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# Treatment of recurrent hepatocellular carcinoma confined to the liver with repeated resection and radiofrequency ablation: A single center experience

R.M. Eisele[a,*], S.S. Chopra[a], J.F. Lock[a] and M. Glanemann[b]
[a]*Department of General, Visceral and Transplantation Surgery, Charité Virchow-Clinic, Berlin, Germany*
[b]*Department of General, Visceral, Vascular and Pediatric Surgery, Medical Faculty of the University of Saarland, Homburg/Saar, Germany*

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**Abstract.**
**BACKGROUND:** Recurrence of hepatocellular carcinoma (HCC) after surgical treatment is a common problem. It can be treated by radiofrequency ablation (RFA) or repeated hepatic resection (HR). This report compares both in a retrospective, single-institution database.
**PATIENTS AND METHODS:** A prospectively collected database was retrospectively analyzed. RFA was performed under ultrasound control using two different monopolar devices. All kinds of access were used: open surgical ($n = 10$), percutaneous ($n = 13$) and laparoscopic ($n = 4$). HR was performed using an ultrasound aspiration device. Indication for a particular treatment was allocated on a case-by-case basis; the final decision was often made intraoperatively.
**RESULTS:** Survival after RFA (median 40 months) was similar compared to that after HR (48 months, $p = 0.641$, logRank-test). Tumor-free survival was markedly impaired after RFA (15 vs. 29 months). This difference was however not significant ($p = 0.07$, logRank-test). Both groups were different regarding occurrence of cirrhosis, maximal tumor size, time after initial diagnosis and duration of the procedure.
**CONCLUSION:** In this non-randomized retrospective trial, survival and disease-free survival was not significantly different when compared between patients treated by RFA and HR. There was however a tendency towards a longer tumor-free survival in the resected patients.

Keywords: Hepatocellular carcinoma, recurrence, radiofrequency ablation, hepatic resection, repeat resection



## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent and most important cancers worldwide. Its prevalence is rapidly growing with more than 1 million new diagnoses per year [1]. The mainstay

*Address for correspondence: Robert M. Eisele M.D., Department of General, Visceral and Transplantation Surgery, Charité Virchow-Clinic, Augustenburger Pl. 1, 13353 Berlin, Germany. Tel.: +49 30 450 652 483; Fax: +49 30 450 552 930; E-mail: robert_m.eisele@charite.de.

for treatment of disease exceeding the criteria for liver transplantation (LT), or for patients not amenable to LT, is hepatic resection (HR). Recently some data suggested also the use of radiofrequency ablation (RFA) for small tumors in cirrhotic livers [2–4]. Recurrence rates are fairly high with a cumulated risk for the development of either local recurrence or new distant intrahepatic tumor growth of approximately 50 % after 3 years and 80 % after 5 years following RFA for HCC [5]. However, HCC recurrence is also rather common after HR. Salvage transplantation remains a case of controversy [6]. There is no clearly elucidated standardized algorithm for the treatment of recurrent HCC so far. The feasibility of repeated HR could be demonstrated in the treatment of colorectal liver metastases [7]. In case of HCC, the underlying liver disease often precludes re-resection due to concomitant loss of functional parenchyma, and in such irresectable disease, RFA is usually suggested. There is no evidence found in the current literature, whether HR or RFA is the preferred treatment for HCC recurrence. We intended to compare both in a retrospective analysis with results of a single center treating recurrent HCC by HR or RFA after curative initial treatment.

## 2. Patients and methods

### *2.1. Inclusion criteria*

All patients with distant intrahepatic recurrence of HCC following previous surgical treatment, whether by resection or RFA, were included. Patients were excluded if a second RFA or HR was performed only for incomplete ablation or local recurrence. Liver transplant candidates and recipients as well as patients following palliative treatment, like chemoembolization and chemotherapy and patients with fibrolamellar HCC were excluded from the study. Patients with simultaneous HR and RFA were included in the RFA group.

### *2.2. Surgical technique*

In general, a trans-parenchymal dissection technique was used guided by intraoperative ultrasound to identify tumor margins and segmental vascular pedicles. HR was conducted using the Cavitron Ultrasonic Surgical Aspirator (CUSA Excel®, Valleylab, Boulder, CO/USA) and bipolar coagulation with a saline irrigation system, or crush-clamping technique. If necessary, non-absorbable titanium clips for hemostasis and biliostasis were applied. The transected liver surface was coated with fibrin sealant (Ticcucol®, Baxter, Munich, Germany), if appropriate. The type and extent of the resection was based on tumor location, parenchymal condition and the patient's general condition.

