced everyday practice. A survey from Germany reported that 25.9% of hospitals performed RFA for resectable tumors.[49] In the near future, the surgical community will have to respond to the challenge of less invasive alternatives to hepatic resection. Simply repeating the surgical dogma that resection is the only valid technique for resectable liver metastases no longer seems to be an option because this is being overthrown by everyday practice.[49] A better option might be to scientifically analyze in detail potential advantages and disadvantages of resection versus RFA for resectable CRLM, and to find out whether RFA might, in theory, be oncologically at least equivalent to resection for certain indications. 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 evaluate whether the time has indeed come to consider such a randomized trial.

MATERIALS AND METHODS

A review was carried out according to recent guidelines,[50] looking for potential oncological advantages and disadvantages of RFA versus resection for resectable CRLM. 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 by using the keywords (radiofrequency OR radio-frequency OR radio frequency) AND (liver OR hepatic OR hepatocellular), without language restriction, from January 1, 1990, to May 1, 2007. Additional articles and book chapters were identified by a cross-reference search. To include as much gray literature[50] as possible, all abstract supplements from the same period published in *American Journal of Radiology, Journal of Vascular and Interventional Radiology, European Radiology, Surgical Endoscopy, European Journal of Surgical Oncology*, and *Acta Chirurgica Belgica* were screened for abstracts on hepatic RFA, as well as all the proceedings of the annual meetings of the RSNA. The proceedings of the annual general and gastrointestinal meetings of the ASCO (http://www.asco.org/) were screened electronically.

The PubMed search yielded 1837 articles; the additional search for cross references and gray literature yielded another 1852 papers and abstracts, for a total of 3689 papers and abstracts. From this raw material, articles and abstracts were included when they described potential oncological advantages or disadvantages for RFA or resection in the treatment of resectable CRLM. Both positive and negative

TABLE 2. *Five-year-survival of RFA for unresectable CRLM*[a]

Reference	No. of patients	No. of tumors per patient	Diameter of tumors (cm)	Approach	Mortality (%)	5-Year survival (%)	7-Year survival (%)
20	423	1.5	2.7 ± 0.9 (0.5–5)	P	NA	24	NA
21	177	2.2	2.2 (0.4–8)	P	NA	55	NA
22	167	4.1	3.9 (1–12)	P	0	14	NA
23	121	2.6	2.1 ± 0.9 (0.9–4)	P	0	35	28
24	100	5.1	3 ± 1.6 (0.3–17.4)	P, L, Q	1	31	NA
25	50	3.2	4.2	O	0	32	NA
26	47	3.1	2.4 ± 1.6	P, L, O	0	21	NA
16	30	1.0	3 (1–7)	P, O	0	27	NA

RFA, radiofrequency ablation; CRLM, colorectal liver metastases; NA, data not available; P, percutaneous; L, laparoscopic; O, laparotomy.

[a] Only independent series with data on 5 year survival calculated from the time of RFA were retained.

TABLE 3. *Survival after RFA for unresectable CRLM versus after resection for resectable CRLM*

Reference	Treatment	No. of patients	Median survival (months)	1-year survival (%)	3-Year survival (%)	5-Year survival (%)	*P* value	Remarks
6	RFA	57	25	92	37	NA	<0.0001	
	Resection	190	>72	95	73	58		
16	RFA	30	47	97	57	27	<0.001	Solitary CRLM[a]
	Resection	150	126	97	78	71		
45	RFA	25	37	100	53	43	NS	Solitary CRLM[b]
	Resection	20	41	90	55	34		

RFA, radiofrequency ablation; CRLM, colorectal liver metastases.

[a] Partial overlap with Ref. 6.

[b] Survival since diagnosis of CRLM.

studies were included. Papers or abstracts were excluded if they described clinical series that were partially or completely contained in material that was later published. In case of overlap, only the most recent and complete report was retained. In the end, 107 papers and 16 abstracts met the inclusion and exclusion criteria.

Evidence was ranked according to recent guidelines.[50]

RESULTS

Survival After RFA

There are no 5-year survival data available yet after RFA for resectable CRLM. Five-year survival data after RFA for unresectable CRLM are available from eight independent studies[16,20–26] (Table 2). Survival varied between 14% and 55%. Subgroups of patients with solitary or small metastases had a better prognosis (data not shown).

