Solitary Colorectal Liver Metastasis

Resection Determines Outcome

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Background: Hepatic resection (HR) and radiofrequency ablation (RFA) have been proposed as equivalent treatments for colorectal liver metastasis.

Hypothesis: Recurrence patterns after HR and RFA for solitary liver metastasis are similar.

Design: Analysis of a prospective database at a tertiary care center with systematic review of follow-up imaging in all of the patients.

Patients and Methods: Patients with solitary liver metastasis as the first site of metastasis treated for cure by HR or RFA were studied (patients received no prior liver-directed therapy). Prognostic factors, recurrence patterns, and survival rates were analyzed.

Results: Of the 180 patients who were studied, 150 underwent HR and 30 underwent RFA. Radiofrequency ablation was used when resection would leave an inadequate liver remnant (20 patients) or comorbidity precluded safe HR (10 patients). Tumor size and treatment determined recurrence and survival. The local recurrence (LR) rate was markedly lower after HR (5%) than

after RFA (37%) ($P<.001$). Treatment by HR was associated with longer 5-year survival rates than RFA, including LR-free (92% vs 60%, respectively; $P<.001$), disease-free (50% vs 0%, respectively; $P=.001$), and overall (71% vs 27%, respectively; $P<.001$) survival rates. In the subset with tumors 3 cm or larger (n=79), LR occurred more frequently following RFA (31%) than after HR (3%) ($P=.001$), with a 5-year LR-free survival rate of 66% after RFA vs 97% after HR ($P<.001$). Patients with small tumors experienced longer 5-year overall survival rates after HR (72%) as compared with RFA (18%) ($P=.006$).

Conclusions: The survival rate following HR of solitary colorectal liver metastasis exceeds 70% at 5 years. Radiofrequency ablation for solitary metastasis is associated with a markedly higher LR rate and shorter recurrence-free and overall survival rates compared with HR, even when small lesions (≤3 cm) are considered. Every method should be considered to achieve resection of solitary colorectal liver metastasis, including referral to a specialty center, extended hepatectomy, and chemotherapy.

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F OR PATIENTS WITH RESECT- able colorectal liver metastasis (CLM), the efficacy of hepatic resection (HR) is established. Not only is HR associated with low morbidity and mortality,[1-3] but 5-year survival rates following HR as high as 58% have been reported.[4-7] Analyses of outcome following HR have consistently identified prognostic factors, including stage of the primary tumor,[8-11] synchronous presentation,[8,10,11] tumor size,[8,11] and tumor number.[8,10,12,13]

For patients who are not candidates for complete HR of CLM, alternatives and adjuncts to HR have been proposed to expand the indications for potentially curative therapy. The most studied and widely used modality for tumor destruction is radiofrequency ablation (RFA), which uses heat produced by a radiofrequency energy generator to destroy tumors and a surrounding rim of normal parenchyma.[6,14-20] Some propose that RFA be limited to use in un-

resectable patients or for treatment of small lesions in the liver remnant at the time that HR is used to treat dominant lesions.[14,21]

More recently, however, RFA has been proposed as an alternative to HR in patients with limited hepatic involvement[22] and in patients with solitary liver metastasis.[20] Although recurrence and survival rates reported in these and other studies are variable, tumor size has emerged as an important factor related to complete ablation and tumor recurrence following RFA. Specifically, local recurrence (LR) rates following RFA rise sharply when the technique is applied to tumors larger than 3 cm in transverse diameter.[14-18,23]

To clarify the utility of RFA as a local treatment modality for CLM, we studied a uniform cohort of patients with solitary tumors. Systematic review of posttreatment imaging for all of the patients in this homogeneous population was performed to determine the impact of treatment (HR vs RFA) on recurrence patterns and survival rates, and the

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group of patients with tumors 3 cm or larger in diameter was specifically assessed.

PATIENT SELECTION AND DATA COLLECTION

Consecutively treated patients identified from a single-institution, prospective hepatobiliary database were studied retrospectively. Patients with solitary CLM who had undergone previous liver-directed therapy (HR or RFA) were excluded, and in all of the cases, the liver metastasis was the first manifestation of M1 disease. Only patients with complete radiologic follow-up at our institution were included. The study population included 180 patients treated from November 1993 to January 2005; 150 patients (83%) were treated with HR and 30 (17%) were treated with RFA. All of the patients treated with RFA had lesions proven to be metastases based on classic imaging findings on computed tomography (hypodense lesion with rim enhancement during the arterial contrast phase) combined with positive biopsy findings (19 patients), hypermetabolism on positron emission tomography (4 patients), or size greater than 2 cm after response to chemotherapy (7 patients).

