Radiofrequency Ablation as First-Line Treatment in Patients With Early Colorectal Liver Metastases Amenable to Surgery

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Objective: Aiming at avoidance of futile surgery, we have tested whether radiofrequency ablation (RFA) may be used as first-line treatment in patients with colorectal metastases (CRLM) occurring within the first year after colorectal surgery.

Summary Background Data: Surgical resection is the standard treatment in patients with CRLM. Major retrospective analyses have identified the interval between colorectal surgery and the occurrence of CRLM to be of prognostic importance. So far, it is unknown whether survival of the respective patients is hampered if RFA is used as first-line treatment.

Methods: According to a clinical pathway, we have treated patients with CRLM detected within the first year after colorectal surgery preferentially by RFA (n = 28). Resection (n = 82) was performed in patients who were deemed not amenable to RFA due to number, size, or location of metastatic lesions. The diameter of lesions differed between the groups. All other characteristics of patients and lesions were comparable. Local recurrence and new hepatic lesions were treated with repeated RFA or surgery whenever possible.

Results: Local recurrence at the site of ablation or resection occurred in 32% and 4% ($P < 0.001$), new metastases apart from the site of previous treatment in 50% and 34% ($P = 0.179$), and systemic recurrence in 32% and 37% ($P = 0.820$) of the patients after RFA and surgery, respectively. Time to progression was significantly shorter in patients primarily treated with RFA (203 vs. 416 days; $P = 0.017$). After primary treatment, 9 RFA patients and 8 surgery patients were amenable to repeated RFA or repeated surgery resulting in identical rates of disease-free patients and identical 3-year overall survival in both treatment groups: 67% and 60%, respectively; $P = 0.93$.

Conclusions: Despite striking differences in local tumor recurrence and shorter time to progression, survival in patients with early CRLM does not depend on the mode of primary hepatic treatment.

(*Ann Surg* 2010;251: 796–803)

Surgery is capable of substantially prolonging survival and may even be curative in some patients with colorectal liver metastases (CRLM). Even if randomized studies providing unequivocal evidence are not available, the benefit of surgery can clearly be shown by studies comparing resected to nonresected patients, and by a huge body of literature.[1–4] Although 5-year survival without surgery approaches 0%, it has been shown to reach 25% to 30% after liver resection. In recent publications, 5-year survival between 30% and 50% has been reported.[5–10] About a decade ago, several forms of local ablative treatment were broadly introduced into clinical practice. Radiofrequency ablation (RFA) has preferentially been used as its handling is particularly simple, safe, and cheap compared with cryotherapy or laser coagulation.[11–16] Despite the large number of patients treated by RFA worldwide, a randomized study comparing this approach with surgery has not been performed. In the available studies, RFA patients constitute a poor-risk group compared with surgery patients. Apart from small and oligocentric lesions usually included in the resection group, RFA patients may suffer from considerable comorbidity preventing surgery, may have undergone prior surgery, and CRLM treated by RFA may represent a different biologic entity as reflected by elevated levels of carcinoembryonic antigen (CEA) and even extrahepatic disease.[17–23] Regardless of the uncertainties as to its efficacy, RFA has gained widespread acceptance as the patients welcome an approach capable of avoiding surgery shortly after previous intestinal resection.

The interval between resection of the primary colorectal carcinoma and the occurrence of CRLM has been reported to impact the results of liver surgery. Patients with CRLM diagnosed within 1 or 2 years after primary bowel resection have a worse prognosis compared with patients with a longer disease-free interval.[24–26] The more aggressive tendency to disseminate obviously reflects unfavorable biologic properties of the primary tumor. When first hepatic lesions are diagnosed, additional hepatic metastases or extrahepatic disease may develop in the near future. While new liver metastases (NLM) may eventually prompt repeated hepatic surgery, extrahepatic disease may reduce the benefit of preceding liver resection. To avoid futile surgery in early occurring hepatic metastases, we adapted percutaneous RFA as the method of first choice even where the lesions were amenable to surgery. In cases with local recurrence after RFA or surgery and in patients with de novo lesions, repeated intervention was scheduled. When this clinical pathway was introduced, we were aware of the fact that surgical resection has been the gold standard in the treatment of the respective patients. This is of particular importance as patients with small and oligocentric lesions amenable to surgery are preferentially included in the RFA group when using our approach to treat CRLM. Thus, the questionable benefit of RFA to avoid surgery in patients with early metastases must be balanced against potentially better results after surgery. The aim of this retrospective analysis was to critically appraise our approach.