Two groups have compared survival after RFA for unresectable CRLM versus after resection for resectable CRLM[6,16,45] in a nonrandomized study (Table 3). The two M. D. Anderson Cancer Center studies found a much better survival after resection.[6,16] In the study by Oshowo et al.,[45] no statistically significant difference was found, but 5-year survival after resection for solitary metastases was unusually low (especially taking into account that it was measured since diagnosis of CRLM and not since resection), and 6-year survival after resection was zero. Unfortunately, these studies do not allow us to answer 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.[38,51]

Oncological Arguments With Direct Evidence For and Against RFA for Resectable CRLM (Table 4)

Local Recurrence After RFA for Unresectable CRLM

The rate of local recurrence at the site of the ablation after RFA for CRLM varies widely, between 2% and 40%.[6,14,16,23,26,30,45,52–54] In a recent meta-analysis of 763 RFA-treated CRLM with a minimum follow-up of 6 months, a mean local recurrence rate of 14.7% was found.[55] The same study extensively analyzed the factors influencing local recurrence rate after RFA.

TABLE 4. *Oncological for and against RFA for resectable CRLM*

	Level of evidence[a]	Type of evidence
Arguments with direct evidence		
In favor of resection		
Better local control (except for tumors ≤3 cm using RFA via a surgical 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		
No arguments with direct evidence found		
Arguments with indirect evidence		
In favor of resection		
Risk of post-RFA intrahepatic seeding	VII	Level V evidence for increased seeding after RFA in HCC
Risk of increased local and distant spread through increased matrix metalloproteinase (MMP) activity	VII	Level II evidence for increased MMP activity after 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 after RFA vs. after resection	VII	Level V evidence for less blood loss after RFA; level V evidence for relation between perioperative transfusion and survival
Stronger stimulation of cellular immunity after RFA vs. after resection	VII	Level II evidence from animal RCT
Balance between resection and RFA unknown		
Stimulation of growth of residual tumour cells after RFA vs. after resection	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 tumour cells in peripheral blood, both after RFA and after resection	VII	Level V evidence for increased presence of tumour cells in peripheral blood both after 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 after RFA; level II evidence for beneficial effects of increased HSP expression; level V evidence of detrimental effects of increased HSP expression

RFA, radiofrequency ablation; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; RCT, randomized controlled trial; HSP, heat shock protein.

[a] Levels of evidence according to Mahid et al.[50]

In a univariate analysis, factors with significantly less local recurrences included the following: small size, surgical (open or laparoscopic) approach, location away from large vessels, a 1 cm intentional margin, and a greater physician experience. In a multivariate analysis, significantly fewer local recurrences were observed for small size and for a surgical approach (Table 5). The local recurrence rate after RFA of CRLM was 3.5% after a surgical approach versus 26.4% after a percutaneous approach ($P < .0001$). (Unpublished subgroup analysis from ref.[55]) These superior results for the surgical approach have been confirmed in comparative studies published since then.[56–60] 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% vs. 6.3% for tumors away from these vessels.[55,61] The local recurrence rates after RFA for tumors with an intentional margin of 0 cm, 0.5 cm, and 1 cm are 14.5%, 16.4%, and 6.5%, respectively.[55]

Three recent studies[55,56,58] confirm that authors who treated large numbers of tumors had patients with fewer local recurrences than authors who treated fewer tumors. Significant improvement occurs after 40–50 cases,[56,58] although the plateau phase in the learning curve is reached only at 100 procedures.[55] Local recurrence also seems to be lower when newer-generation electrodes are used.[26,62]

TABLE 5. *Local recurrence rate after radiofrequency ablation of hepatic tumors according to size and approach*

Size	Percutaneous	Laparoscopy/laparotomy
< 3 cm	16.0%	3.6%
3–5 cm	25.9%	21.7%
5cm	60.0%	50.0%

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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 40%.[30]

In a series of 47 patients with resectable recurrent liver tumors after a first hepatectomy (62% with CRLM) treated with percutaneous RFA, patient-based local recurrence rate after a follow-up of 18 months was 34%.[34]