Indication for the treatment approach selected for each patient was closely examined. Tumors were deemed resectable when the anticipated hepatic parenchymal transection plane would yield a tumor-free margin but preserve an adequate liver remnant.[24] All of the patients whose tumors met these criteria and who were medically fit underwent HR. Radiofrequency ablation was used when HR would have left an inadequate liver remnant (20 patients: 13 with steatosis, steatohepatitis, or fibrosis and 7 judged to have a remnant too small to permit safe hepatectomy) or when comorbidity precluded safe HR (10 patients: 3 were treated percutaneously in the operating room under general anesthesia by a hepatic surgeon and 7 were treated at open laparotomy). The RFA technique has been previously described in detail.[6] In all of the patients treated with RFA, complete necrosis of the CLM was confirmed by intraoperative ultrasound, postoperative computed tomography, or both.

Potential prognostic factors were recorded from the database and grouped into 4 categories (clinical, primary tumor, liver tumor, and surgical) based on previously documented prognostic groups.[8] Positive and negative resection margins were reported as recently defined in a study from our institution.[7] For statistical analysis, metastases diagnosed 12 or fewer months before the date that the primary tumor was diagnosed were considered synchronous and those diagnosed after 12 months were considered metachronous. Recurrence patterns were assessed by systematic review of all of the preoperative and postoperative cross-sectional imaging by a dedicated hepatobiliary radiologist. On review of imaging, recurrence was further classified as LR (recurrence at the ablation site or at the hepatic transection margin), distant hepatic recurrence (DHR) (recurrence in the liver remote from the ablation or resection site), extrahepatic, or a combination of sites. Outcome data, including recurrence site, time from hepatectomy to recurrence, and overall survival time, were analyzed for all of the patients.

STATISTICAL CONSIDERATIONS

To compare the distribution of variables between treatment groups, the Mann-Whitney U test was used for continuous data and the χ^2 test was used for categorical data. Clinical outcomes, including recurrence-free survival (RFS), LR-free survival (LRFS), disease-free survival (DFS), and overall survival (OS), were analyzed by the Kaplan-Meier method. To determine the prognostic value of study variables, survival rates were compared with the log-rank test. Factors with univariate sig-

Table 1. Analysis of the Distribution of Potential Prognostic Factors Between Hepatic Resection vs Radiofrequency Ablation Treatment Groups

Prognostic Factor	Patients Who Underwent Resection, %	Patients Who Underwent RFA, %	P Value
Sex			
Male	57	77	.048
Female	43	23	
Primary tumor location			
Colon	65	70	.62
Rectum	35	30	
Primary tumor stage			
1-2	16	20	.59
3-4	84	80	
Primary tumor node status			
Positive	54	61	.52
Negative	46	39	
Metastasis diagnosis			
Synchronous*	49	60	.29
Metachronous	51	40	
Metastasis diameter, cm			
≤3	42	53	.25
>3	58	47	
Pre-HR CEA level, ng/mL			
≤200	95	93	.79
>200	5	7	

Abbreviations: CEA, carcinoembryonic antigen; HR, hepatic resection; RFA, radiofrequency ablation.

*Synchronous is defined as detection of a colorectal liver metastasis 1 year or sooner after treatment of the primary tumor.

nificance at a level of $P \leq .15$ were entered into Cox regression models to determine multivariate significance, odds ratios, and 95% confidence intervals. Final statistical results were considered significant at $P \leq .05$.
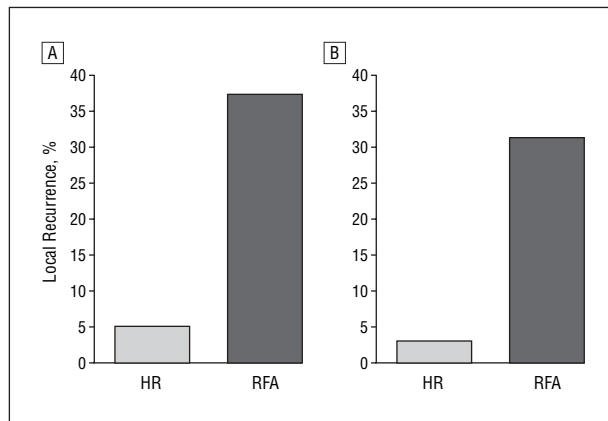
COMPARISON OF PROGNOSTIC FACTORS BETWEEN TREATMENT GROUPS

The study population comprised 109 men and 71 women. The median age was 61 years, with an age range of 23 to 88 years. Laparotomy and open-surgical RFA were performed in 27 (90%) of the 30 patients treated with RFA. The median tumor diameter in the 2 treatment groups was not statistically different (HR: median tumor diameter, 3.5 cm [range, 0.5-17.0 cm]; RFA: median tumor diameter, 3.0 cm [range, 1.0-7.0 cm]; $P = .23$). Among the 150 patients treated with HR, 137 patients underwent anatomic resection (extended hepatectomy in 22 patients, hemihepatectomy in 63, bisegment resection in 14, and single-segment resection in 38). The remaining 13 patients underwent subsegmental wedge resection. Pathologic analysis revealed tumor-free hepatic parenchymal transection margins in 143 (95%) of the HR cases and microscopic evidence of tumor at the transection margin in 7 patients (5%). One patient (1%) died within 30 days of undergoing HR; there were no 30-day mortalities in the RFA group ($P = .65$). With the exception of sex, the distribution of potential prognostic factors that were studied was not different between treatment groups (**Table 1**).