PATIENTS AND METHODS

In January 2002, a treatment protocol for patients with metastases diagnosed within the first 12 months after primary colorectal surgery was initiated by the Department of Transplantation/Hepatobiliopancreatic Surgery and the Department of Diagnostic and Interventional Radiology. As the definition of synchronous metastases usually includes only patients with CRLM detected at the time of primary colorectal surgery, the term "early metastases" is used to characterize CRLM occurring within 12 months after primary surgery. All respective patients admitted to our center, a tertiary treatment institution, and amenable to local hepatic treatment, were prospectively considered for inclusion into this protocol. As the

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ISSN: 0003-4932/10/25105-0796
DOI: 10.1097/SLA.0b013e3181bc9fae

protocol was part of a clinical pathway to treat patients with CRLM and not a study protocol, approval of our ethics committee was not required. All patients gave their full informed consent to undergo preferentially RFA even if surgery was possible.

Treatment Protocol

The protocol was restricted to patients with early CRLM after primary colorectal surgery. Salvage therapy (repeated hepatic intervention) was an integral part of the protocol in the case of recurrent disease.

The first-line treatment was RFA. To avoid any surgery, RFA was performed using the percutaneous approach. Patients were considered for RFA if the number of lesions did not exceed 5. The maximum diameter of a lesion to be treated by RFA was 5 cm. In patients with 4 or 5 lesions, a 2-step procedure with an interval of several weeks was scheduled. Patients were not treated by percutaneous RFA if the lesions were localized superficially, ie, adjacent to vulnerable structures such as diaphragm, stomach, colon, or duodenum. In the respective patients surgery or RFA after laparotomy (or during laparoscopy) was performed. In addition to this, RFA was considered inadequate in lesions adjacent to large vessels preventing incomplete tumor destruction and in lesions adjacent to larger bile ducts. In other words, patients with metastases exceeding 5 cm in diameter, more than 5 lesions, superficial lesions, and lesions in proximity to large vessels or bile ducts were treated by surgery.

Salvage therapy was scheduled for patients with recurrent disease after primary RFA or surgery. Irrespective of the primary form of treatment but depending on the respective recurrent disease, the second approach was RFA, surgery, or both. Pulmonary involvement, when amenable to surgery or RFA, was not considered a contraindication for repeated hepatic intervention. Any other localization of recurrent disease was considered an indication for chemotherapy and not for local treatment.

Patients

All patients included in the analysis fulfilled the criteria mentioned in the description of the treatment protocol as to size, number, and localization of lesions (Table 1). In the RFA group, none of the patients suffered from comorbidity precluding surgery. Only patients with percutaneous RFA were considered for the analysis. All patients with RFA after laparotomy or during laparoscopy were eliminated. Regardless of the kind of treatment performed, the following patients were excluded from the present analysis.

1. Patients previously treated by hepatic surgery or local ablative approaches.
2. Patients with hepatic metastases only amenable to surgery (or RFA) after downstaging by previous chemotherapy.
3. Patients with portal vein embolization before treatment.
4. Patients with dissemination of the primary colorectal carcinoma in addition to liver metastases.
5. Patients with local recurrence or colorectal de novo cancer.

Patients' and tumor characteristics, including details of previous treatment, are shown in Table 1. The majority of the patients, with a comparable rate in both groups, were treated by previous chemotherapy. In patients with CRLM detected within the first 3 months after primary surgery, chemotherapy was used in only 5 of 31 patients, whereas 63 of 79 patients with metastases diagnosed at a later date had chemotherapy before hepatic treatment. In the latter group, this was mainly due to lymph node positive primaries treated by adjuvant chemotherapy (56 of 63 patients with lymph node involvement had been treated). Biologicals (Bevacizumab) were given in only 2 patients, one treated by RFA and other by surgery.

No patient was lost to follow-up. All data required for the analysis were drawn from our department's prospectively maintained database.

Diagnostic Workup

The diagnostic Workup was based on a CT protocol of the abdomen including the pelvis and high resolution CT scans of the thorax for all patients before surgery or RFA. CT scanning was performed using 3-CT scanners as follows: from 2002 to 2003, a 4-row MDCT, Somatom Volume Zoom, Siemens Erlangen, Germany; from 2003 to 2006, a 16-row MDCT and from 2007, a 64-row MDCT, Brilliance, Philips, Eindhoven, The Netherlands, reflecting the ongoing technical progress during this 6-year period and the respective CT equipment of our department. The protocol included unenhanced and biphasic contrast-enhanced CT scans (arterial and portal venous phase) in inspiratory breath-hold (120 mL Imeron 300, Altana Pharma AG, Konstanz, flow rate 4 mL/s by power-injector—LF CT 9000, Liebel Flarsheim, Cincinnati—followed by a 50 mL saline chaser). Reconstructed slice thickness was $\leq$3 mm, and the reconstruction interval was $\leq$2 mm. Data acquisition was started by bolus trigger for the arterial scans and portal-venous scans were obtained at 90 seconds delay.