Local Recurrence After Resection for Resectable Liver Metastases

Large series that describe true local recurrence rates after hepatectomy are scarce. In a series of 183 patients with a median follow-up of 29 months, local recurrence rate was 10.4%.[63] In another series of 557 patients with a median follow-up of 29 months, local recurrence rate was 3.8%.[14] In a very recent series of 60 patients with a median follow-up of 16 months, local recurrence rate was 8.3%.[64]

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

Three studies from the same group have compared local recurrence rates after RFA versus after resection for CRLM.[6,14,16] Local recurrence was found to be higher after RFA than after resection. Unfortunately, all three studies are comparing resection for resectable metastases versus RFA for unresectable metastases, so that no definite conclusions can be drawn about the outcome of RFA for resectable CRLM.[38,51]

Staging

A surgical approach (hepatectomy, or open or laparoscopic RFA) allows a better staging than a percutaneous approach (percutaneous RFA).[55] In approximately 30% of patients, additional hepatic tumors are found by intraoperative ultrasound during laparoscopy[53] or laparotomy[65] compared with state-of-the art preoperative imaging. They can be treated with curative intent during the same procedure.[65] These findings are a theoretical argument against the use of percutaneous RFA 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[65] remains to be seen. The missed tumors can often be treated with a new percutaneous approach as soon as they appear.

In approximately another 10% of patients, surgical exploration allows the detection of peritoneal metastases,[65] or lymph node invasion of the hepatic hilum.[65] The presence of peritoneal metastases[66] or (extensive) hepatic hilum lymph node metastases[67,68] seriously decreases the chances of 5-year survival, so most authors refrain from liver resection.[69,70] One author advocates the combined surgical treatment of liver metastases and peritoneal or lymph node disease, respectively, in selected cases.[68,71] Whether such a combined treatment is worthwhile or not, it is hard to believe that percutaneous RFA in these patients could have any effect 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.[22,72–77] The incidence of seeding after RFA of CRLM is 0%–1.4% in large series.[22,73,75,77,78]

Several mechanisms may contribute to seeding.[79] Viable tumor cells may adhere to a biopsy needle[80] or to the electrode[81,82] 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; this is audible as a popping sound. Finally, when a wet electrode is used, cells may leak out the track together with the saline injected into the tumor.[83–85]

Risk factors for the development of track seeding include preprocedure biopsies, multiple electrode placements and sessions, a direct approach to subcapsular tumors, no cauterization of the electrode track, and poor differentiation of the tumor.[22,75,77,79–81,86]

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.[87] Similarly, it is to be feared that seeding after RFA may seriously jeopardize a patient's chance of cure.

Oncological Arguments With Indirect Evidence For and Against RFA for Resectable CRLM (Table 4)

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 on, mortality decreased from 2.7% to 0%, reresection rate in case of hepatic recurrence increased from 39.2% to 58.2%, and 5-year survival increased from 24% to 49.2%.[88] The parenchymal sparing strategy thus was associated with resection of more patients with a higher number of metastases, with an increased reresection rate in patients with liver recurrence and with a better 5-year survival.[88] For the same oncological reasons, a recent editorial cautiously wondered whether RFA should replace resection for small central lesions that would require large resections.[38] Other authors have already been applying this idea for several years.[22,26,35,89]

Intrahepatic Seeding

Thirty-five cases of rapidly progressive scattered recurrences after RFA for a small HCC have recently been described.[90–96] The mean incidence of scattered recurrences after RFA of HCC in these series was 3% (range, .8%–8.0%).[92–96]

Scattered recurrences have some common characteristics.[94] First, recurrences occur rapidly after 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.[90,91,93,95,96] The most probable hypothesis is that they are caused by a too-fast coagulation process.[94] Under these circumstances, intratumoral steam production and a steep buildup of intratumoral pressure has been demonstrated.[97] 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,[94] which increased intratumoral pressure much less.[97] Survival of patients with scattered recurrences is far worse.[94]