There was no statistical difference in the use of chemotherapy between the HR (66%) and RFA (80%) groups (P=.32). The proportions treated with systemic chemotherapy regimens containing irinotecan or oxaliplatin were also similar (36% in the HR group vs 30% in the RFA group; P=.53).

LOCAL AND SYSTEMIC RECURRENCE PATTERNS

At a median follow-up of 31.3 months (range, 4-138 months), a total of 19 patients (11%) had developed LR confirmed by systematic review of follow-up imaging. These included recurrence at the resection margin in 8 (5%) of the 150 patients treated with HR, with a median time to LR that was not reached by the time of analysis. In contrast, during follow-up of the 30 patients treated with RFA, 11 (37%) had recurrence at the RFA site (P<.001) (**Figure 1**). Three- and 5-year LRFS rates after HR (95% and 92%, respectively) were superior to LRFS rates after RFA (60% and 60%, respectively) (P<.001) (**Figure 2**). Only treatment type (HR vs RFA) was associated with risk for LR; other studied prognostic factors were not predictive (**Table 2**).
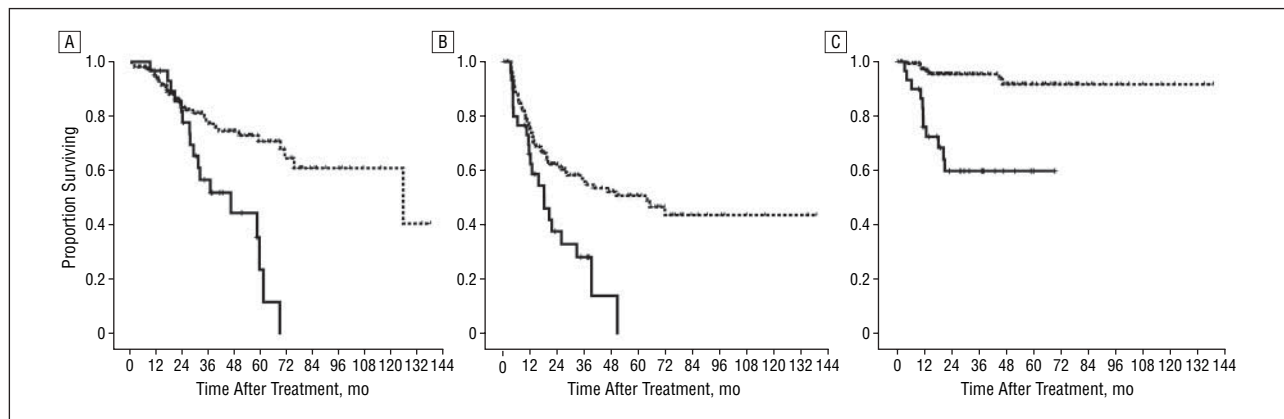
Proximity to major vascular structures has been proposed as a factor associated with incomplete RFA and risk for LR after RFA.[25] Review of imaging permitted analysis of LR after RFA based on contiguity of the treated tumor with a major vascular structure (in all of the cases, a main hepatic vein or veins). Fifteen (50%) of the 30 RFA-treated tumors were in contact with a main hepatic vein. Among these 15 patients, 4 (27%) had LR. Three of these 4 LRs were in patients with metastases larger than 3 cm in diameter. Fifteen (50%) of the 30 tumors treated with RFA were not adjacent to any major vascular structure. Among these 15 patients, 7 (47%) had LR. Three of these 7 LRs occurred in patients with metastases larger than 3 cm in diameter. Thus, there was no association between LR and tumor proximity to major hepatic veins (P=.26).

Among the 11 patients who developed LR after RFA, 7 (64%) were thought to have potentially treatable recurrent lesions. Four of these patients were treated with salvage HR, 2 of whom were disease free at last follow-up; a fifth patient was surgically explored for HR but was found to have unresectable peritoneal disease. Two others underwent repeat RFA, but both progressed despite retreatment. One patient with LR after HR will undergo reresection on completion of ongoing systemic therapy.

Distant hepatic recurrence developed in 32 patients (18%). In both univariate and multivariate analyses, the factors that predicted DHR were tumor size and interval between treatment of the primary tumor and diagnosis of liver metastasis. Patients with tumors larger than 3 cm and those with synchronous presentation were twice as likely to develop DHR (multivariate P values of .047 and .02, respectively). In contrast, the incidence of DHR was equivalent in the HR group (18%) and the RFA group (17%) (P=.86).