In addition to this, coloscopy was repeated if it had been performed more than 6 months before. Postinterventional and post-

TABLE 1. RFA Versus Resection in Early Occurring Colorectal Liver Metastases. Characteristics of Patients and Metastases

	RFA	Resection	*P*
No. patients	28	82	
Age (median, range)	64 (42–78) yr	62 (38–80) yr	0.123
Gender (m - f)	20–8	49–33	0.366
Median follow-up	814 (49–1642) d	644 (7–2452) d	0.414
Median time from primary to hepatic treatment	268 (26–554) days	252 (0–1184) days	0.621
T1/2 vs. T3/4 of the primary	4–24	11–71	1.0
N0 vs. N1/2 of the primary	5–23	22–60	0.449
Patients with chemotherapy after primary surgery (no—yes)	8–20	34–48	0.265
Mode of chemotherapy 5FU/Folinate vs. FOLFOX, FOLFIRI, others	14/6	27/21	0.417
CEA (ng/mL) (median, range)	5.6 (0.6–1575)	11.6 (0.5–726)	0.341
Median no. metastases	2 (1–5)	2 (1–11)	0.985
Median diameter of dominant lesion (median, range)	30 (10–50) mm	50 (10–140) mm	0.004

CEA indicates carcinoembryonic antigen.

operative follow-up included abdominal and thoracic CT scans using identical technique as in preoperative assessment. CT scans were performed at 1, 3, 6, and 12 months, thereafter every 6 months, and from the third year onwards every year. In addition to CT scanning, patients were followed up by CEA (normal <5 ng/mL; >10 ng/mL highly suggestive for recurrence) monitoring performed every 3 months.

Technique of RFA and Surgery

RFA was performed under general anesthesia using a 200 watt generator (RF3000, Boston Scientific) and a 4-cm LeVeen needle. The electrode was guided under CT fluoroscopy (Volume Zoom, Siemens). In tumors ≤2 cm, the electrode was placed concentrically within the nodule to cover the whole nodule, with the antennas including a safety margin of at least 1 cm around the nodule. Larger tumor nodules were ablated by overlapping ablation volumes until the tumor and a respective safety margin were included. The ablation was performed according to the manufacturer's instructions and was finalized by an increase of the impedance. The immediate treatment results were documented by means of CT to ensure that the tumor was completely enclosed by the necrosis.

Hepatic resection was performed in 82 patients as follows: extended right hepatectomy (n = 10), extended left hepatectomy (n = 3), right hepatectomy (n = 20), left hepatectomy (n = 5) left or right hepatectomy plus wedge resection (n = 6), and segmental or wedge resection (n = 38). After surgery or RFA, systemic chemotherapy was used only in cases of hepatic or systemic tumor recurrence, and only in those patients with recurrence not amenable to repeated resection or RFA.

Definition of Recurrence

Three forms of recurrence have to be distinguished: tumor growth at the site of surgery or RFA, NLM at a site different from the previous treatment localization, and tumor at any site outside the liver, including recurrence at the site of the primary. These 3 patterns of tumor recurrence were named as local recurrence, NLM, and systemic recurrence, respectively.

Statistics

All statistical analyses were performed using the statistical software SPSS 15.0. For the comparison of patient's characteristics, cross tables including χ^2 or Wilcoxon test were used. Survival data are intention-to-treat analyses calculated according to Kaplan Meier, and significance was assessed by the log rank-test. Hazard ratios for time-to-progress and survival and 95% confidence intervals, as well as multivariate analysis based on prognostic factors significant in the univariate analysis were calculated using Cox regression analysis. The influence of the type of recurrence on survival was assessed by fitting a Cox model with time-dependent covariates. Time was assumed to start with hepatic intervention. All reported P values are 2-sided, and denoted as statistically significant if they did not exceed 0.05.

RESULTS

Between January 2002 and March 2008, 337 patients with CRLM amenable to local hepatic treatment were referred to our center. Of these, 269 patients were treated by surgery and 68 by RFA or combined approaches. A total of 28 patients treated by RFA and 82 treated by hepatic resection fulfilled the criteria to be included in the analysis. As shown in Table 1, age of the patients, gender, and median follow-up are not significantly different in patients treated with RFA or surgery. Most, but comparable rates of patients in either group had been treated by chemotherapy after colorectal surgery for cancers with lymph node involvement or after diagnosis of hepatic metastases. Expectedly, the diameter of metastases was significantly different between the groups ($P = 0.004$). The time between surgery of the primary tumor and treatment at our institution was comparable. CEA as a marker of biologic activity and tumor, nodule, metastasis classification were also comparable in both groups.

Treatment and Recurrent Disease

RFA required median hospital stay of 2 (1–9) days, whereas after surgery hospital stay was 13 (5–55) days. Complications occurred in 7 and 30 patients after RFA and surgery, respectively. These were hemothorax (2), pneumothorax (3), intrahepatic bleeding (1), and cholecystitis (1) after RFA; and intraabdominal bile collection/abscess formation (10), wound infection (8), impaired hepatic function/ascites formation (4), pleural effusion (3), impaired gastric emptying (2), mental impairment (2), and others (7) after surgery. Six surgery patients had 2 complications each.