After RFA of CRLM, an increase in intrahepatic viable tumor cells has been observed in a small study on eight patients.[98] 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 noncirrhotic 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 hour after RFA.[86] In a study of eight patients with CRLM, tumor cells in peripheral blood were present in 12.5% 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.[98] 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 thousand patients.[99] After RFA, blood transfusion is exceptional.[79] Blood transfusion is associated with adverse perioperative and long-term survival.[99] 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 transfu-

sion at various levels of the immune system may also play a role.[99] A difference in the amount of blood transfusion between hepatectomy and RFA may, at least in theory, translate into a different survival time. This theoretical argument in favor of RFA may disappear with the advent of novel devices that enable nearly bloodless liver resections.[100–105]

Growth Factors

Surgical resection in general stimulates cell division of tumors and facilitates recurrence and spread, in part because of the production and release of growth factors.[106] Hepatectomy in particular is known to stimulate growth of residual, both intra- and extrahepatic, tumor cells in animal experiments.[107–111] The stimulating effect is proportional to the extent of the resection.[107,111] The stimulation is attributed to the production and release of growth factors for liver regeneration,[107–109,112] the intensity of which is also proportional to the extent of the liver resection.[113] 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.[108]

The results of two recent experimental studies on mice on the effect of RFA on the growth of residual tumor are conflicting.[110,112] In a first study, RFA of CRLM promoted intrahepatic growth of residual neoplastic cells compared with a control group.[110] The stimulation of growth of residual tumor cells was found to be higher after RFA than after resection.[110]

In a second and slightly different study, partial hepatectomy, but not RFA, stimulated growth of residual neoplastic cells compared with a control group.[112] The expression of hepatocyte growth factor and basic fibroblast growth factor was increased after hepatectomy, but decreased after RFA.[112]

At present, it is unclear why these only slightly different experiments resulted in a completely different outcome. More experiments are needed to clarify this issue.

Matrix Metalloproteinase Activity

Matrix metalloproteinases (MMPs) are a family of matrix-degrading endopeptidasen that play an important role in the normal turnover of the extracellular matrix. The activity is enhanced in inflammation and in tissue repair.[114] Increased expression of MMPs is also noted in oncological processes such as tumor cell invasion, metastasis, and angiogenesis. MMP-2 and MMP-9 degrade the basement membrane, which allows tumors to spread locally and distally. MMP-2 and MMP-9 contribute to colorectal cancer progression in experimental models,[114] are overexpressed in patients with CRLM,[115–117] and are associated with increased risk of tumor recurrence and decreased survival in patients with colorectal cancer.[118] 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.[119] 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 in general has been long known to cause generalized immunosuppression, including depressed function of immune cells, such as lymphocytes, natural killer cells, and Kupffer cells.[106,120] This immunodepression in turn may enhance the growth of liver metastases.[120] Hepatectomy in particular is also an immunosuppressive event that results in marked Kupffer cell and T cell dysfunction.[121]

RFA is followed by a marked local inflammatory response with a dense T cell infiltrate in the liver of tumor-free domestic pig[122] and in the liver of rabbits implanted with a VX2 tumor.[123] Moreover, in several animal models[123–126] as well as in human primary[127–129] or secondary[127,128] 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.[123] 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.[124] 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.[125]

In a study with 20 patients with a HCC, RFA induced a tumor-specific T cell response.[129] 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. However, this tumor-specific T cell response was not associated with protection from HCC relapse. 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.[127] In a study of six patients with HCC and six patients with CRLM, RFA induced a tumor-specific cytotoxic T cell stimulation with a dramatically increased tumor-specific cytolytic activity of $CD8^+$ T cells.[128] However, this tumor-specific T cell response was not[129] or was only weakly[124] associated with protection from tumor recurrence.

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. Evidence for a similar immune stimulation after cryoablation has been provided by Den Brok et al.[130,131] They demonstrated a specific immune response when the tumor debris was left in situ, which was abrogated by resection of the ablated area. The authors showed that tumor destruction creates a source of antigens for the antigen-presenting dendritic cells, which play a pivotal role in the induction of immunity.