In the RFA group, 2 patients with DHR were treated with repeat RFA, but both had tumors that recurred or persisted despite the second intervention. One patient was surgically explored with the intent of curative resection but was found to have peritoneal disease, so the planned resection was not performed. In the HR group, 3 patients with DHR were re-treated (2 by resection and 1 by RFA), and all of them remained disease free at a median follow-up of 75 months.

Figure 1. Local recurrence after hepatic resection (HR) or radiofrequency ablation (RFA) for all of the patients with solitary colorectal liver metastasis (P<.001) (A) and for those patients with tumors 3 cm or smaller (P=.001) (B).

Figure 2. Kaplan-Meier analysis of overall (P<.001) (A), disease-free (P=.001) (B), and local recurrence–free (P<.001) (C) survival proportions for all of the study patients treated with hepatic resection (n=150; dotted lines) vs radiofrequency ablation (n=30; solid lines).

Table 2. Univariate Analysis of Clinicopathological Variables Associated With Local Recurrence

Factor	Patients With Local Recurrence, No./Total Patients, No. (%)*	P Value
Sex		
Male	15/109 (14)	.10
Female	4/71 (6)	
Primary tumor location		
Colon	10/119 (8)	.26
Rectum	9/61 (15)	
Primary tumor stage		
1-2	2/29 (7)	.44
3-4	16/145 (11)	
Primary tumor node status		
Negative	8/69 (12)	.81
Positive	8/85 (9)	
Metastasis diagnosis		
Synchronous†	10/92 (11)	.77
Metachronous	9/88 (10)	
Metastasis diameter, cm		
≤3	7/79 (9)	.40
>3	12/101 (12)	
Pre-HR CEA level, ng/mL		
≤200	14/150 (9)	.94
>200	1/9 (11)	
Treatment		
Resection	8/150 (5)	<.001
RFA	11/30 (37)	

Abbreviations: CEA, carcinoembryonic antigen; HR, hepatic resection; RFA, radiofrequency ablation.

*Local recurrence is defined as recurrence at resection margin or ablation site. Median time to recurrence was not reached in any group or subgroup.

†Synchronous is defined as detection of a colorectal liver metastasis 1 year or sooner after treatment of the primary tumor.

Table 3. Multivariate Analysis of Factors of Outcome

| Outcome	OR (95% CI)	Multivariate P Value
Local recurrence		
RFA (vs HR)	7.35 (2.91-18.52)	<.001
Distant intrahepatic recurrence		
Synchronous (vs metachronous)	2.33 (1.11-4.89)	.02
Tumor size >3 cm (vs ≤3 cm)	2.17 (1.01-4.65)	.047
Any recurrence*		
Tumor size >3 cm (vs ≤3 cm)	1.90 (1.26-2.88)	.002
Primary tumor location in rectum (vs colon)	1.67 (1.11-2.52)	.01
RFA (vs HR)	2.29 (1.40-3.75)	.001
Death		
Tumor size >3 cm (vs ≤3 cm)	1.94 (1.06-3.55)	.03
RFA (vs HR)	3.22 (1.74-5.96)	<.001

Abbreviations: CI, confidence interval; HR, hepatic resection; OR, odds ratio; RFA, radiofrequency ablation.

*Any recurrence includes local, distant intrahepatic, and extrahepatic recurrence as well as their combinations.

During follow-up, 72 patients (40%) developed distant recurrence. In the HR group, 58 patients (39%) experienced distant recurrence—14 in combination with intrahepatic recurrence and 44 with distant-only recurrence. Sites of first distant recurrence after HR included the lung in 41 patients (70%), peritoneum or lymph nodes in 12 (21%), bone in 4 (7%), and brain in 1 (2%). Eight patients in the HR group with isolated pulmonary recurrences underwent pulmonary metastatectomy, and they all remained disease free with a median follow-up interval of 50 months. In the RFA group, 14 patients (47%) experienced distant recurrence—4 in combination with intrahepatic recurrence and 10 with distant-only recurrence. The distribution of first distant recurrence after RFA was similar to that observed after HR and included the lung in 8 patients (57% of recurrences), peritoneum or lymph nodes in 5 (36%), and bone in 1 (7%). In contrast to the HR group, however, no patient with systemic recurrence after RFA was a candidate for retreatment with curative intent.

SURVIVAL ANALYSIS

Univariate analysis of RFS showed that both tumor size and treatment modality were associated with the development of recurrence. The overall recurrence rate was not statistically different in patients with a tumor larger than 3 cm compared with tumors 3 cm or smaller in diameter (62% vs 48%, respectively; P=.06), but those with tumors larger than 3 cm had recurrence sooner after treatment (median RFS, 19 months vs 32 months, respectively; P=.02). Patients treated with RFA were significantly more likely than patients treated with HR to have recurrence (77% vs 52%, respectively; P=.01) and had a shorter median RFS (18 months vs 31 months, respectively; P=.006) regardless of tumor size. Tumors larger than 3 cm (odds ratio=1.90), primary tumors located in the rectum (odds ratio=1.67), and treatment with RFA (odds ratio=2.29) were associated with a significant increased risk for recurrence in multivariate analyses (**Table 3**). For HR as compared with RFA, the 5-year RFS rates (40% vs 0%, respectively; P=.006) and DFS rates (50% vs 0%, respectively; P=.001) were significantly higher (Figure 2). In addition, 3- and 5-year OS rates were higher after HR (79% and 71%, respectively) compared with RFA (57% and 27%, respectively) (P<.001).