In all of the 28 patients, the result of RFA was deemed complete in the control CT scan after 1 month. Therefore, additional ablations following this CT scan were not performed. There were 2 patients each with 4 nodules, and further 2 each with 5 nodules. In these 4 patients, RFA was performed as a 2-step procedure with scheduled intervals of 2 weeks (1 patient) and 4 weeks (3 patients). One of these patients remained free of recurrence, 1 had NLM, 1 systemic, and 1 had local/systemic recurrence. Among the patients who underwent surgery, resection was radical (R0) in 77 of the 82 patients (94%). R1 and R2 resections were performed in 2 and 3 patients, respectively. Local recurrence occurred in 2 of the 5 cases, systemic diseases in further 2, and 1 patient remained recurrence-free. Local, NLM, and systemic recurrences according to Kaplan Meier are shown in Figures 1A–C. Compared with surgical patients, local recurrence occurred more frequently and in shorter intervals in patients treated with RFA (log-rank: $P < 0.001$). The difference in the occurrence of NLM in patients with RFA and after surgery was not significant (log-rank: $P = 0.071$). Systemic recurrence was identical (log-rank: $P = 0.721$). Median time to progress in patients with RFA and surgery was 203 and 416 days, respectively ($P = 0.017$; Fig. 2).

Local recurrence occurred in 9 (32%) and 3 (4%) (Fisher exact test: $P < 0.001$), NLM in 14 (50%) and 28 (34%) ($P = 0.179$), and systemic recurrence in 9 (32%) and 30 (37%) ($P = 0.820$) patients after RFA and surgery, respectively. The distribution of recurrent lesions is summarized in Table 2. Local recurrence per lesion treated by RFA was 16%. In 4 patients with a total of 8 nodules, the maximum tumor diameter exceeded 3 cm. Of these 4 patients, 3 experienced local recurrence (per lesion 38%).

In total, hepatic recurrence ("local" and/or "NLM") occurred in 18 and 30 patients after RFA and surgery, respectively (Fisher exact test: $P = 0.014$). Of these, 9 (50%) patients after RFA and 8 (27%) after surgery were amenable to salvage therapy (Fisher exact test: $P = 0.012$) (Table 3). The Kaplan Meier estimate reflecting repeated hepatic treatment is shown in Figure 3 (log-rank 0.002). After repeated intervention, 17 of 28 (61%) patients in the RFA group and 51 of 82 (62%) patients after hepatic surgery were free of apparent tumor. In 3 surgery patients, additional pulmonary interventions were required to achieve a disease-free situation (2 patients had pulmonary resection, 1 patient underwent pulmonary RFA). Eleven patients (39%) in the RFA group and 31 patients (38%) after surgery were not amenable to repeated local treatment due to NLM or systemic disease and were, therefore, treated by chemotherapy ($P = 1.00$). In the univariate analysis of all 110 patients, RFA versus surgery was the only predictor for time to progression (Table 4) ($P = 0.017$; risk ratio, 0.523; confidence interval, 0.304–0.901).