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 far higher in the RFA group than in the surgical resection group.[125]

Heat Shock Protein Expression

An incomplete coagulation of a liver tumor by radiofrequency is a common event, especially by a percutaneous approach.[55] In the coagulation zone, the temperature between 60°C and 100°C causes immediate cell death through protein coagulation and membrane fusing.[85] In the spared tumor tissue immediately adjacent to the coagulation zone, temperature is insufficient (37°C–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,[132] animal experiments,[106,133,134] and patients.[127,134,135] 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.

HSP 70 is involved in tumor antigen presentation which then triggers a cellular immune response against the tumor cells.[132,133] HSP 70 binds tumor peptides in malignant cells.[136] HSP 70–tumor peptide complexes appear at the cell surface, and are taken up by antigen-presenting dendritic cells and macrophages. Within the neighboring lymph nodes, dendritic cells present the antigens to T cells, which as a consequence may develop into cytotoxic T cells.[137] 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.[132,133]

HSP 70 is known to inhibit apoptosis and thereby increase the survival of cells exposed to a wide range of lethal, including thermal, stimuli.[138] HSP 70 has been shown to render cells resistant to several anticancer drugs, such as gemcitabine, topotecan, cisplatin, doxorubicin, and 5-fluorouracil.[139–141] Overexpression of HSP 70 has been linked to more malignant phenotypes in breast cancer.[142] 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.[138] This may in part explain the poor local control figures after repeat RFA of a local recurrence.[55] In conclusion, an incomplete RFA treatment of a liver tumor is not only bound to 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[17,32,53] and a lower complication rate.[5,8,12,15,17] Most patients undergoing percutaneous RFA require an overnight stay; some can be discharged the same day, while elderly patients stay 2–3 days.[32] After laparoscopic and open RFA, mean hospital stay is 1–3 days[53] and 4–7 days,[53] respectively. When compared with the mean hospital stay of 12.5 days after resection,[17] there is certainly an advantage for RFA, whatever the approach.

In a review of 3670 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%.[79] Mortality after hepatectomy ranges from 0% to 6.6% (median, 2.8%),

TABLE 6. *Proposal of a randomized trial of RFA versus 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 surgical approach, including full exploration for hepatic, peritoneal, and regional lymph node metastases.
• Only tumors > 5 mm away from vessels ≥ 3 mm.
• RFA only by experienced physicians (minimum 50 tumors).
• Intentional margin of 1 cm.
• Only electrodes with sufficient data on size and geometry of the ablation zone.
• Only electrodes with sufficient predictability and regularity of size and geometry of the 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.

RFA, radiofrequency ablation; CRLM, colorectal liver metastases.

with a mortality near to 1% in the most recent articles.[17] Morbidity after resection remains clinically important, between 17% and 37%.[5,8,12,15,17]

In oncology however, the goal is not minimal invasiveness but cure.[6,143–145] RFA as a less invasive technique can replace resection only when 5-year survival in a randomized trial is at least as good.[55]

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 coming in that indicates 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 HSPs 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

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[4,146] or after RFA,[147] the treatment is futile with no impact on survival and no hope of cure. Retreatment of an established local recurrence by RFA is often impossible or is followed by a high failure rate,[16,52,55] in contrast to what is sometimes claimed.[22,32]

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 or other of two treatments is superior to the other.[148] 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 the inclusion and exclusion criteria for such a trial. A 2002 French attempt for a randomized phase 3 study (essai FFCD 2002-02) failed because too few centers agreed to participate.[149] It is very likely that in 2002, the 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.

In our view, the very recent arrival of data on long-term survival after RFA,[16,20,21–26] data on factors influencing local recurrence,[55] and data on size and geometry of the ablation zone[144,150] 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 cost.

To prove by a noninferiority trial that the difference in 5-year survival is less than 10% (on the basis of an estimated 5-year survival in both groups of 45%,[5–16,20–26] a hypothesized exponential distribution, and α and β risks of .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 to be discussed, as do the other parameters involved in the computation. Approximately 48% of patients with resectable CRLM have lesions with a maximum diameter of 3 cm.[9] In other words, nearly half of the patients currently undergoing resection for CRLM can be included in this trial.

We hope that the current analysis and proposal strengthens the opinion of the numerous proponents[22,24,27,32,33,38,41,43,45,51,61,74,98,149,151–154] of such studies and contributes to convince its opponents.[16,155] We also 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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