OUTCOME FOR PATIENTS WITH SOLITARY CLM 3 CM OR SMALLER

A separate assessment of intrahepatic and distant recurrence patterns and survival rates for the 79 study patients with tumors 3 cm or smaller indicates that both LR and OS rates significantly differed between patients treated with RFA and HR. Of the 63 patients with tumors 3 cm or smaller treated with HR, only 2 patients (3%) recurred at the resection margin. In contrast, 5 (31%) of the 16 patients treated with RFA with metastasis smaller than 3 cm had recurrence at the RFA site (P=.001) (Figure 1). Thus, the 5-year LRFS rate for patients treated with HR was higher than after treatment with RFA (97% vs 66%, respectively; P<.001) (**Figure 3**). For patients with small tumors, RFA was also associated with a marked decrease in 5-year OS rates compared with HR (18% vs 72%, respectively;
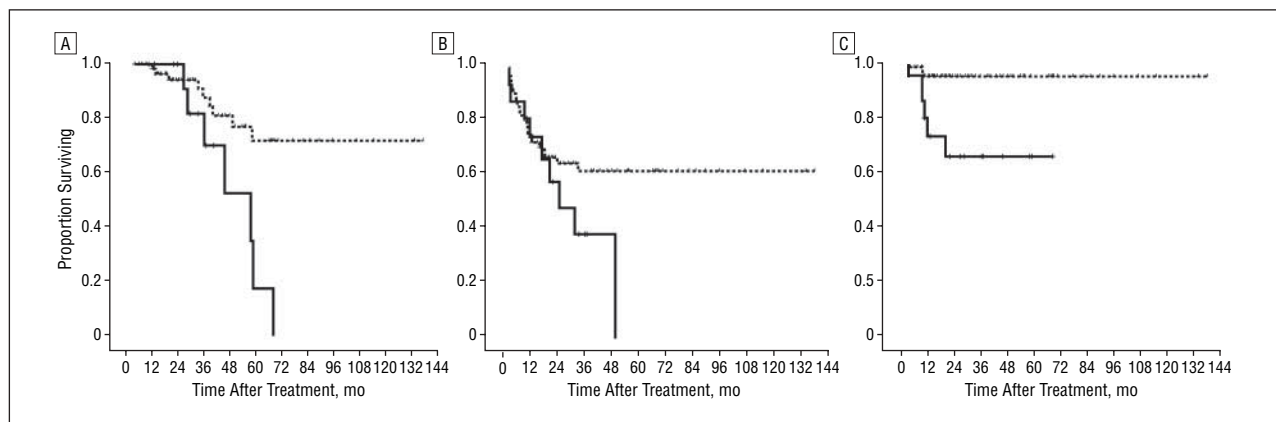
Figure 3. Kaplan-Meier analysis of overall (*P*=.006) (A), disease-free (*P*=.15) (B), and local recurrence–free (*P*<.001) (C) survival proportions for study patients with maximal tumor diameter 3 cm or smaller treated with hepatic resection (n=63; dotted lines) vs radiofrequency ablation (n=16; solid lines).

P=.006) (Figure 3). A trend in DFS rate difference was noted, but it was not statistically significant (*P*=.15).

COMMENT

Here we report the 5-year OS rate of 71% and the 5-year DFS rate of 50% following HR in 150 patients with solitary colorectal metastasis. These rates exceed the 58% 5-year survival rate following HR reported in single-institution series[4-6] and a multicenter series[7] that included all of the patients (with solitary and multiple metastases) resected during a similar time period. These findings reveal that the survival rate in the subset of patients with CLM who have solitary lesions is far higher than the rate published in historical series describing HR for CLM.[11]

In contrast, survival was significantly shorter in patients treated with RFA. Local tumor recurrence appeared to be the major explanation for inferior survival after RFA (37% of patients found to have LR at a median follow-up interval of 31 months), which was reflected in the markedly reduced DFS rate in patients treated with RFA (0% at 5 years). Whereas the 5-year OS rate after HR was 71%, it was only 27% after RFA. This outcome after RFA is only marginally better than the carefully documented natural history of untreated solitary CLM in patients without extrahepatic disease reported by Wagner et al[26] more than 20 years ago.