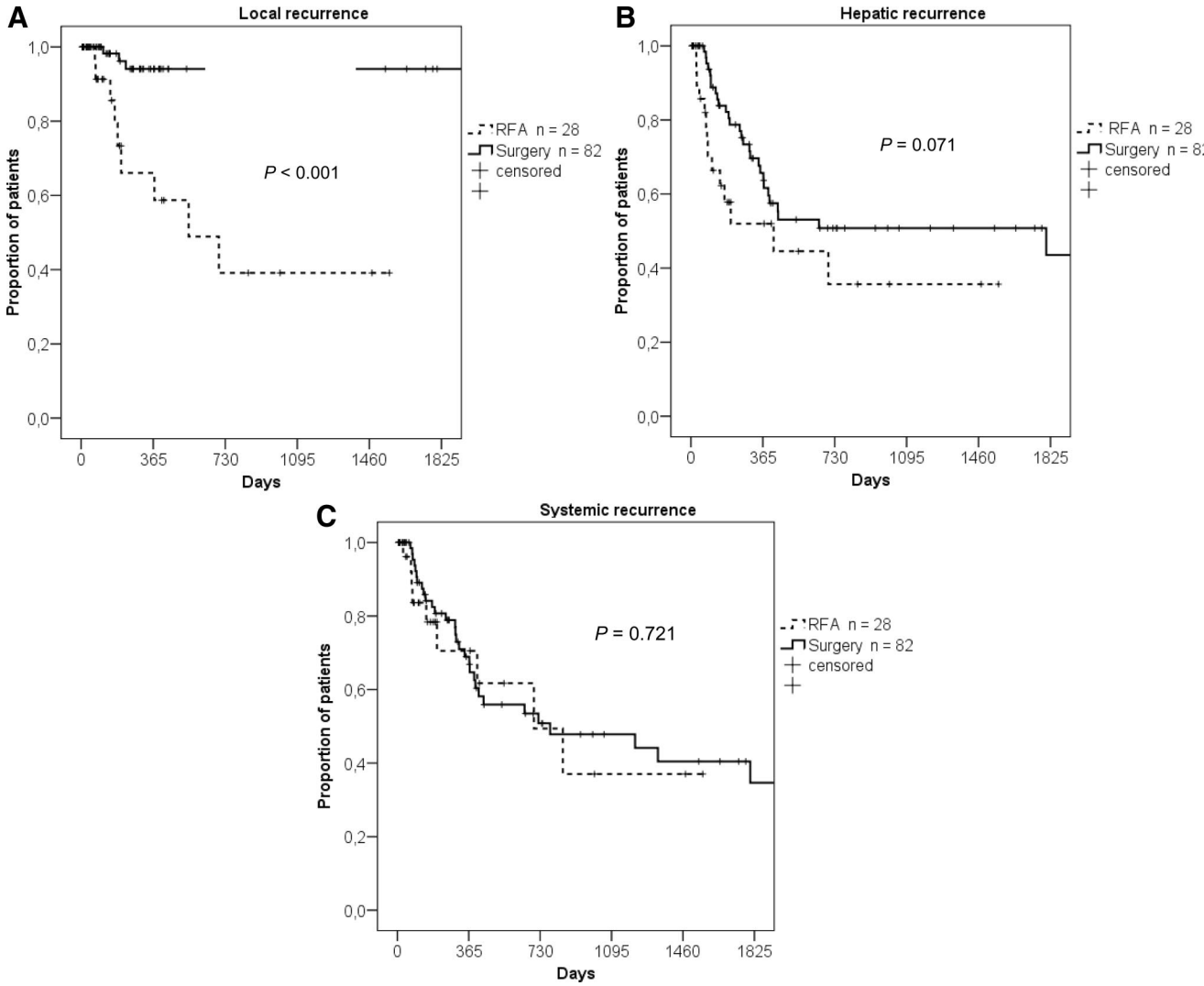

FIGURE 1. Local (A), hepatic (B), and systemic (C) recurrences in patients treated with RFA versus hepatic resection for early occurring colorectal liver metastases.

Survival

Intention-to-treat analyses of survival were performed using the Kaplan Meier method. In patients with RFA, the death rate required for assessment of median overall survival was not reached during the follow-up. (The last event counted in the Kaplan Meier estimate occurred on day 1352 resulting in a survival rate of 50.6%. Therefore, it can only be stated that median survival is beyond day 1352.) The estimated 3-year overall survival in this group was 67%. In surgical patients, the median survival was 1694 days, 3-year survival was 60%, and 5-year survival 44% (Fig. 4; $P = 0.930$). Procedure-related mortality was 0% after RFA and after surgery. The Kaplan Meier curves indicate identical results after the 2 approaches. Overall survival since treatment of the primary tumor was also comparable (median survival, 1751 vs. 1852 days; estimated 5-year survival, 48% vs. 51% in patients treated with RFA vs. Surgery, respectively; $P = 0.961$).

The results of the univariate analyses assessing the influence of tumor characteristics on overall survival are presented in Table 4. NLM, extrahepatic, and number of metastases were significant as to survival. The multivariate analysis resulted in 2 independent predictors: number of hepatic metastases ($P = 0.031$; risk ratio: 2.337; confidence interval: 1.237–5.027) and NLM ($P = 0.007$; risk ratio: 2.658; confidence interval: 1.314–5.377).

DISCUSSION

Long-term prognosis after resection of CRLM is mainly influenced by biologic factors such as number and size of lesions, CEA, grading, time between primary tumor and metastases, and extrahepatic disease.[24–26] The sole prognostic factor that can be influenced by the surgeon is the resection margin. Although the width of the required tumor free margin has remained a matter of ongoing debate,[5,27,28] the necessity to achieve a negative margin is universally accepted. As the radical removal of metastatic lesions is crucial in the surgical treatment of CRLM, the question if alternative approaches may be considered equally radical compared with surgery is justified. Bearing in mind that RFA is clearly less radical than surgery, the feasibility of repeated local treatment as a second step to achieve removal of CRLM was part of our protocol.