Several factors have been associated with a higher risk of LR after RFA. The factor described most often is tumor size. To address this issue, our study analyzed patients with tumors 3 cm or smaller; even in this subset with small tumors, the recurrence rate was high after RFA (31%) compared with only 3% after HR. Although tumor location adjacent to a major hepatic vein has never been suggested as an indicator of tumor biological aggressiveness for CLM, a cold-sink effect has been proposed as an explanation for LR when tumors are treated in this location.[25] We found no difference in LR among patients with tumors in contact with major hepatic veins (27%) compared with patients with tumors remote from major veins (47%). Recent laboratory data suggest that RFA not only increases survival of residual neoplastic cells but also strongly promotes intrahepatic proliferation of CLM,[27] which may further explain the inferior outcome after RFA compared with HR in our study and in the literature.[22,28]

Several groups have proposed RFA as an alternative to HR, but none have shown equivalence, much less superiority. Early studies by Solbiati et al[29] and Lencioni et al[19] revealed a 34% incomplete ablation rate, a 23% to 34% LR rate (per lesion), and a 12% progression rate (per lesion) at a follow-up of only 6.5 months. Subsequent studies revealed little improvement over initial results. In 2001, Solbiati et al[16] described 117 patients with 179 metachronous CLMs and found a 39% LR rate (per lesion) after RFA; in 2003, Solbiati et al[30] updated the follow-up including 278 lesions in 166 patients with a 5-year survival rate of only 22%. Livraghi et al[22] described patients who were considered to be potentially resectable and had limited disease (1-3 lesions, all <4 cm in diameter; 50% of studied patients had solitary lesions) but again found a treatment failure rate of 40% and, despite retreatment, a 40% LR rate at a median follow-up interval of 28 months.

Important preliminary results of a 423-patient Italian multicenter trial[28] are illustrative of the outcome from RFA in CLM. Inclusion in this study required 4 or fewer metachronous CLMs, all 5 cm or smaller, and no evidence of extrahepatic disease. The number of lesions per patient was few (mean±SD, 1.4±0.7 lesions per patient), and the tumor sizes were small (mean±SD, 2.7±0.9 cm; range, 0.5-5 cm). At a mean follow-up of only 19 months, the LR rate was 25%. The 5-year survival rate for patients with multiple tumors was only 11%, and the survival rate for patients with solitary lesions larger than 2.5 cm was equally poor (13% at a follow-up of 5 years). The finding that patients with single lesions that were 2.5 cm or smaller had a better survival rate (56% at a follow-up of 5 years) is tempered by the inclusion of patients with tiny lesions (0.5-1 cm)— absence of pathologic proof that all of these lesions were metastases leaves open the question of whether some were benign lesions. The Italian multicenter trial data are even more striking when viewed in the setting of the overall 5-year survival rate of 72% for patients with resected solitary lesions smaller than 3 cm in the present series (with all of the treated lesions proven pathologically to be metastases).

Finally, Oshowo et al[20] reported a comparative series of patients with solitary CLM treated by RFA or HR. Although their study found similar 3-year survival rates in the 2 groups (53% for RFA and 55% for HR), it is striking that there were no long-term survivors following HR in their study. These results conflict with the finding in the present study of an 80% 3-year survival rate (and a 71% 5-year survival rate) after HR and well-established data showing 10- and 20-year survivors after HR of solitary and multiple metastases, even without adjuvant chemotherapy.[11] Thus, the proposal by Oshowo and colleagues for a randomized study of RFA vs HR cannot ethically be supported at this time.

To our knowledge, no study to date has demonstrated that RFA is equivalent to resection for CLM, and the current analysis, which focuses on a homogeneous group of patients, supports this finding. Comparison of RFA and HR in the present study is appropriate because the 2 groups are oncologically similar. All of the factors known to influence prognosis after surgical treatment of CLM[8] were evenly distributed between the 2 groups—only the treatments differed. Selection criteria for RFA, including the presence of liver disease, small predicted liver remnant, and patient comorbidity, are unlikely to explain the differences observed in OS rates and do not explain differences observed in disease-specific survival rates between groups.

The increased risk for complications associated with resection in patients with extensive underlying liver disease is recognized and of growing concern.[31,32] There are no data to support the use of RFA as a replacement for resection; therefore, the utility of RFA has been explored at our institution to treat patients not suitable for HR for the indications described in the present study. Analysis of our own results with maturing follow-up and analysis of data from other groups has led to decreasing use of RFA at our institution (9 RFAs for CLM in 2005 compared with 20 RFAs for CLM per year on average prior to analysis of our own data).[6] Furthermore, we have established a program of liver volumetry in candidates for extended resection[24,33] and systematic use of preoperative portal vein embolization when the liver remnant is inadequate.[24,33-35] This practice has led to a shift away from RFA toward extended hepatectomy, a valid approach with very low mortality (0.8%) for patients previously considered unresectable.[3] In addition, use of effective systemic therapy has enabled downsizing of unresectable tumors[36]; staged resection with or without portal vein embolization is being used with improving long-term outcomes.[24,37,38]

In conclusion, hepatic resection is the preferred treatment for solitary CLM. Local recurrence following hepatic resection is uncommon, and long-term survival is achieved in the majority of patients. Radiofrequency ablation is associated with a high local failure rate regardless of tumor size, and long-term survivors are rare following this treatment. Careful consideration must be given to selection of patients for surgical treatment of colorectal metastases. Every effort must be made to use advances in patient preparation for surgery, including carefully planned chemotherapy, portal vein embolization, 2-stage hepatectomy, and referral to a specialty center before noncurative treatments such as ablation are used.