According to numerous publications, RFA should be restricted to patients with CRLM limited in size and number. Although

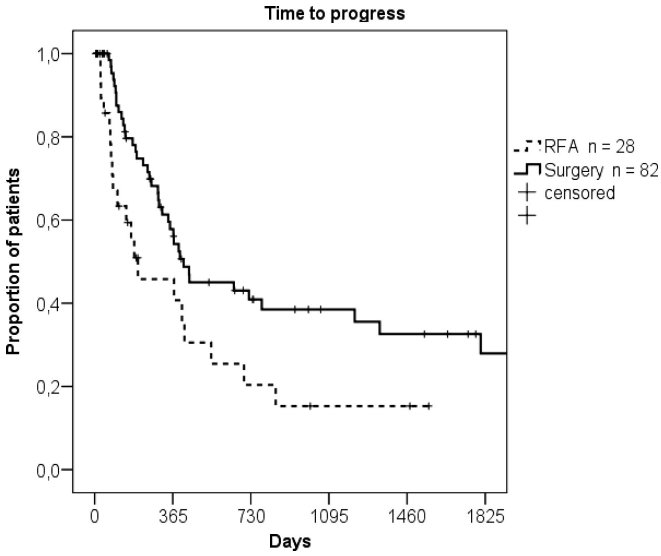

FIGURE 2. Time to progress in patients treated with RFA versus hepatic resection for early occurring colorectal liver metastases.

TABLE 2. Pattern of Recurrent Lesions After RFA or Surgery for CRLM and Feasibility of Further Treatment

Pattern of Recurrence	RFA n = 28	Surgery n = 82
Local recurrence only	3	2
Local and NLM	1	0
Local and systemic lesions	1	0
Local NLM and systemic lesions	4	1
NLM	7	7
NLM and systemic lesions	2	20
Systemic lesions only	2	9
Patients without any recurrence	8	43
Patients amenable to local treatment	9	8
Recurr. not amenable to local treatment	11	31

local recurrence in lesions <3 cm in diameter is only 16%, it reaches 60% in patients with tumors measuring 5 cm in diameter. Size and number of lesions, open surgery, laparoscopic or percutaneous approach, proximity to large vessels, CEA, margin to healthy tissue, and even experience of the interventionalist have been recognized to influence outcome in multivariate analyses.[16,29–31]

The question as to superiority of RFA or surgery in the treatment of CRLM is so far answered in favor of surgery. This statement is corroborated by several nonrandomized studies demonstrating superior survival in patients who underwent resection.[17–19,22] However, equivalent survival has also been reported.[20,23] In another study, survival of subgroups of patients appeared to be comparable after RFA and surgery.[19] In these studies, the RFA patients, generally small in number, were not eligible for surgery due to higher comorbidity, previous surgery, higher rates of extrahepatic disease, and other cofactors.

To our knowledge, this study is the first to compare RFA to surgery focusing on patients in the RFA arm who could have also been treated by surgery. Similar to other comparative studies, the major drawback is the limited number of patients included in the RFA group. However, while more than 150 patients were treated by

TABLE 3. Repeated Treatment of Patients With Intrahepatic ("Local" and/or "NLM") Recurrence After Treatment of Early Colorectal Liver Metastases by RFA or Surgery

	Intrahepatic Recurrence	Eligible to Local Treatment	
RFA	18/28	Local treatment	9
		RFA	4
		Res.	2
		RFA + res.	3
		Systemic treatment	9
Surgery	30/82	Local treatment	8
		RFA	5
		Res.	2
		RFA + res.	1
		Systemic treatment	22

The most important reason preventing/to refer from repeated hepatic treatment was systemic disease (compare Table 2).

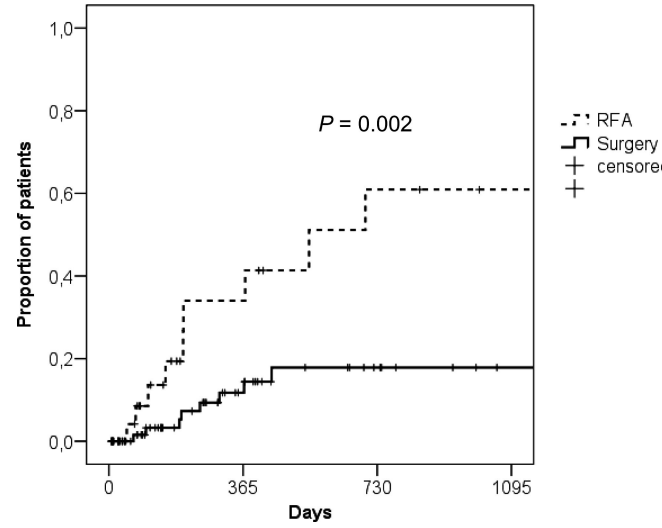

FIGURE 3. Patients undergoing second interventions after primary hepatic treatment using RFA or surgery.