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DISCUSSION

David M. Nagorney, MD, Rochester, Minn: I would like to congratulate Dr Abdalla and colleagues for evaluating 2 interventional approaches for the treatment of the solitary hepatic metastasis from colorectal carcinoma. The null hypothesis, that is, no difference in outcome, clearly appears rejected by their findings of significantly prolonged local recurrence–free, disease-free, and overall survival after hepatic resection. Indeed, the 5-year survival of nearly 70% is striking. Being a staunch resectionist myself, I applaud these results.

Your message is clear: think resection first and foremost and RFA only as an alternative. These data should provide a cautionary notice for those embracing RFA as the primary treatment modality for metastases.

These groups were disparate only in size of sample and selection factors, so why such a big difference? Resection is clearly a mature technique and RFA is evolving, but I think that there is probably something more than technique that accounts for these differences. In this regard, I have several questions related to RFA. Is it an inferior technology? Is the technology sound but the application errant? Or is patient selection the issue?

First, your data clearly show that RFA can destroy some tumors but not others. Why are some tumors susceptible and others not? Clearly, it was not size or position next to major vessels. Is susceptibility to RFA in part tumor inherent? Could there be morphologic, histologic, or even genetic factors of the metastasis that account for RFA susceptibility to heat-induced necrosis?

Second, is the application errant because of limitations of accurately defining the zone of destruction intraoperatively or other technical issues? The Achilles heel of this technique is accurate probe placement and tine deployment. Were these factors, RFA duration, type of device, or individual experience also evaluated? And, do you have any caveats for those who use RFA to ensure effectiveness?

Third, because most patients who underwent RFA had recurrence, was selection an issue? Was the preoperative evaluation of these patients similar to the resection group? Was their nonsurgical treatment similar? Finally, using the "retrospectscope," would patients undergoing RFA still be considered now unresectable?

I learned a lot from the presentation. I really enjoyed the paper. I will put it in my reading list and recommend it to my residents. I thank the society for the opportunity to comment.

Dr Vauthey: Dr Nagorney, thank you for the insightful comments regarding our study. In the day and age of bigger needles for RFA and more powerful generators, I think your questions regarding factors other than technique are quite legitimate.

In answer to your question regarding tumor type and recurrence, if you look at hepatocellular carcinoma and look at the data from the explant specimens of patients who underwent radiofrequency before transplantation, you will find very similar numbers to those presented here, with 35% or higher residual tumor. The groups in Toronto and in Italy have confirmed these numbers.

Regarding the biologic factors, I think we have too few patients to look at specific factors affecting local recurrence after radiofrequency ablation. I submit to you that these factors are probably similar to factors associated with local recurrence after resection (*Ann Surg*. 2005;241:715-722), but the main factor is likely to be incomplete ablation since all patients but 2 died of disease.

Is it experience related? Three surgeons performed the radiofrequency ablations. The surgeon who did more than 10 had as many recurrences as the other 2 surgeons who did less than 10. This is obviously a small series and will not give us a lot of information about the learning curve of the technique, but the proportion of recurrences was similar.

Regarding the imaging evaluation, these patients were similarly evaluated with a liver-protocol computed tomography with thin cuts, which includes a precontrast study followed by contrast-enhanced arterial and early and late portal phases.

We did review all the images, and recurrence rates after radiofrequency ablation were not associated with close proximity with major veins (hepatic vein, portal vein, vena cava).

Was the nonsurgical treatment similar? There was a similar proportion of patients receiving chemotherapy in both groups, so progress may rest on improving technique. So, there is a need for better imaging while radiofrequency is being performed. Perhaps we should look at better ways of using intraoperative ultrasound with the use of contrast agents. Some groups in Japan recommend postradiofrequency mapping of the ablation zone within 10 days after radiofrequency ablation and compare with the preoperative computed tomography, and if necessary, reablate to achieve a wider area of ablation.

Using the retrospectscope, yes, we could have resected some patients. In fact, I myself resected 2 of these patients who recurred after radiofrequency ablation. We have now a program of liver volumetry and portal vein embolization, which we presented to this association 3 years ago (*Arch Surg*. 2002;137:675-

680). And, we use portal vein embolization in patients who need extended liver resection and do have a small liver remnant.

Finally, to go back to the main message of this paper, I think this paper shows that regardless of the biology of the tumor, resection is superior, provides evidence of long-term survival, and radiofrequency even in patients who did not recur locally does not provide the shoulder in the survival curve. And this is concerning, and therefore, every patient should be considered for resection.