RFA or surgery according to the clinical pathway mentioned above, the selection of patients meeting strict inclusion criteria resulted in comparable treatment groups: all patients were treated during identical periods of time, metastases were diagnosed within the first year after primary colorectal surgery, previous local hepatic treatment, previous downstaging, and additional extrahepatic tumor or de novo cancer had been excluded. As shown in Table 1, patient and tumor characteristics were identical, except for the diameter of metastases which was significantly larger in patients undergoing surgery. This imbalance might have favored the outcome in patients with RFA but, as expected, neither time to progression nor overall survival were finally influenced by the diameter of the lesions (Table 4). Notably, chemotherapy after primary surgery, a confounding factor, was equally distributed in both groups. Time to progression and overall survival were not influenced by previous chemotherapy. From a statistical point of view, the influence of chemotherapy on the outcome of RFA or hepatic surgery can therefore be neglected. In addition to this, the majority of patients need chemotherapeutic

TABLE 4. Univariate Analysis of Predictors of Time to Progress and of Survival After Primary RFA (n = 28) or Surgery (n = 82)

	n	Median Time to Progress (d)	HR	Confidence Interval	*P* Log-Rank	Median Survival (d)	HR	Confidence Interval	*P* Log-Rank
RFA vs. resection	28	203	0.523	0.304–0.901	0.017	n.r.	1.035	0.478–2.239	0.93
	82	416				1694			
Minor vs. major surgery*	38	443	0.962	0.7–1.321	0.809	2262	1.302	0.878–1.930	0.185
	44	416				1332			
Chemotherapy after primary surgery (no vs. yes)	40	545	1.328	0.762–2.315	0.316	1853	1.887	0.859–4.143	0.108
	70	371				1352			
T1/2 vs. T3/4 (primary)	15	371	1396	0.633–3.079	0.407	1269	1.752	0.618–4.967	0.285
	95	393				1352			
N0 vs. N+ (primary)	26	1804	0.576	0.291–1.138	0.107	1854	0.539	0.210–1.388	0.193
	84	352				1357			
G1/2 vs. G3 (primary)	70	420	1.460	0.832–2.560	0.184	1854	1.498	0.729–3.080	0.158
	29	296				1133			
No. nodules 1/2/3 vs. multiple	89	393	1.091	0.577–2.060	0.789	1854	2.298	1.095–4.824	0.028
	21	301				941			
Unilobar vs. bilobar	74	399	1.250	0.719–2.174	0.427	1854	1.440	0.700–2.964	0.319
	35	296				1164			
Diameter ≤3 cm vs. >3 cm	34	443	0.982	0.527–1.828	0.953	1777	0.925	0.428–1.998	0.843
	43	416				n.r.			
CEA ≤10 vs. >10 ng/mL†	50	416	1.425	0.841–2.416	0.186	2262	1.933	0.946–3.947	0.066
	55	344				1164			
Time from primary to treatment by RFA or surgery: ≤258 vs. >258 d	56	368	0.981	0.588–1.638	0.941	1777	1.396	0.713–2.733	0.328
	54	441				1352			
Local recurrence‡									
No	98	—	—	—	—	n.d.	1.574	0.647–3.831	0.317
Yes	12								
NLM‡									
No	67	—	—	—	—	n.d.	3.067	1.522–6.179	0.002
Yes	42								
Extrahep. recurrence‡									
No	71	—	—	—	—	n.d.	2.685	1.373–5.248	0.004
Yes	39								

*Minor surgery = atypical or segmental resection, major surgery = hemihepatectomy or extended resection.
†CEA indicates carcinoembryonic antigen; data lacking in 5 patients.
‡Defined as a time-dependent covariate.
n.r. indicates not reached; n.d., not defined for time-dependent covariates.

treatment after colorectal surgery and their elimination would make any study impossible.

As a first important result, the proportion of patients eligible for percutaneous RFA was much lower than that of patients amenable to surgery during the 6-year study period. This corroborates the importance of surgery in the treatment of these patients. On the other hand, patients were clearly more aggressed by surgery reflected by the higher rate of complications and the longer hospital stay (13 days) of surgery patients compared with RFA patients (median, 2 days).

Second, the time to recurrence was significantly shorter in patients after RFA compared with surgical patients (Fig. 2; $P = 0.017$). Factors such as TNM status and grading of the primary, time from primary to hepatic treatment, size and number of hepatic nodules, CEA and uni- versus bilobar involvement did not influence time to recurrence. In total, 20 of 28 (71%) patients after RFA compared with only 39 of 82 (48%) patients after surgery (Fisher exact test: $P = 0.047$) experienced tumor recurrence. It appears to be important to distinguish between local recurrence and NLM. The rate of local recurrence was significantly higher in patients treated by RFA, which is the main causative factor for the inferior time to recurrence in RFA patients. This result is identical to all other studies comparing RFA to surgery.[17,19,21,22] The marked difference in local recurrence cannot be explained by unfavorable location of lesions, as supposed in other studies, but must be attributed to the approach to treatment with RFA being clearly less radical than surgery.