Merril T. Dayton, MD, Buffalo, NY: Given what appears to be the superiority of resection over RFA, other than patients with severe comorbidity, is there any other use for RFA in your view? In other words, what role will RFA play in the future?

Dr Vauthey: I think less and less. I think there are patients with severe underlying liver disease in whom you cannot do a major resection. We have now a number of patients who develop hepatic injury from chemotherapy. And, I think we have to look at these patients as carefully as the patients we select for major resection in cirrhosis. So, in cases of patients with ill-located lesions with underlying liver disease who require major resection, alternative treatments such as ablation may remain useful.

Philip D. Schneider, MD, Sacramento, Calif: I agree virtually 100% with everything that your group has presented. But, you mentioned 1 obvious selection criterion which I think you are going to have to address more specifically in the manuscript, and that is the issue of selection based on an estimate that the patient didn't have satisfactory remnant volume. So, at least some RFA patients were selected by apparently having more liver disease than the patients that went on to resection.

How that influences the results I don't know, but it is clearly one of the selection criteria that you haven't addressed that may influence the outcome. So, you may have to specify how many died of liver failure vs how many died of progressive metastatic disease.

Dr Vauthey: There were 7 patients who were selected for radiofrequency ablation based on a small liver remnant. These patients today would be considered for resection, but they underwent radiofrequency ablation prior to the development of our program. Answering your question, the manuscript will provide the disease-free survival, and this should account for deaths unrelated to cancer.

Anton J. Bilchik, MD, Santa Monica, Calif: I enjoyed your presentation. M. D. Anderson has made major contributions to our understanding of both ablation and hepatectomy for liver malignancies.

Can you clarify for me whether the local recurrence rate of 31% in small tumors could be explained by the close proximity to major blood vessels? Do you have any data on what the local recurrence rate at your center is for lesions less than 3 cm not in close proximity to blood vessels?

Second, in the initial study of radiofrequency ablation, your group reported a 1.9% local recurrence rate at a median follow-up of 15 months; this is substantially less than the recurrence rates you reported today. Do you think that the median follow-up in the initial study was too short?

Dr Vauthey: Regarding your second question about the differences in results, there were 2 problems, I think, with these earlier studies. First, the follow-up was much shorter in prior studies than in the current study. Second, in the current study, we excluded patients who did not have complete radiological follow-up at M. D. Anderson. Patients go away and then get no follow-up, and this may lead to an underestimation of local recurrence.

Regarding the proximity to the veins and the higher likelihood of recurrence, you have seen the data regarding recurrence near the hepatic vein for the whole group. I do not have the data for the tumors less than 3 cm. But, I think we would have small numbers without statistical power and I don't think it matters. I think, in fact, an interesting finding of this paper is that, overall, we had no more recurrence near major veins with radiofrequency ablation.

Kelly M. McMasters, MD, Louisville, Ky: Given the fact that this is not a randomized study and that the policy at M. D. Anderson has been, of course, to resect patients with resectable tumors for quite some time, do you think it is really fair to compare the survival of the patients who underwent RFA here to those that underwent resection? Were there other factors such as performance status, comorbidity, etc, that really make these comparisons for survival not valid?

Dr Vauthey: That is why the paper will provide 3 panels that demonstrate consistently divergent outcomes between hepatic resection and radiofrequency ablation in the 2 figures (overall size and size <3 cm). We are looking not only at the overall survival but also at disease-free survival. Again, all but 2 died of disease in the radiofrequency group.

William C. Chapman, MD, St Louis, Mo: I, too, would like to applaud the M. D. Anderson group for reporting the suboptimal results with their experience with RFA and essentially what is an "about-face" compared with your earlier reports with radiofrequency ablation. I have a couple of questions for the authors.

One is, what do you think the role of targeting is in this high failure rate? Is there something that has changed in your program that has led to this higher incidence of local recurrence?

Second, is there any role for preoperative biopsy in patients that you suspect you may discover to have a parenchymal problem at exploration? In other words, this cohort of patients, many of whom had fibrosis or other findings perhaps chemotherapy related, that if you had known about in advance, would you have pushed harder for portal vein embolization or some other approach to allow for safe resection?

Dr Vauthey: Thank you, Dr Chapman. I don't think anything has changed. I think we have a better analysis of the cohort and an extended follow-up. Our initial paper reported mainly safety with short follow-up.

Regarding your recommendation of preoperative biopsy in patients with underlying liver disease, I think it should be studied further prospectively. You can suspect steatosis based on the liver-spleen ratio on the precontrast phase of the computed tomography, and we are currently evaluating this further. The biopsy, however, may not be totally reliable because steatosis may be geographical in distribution and there may be inter- and intraobserver variation in the assessment of steatosis. So, I would recommend considering laparoscopy if you have a suspicion of underlying liver disease before proceeding.