Whereas local recurrence did not influence survival in any way, NLM at sites other than that of primary hepatic treatment appear to be the most important pattern of recurrence being crucial for survival (Table 4). An open question is whether treatment, RFA, or surgery, itself stimulates the development of new liver lesions. RFA may contribute to dissemination of tumor cells and may induce immunologic factors favoring tumor growth,[11,21,31] but the acceleration of growth of NLM by surgery can also not be excluded.[31,32] According to the most probable explanation, NLM are expected to

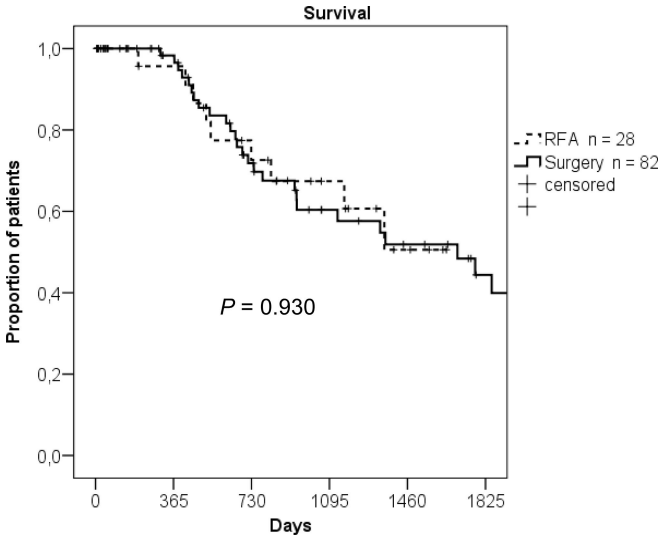

FIGURE 4. Overall survival since beginning of hepatic treatment in patients treated with RFA versus hepatic resection for early occurring colorectal liver metastases.

develop due to cell dissemination from the primary colorectal cancer, a process that is expected to occur with comparable probability in any group of patients. The propensity to disseminate appears to be a biologic property of the primary. Therefore, NLM should be encountered at the same rate independent of the procedure of treatment. Recent published data corroborate this assumption.[23] In our study, the occurrence of NLM was also not significantly different between the groups. While the Kaplan Meier analysis considering the influence of time on the occurrence of recurrent disease resulted in a marginally significant P value ($P = 0.071$), the simple comparison of the number of patients with NLM was clearly not significant (Fisher exact test: $P = 0.179$). As anticipated, the rate of systemic metastases was identical in both groups. Its influence on survival was obviously lower as compared with NLM. In the Cox model analyzing all parameters with potential impact on overall survival, NLM and number of hepatic nodules (1–3 nodules vs. more than 3) were the only significant predictors of survival.

The crucial question is whether the patients were harmed by including them in the RFA protocol. Unequivocally, RFA patients had the shorter recurrence-free interval and more patients in this group experienced recurrence in comparison to surgical patients. It cannot be ruled out that some of the 18 patients with intrahepatic recurrence after RFA would have had different patterns of subsequent metastases or no metastases at all, if hepatic resection had been performed as the first-line option. Nevertheless, this higher rate of tumor recurrence in the RFA group is outweighed by the significantly higher number of patients suitable for repeated local treatment, which might have been impossible if prior surgery had been performed. Figure 3 shows that local retreatment after RFA was performed more frequently and after shorter disease-free intervals than after surgery ($P = 0.002$). This was also because cases with local recurrence and NLM could be treated as the anatomy of the liver was unaltered after RFA. The amenability to repeated intervention was the reason why the proportion of tumor-free patients was consequently identical in both treatment groups (61% after RFA and 62% after surgery). The comparable rates of disease-free patients in the RFA and in the surgery group finally reached during follow-up may explain the identical survival curves shown in Figure 4. A statistically reliable proof of equivalent survival would, of course, require larger study groups.

CONCLUSIONS

According to a clinical pathway introduced in our institution, RFA has been the first-line treatment in patients with early CRLM while surgery was performed in all patients not amenable to RFA due to number, size or location of metastatic lesions. Local recurrence occurred more frequently and time to recurrence was shorter in patients undergoing RFA but the probability to undergo repeated local treatment was higher in patients after RFA compared with surgery. Despite the negative impact of RFA on time to progression, the higher rate of patients suitable for a second hepatic intervention finally resulted in identical rates of absence of disease. Overall survival in patients with early CRLM did not depend on the mode of primary hepatic treatment. It cannot be dismissed that futile surgery might have been avoided in RFA patients with early CRLM, in particular in those with subsequent systemic metastases or no metastases at all. Therefore, it appears justified to perform a randomized study to corroborate this observation and to test the hypothesis if RFA with the option of repeated treatment is capable of avoiding surgery in some patients with early metastases without compromising survival.

ACKNOWLEDGMENTS

The authors thank Florence Samkange-Zeeb for her generous help in critically reviewing the English manuscript.

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