### *2.3. RFA technique*

RFA was performed under general anesthesia with monopolar devices (Starburst XL®, RITAmedical, Mountain View, CA/USA or cool-tip®, radionics, Burlington, CA/USA). RFA was conducted under sonographic guidance. Open surgical or percutaneous access was chosen according to anatomical and clinical reasons. In general, percutaneous access was avoided in superficial lesions and multifocal disease. In one case an HR was intended, however was intraoperatively cancelled in favour of an open surgical RFA, because the liver parenchyma was intraoperatively considered not sufficient to permit a safe HR. The strategy for RFA was to treat one lesion with a single ablation; overlapping ablation areas were considered in tumor sizes exceeding 4 cm.

Table 1
Demographic data (above) and results of survival and recurrence analysis (below)

| Variable | HR | RFA | p | Test |
|---|---|---|---|---|
| Tumor size | $40 \pm 23$ mm | $28 \pm 11$ mm | $< 0.01$ | T-test |
| % solitary nodules (n) | 59 (16/27) | 56 (15/27) | n.s. | Chi-square |
| Age | $60 \pm 17$ years | $68 \pm 7$ years | n.s. | U-test |
| % cirrhotic patients (n) | 37 (10/27) | 82 (22/27) | $< 0.01$ | Chi-square |
| Female:male | 12:15 | 7:20 | n.s. | Chi-square |
| Time since 1st surgery | $39 \pm 27$ months | $21 \pm 17$ months | $< 0.01$ | T-test |
| Duration | $183 \pm 60$ min. | $141 \pm 91$ min. | $< 0.05$ | T-test |
| Median survival (range) [months] | 48 (38–58) | 40 (28–52) | 0.64 | Log-rank |
| Median tumor-free survival (range) [months] | 29 (18–40) | 17 (4–26) | 0.07 | Log-rank |
| Local recurrence | 37% (10/27) | 33% (9/27) | n.s. | Chi-square |
| Distant intrahepatic recurrence | 48% (13/27) | 63% (17/27) | n.s. | Chi-square |
| Systemic progression | 26% (7/27) | 11% (3/27) | n.s. | Chi-square |

### *2.4. Follow-up*

Diagnosis of HCC recurrence as well as tumor recurrence following the repeated HR or RFA was based on imaging findings; histological confirmation was not compulsory to establish the diagnosis of recurrent disease. Recurrence abutting a treated area (resection plane or ablation area) and/or in the same segment was determined as local recurrence. Preoperative examinations included chest X-ray, $\alpha$-fetoprotein (AFP) levels as well as contrast-enhanced sectional imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]). Postoperative follow-up was performed every three months during the first year, every six months during the second and anually thereafter. Further clinical tests were decided on demand.

### *2.5. Statistical analysis*

Survival data are compared using the Kaplan-Meier method. Statistical analysis includes logRank-testing. Contiguous data are presented as mean with standard distribution (SD), if normally distributed, and as median and range in case of non-Gaussian- distribution. According to standard normal distribution assessed by Kolmogorov-Smirnov testing, analysis of metric data is performed using Student's T-test or Mann-Whitney-U-test. For non-parametric data, chi-square tests are applied.

## 3. Results

An overview of the demographic data is shown in Table 1. Out of a total of 425 hepatic resections (HR) and 92 radiofrequency ablations (RFA) for HCC, 27 HR and 27 RFA procedures were performed due to HCC recurrence following previous surgical treatment. The initial treatment was HR (15 in the RFA and 25 in the HR patients) or RFA (12 in the RFA and 2 in the HR patients). Etiology of cirrhosis was predominantly posthepatitic with 11 hepatitis C patients in the RFA and eight patients in the HR group, four with hepatitis B and C each. Ethylism was present in four RFA and two HR patients; in five patients (four in the RFA, one in the HR group), the reason for cirrhosis remained unknown. Only one of the RFA patients suffered from hemochromatosis. Child, Pugh and Turcotte stage of cirrhosis was A except for eight patients out of the RFA group (seven B and one C score).

All resections were performed using open surgical access. No laparoscopic resection was performed for HCC recurrence during the treatment period. The types of resection were major hepatectomies

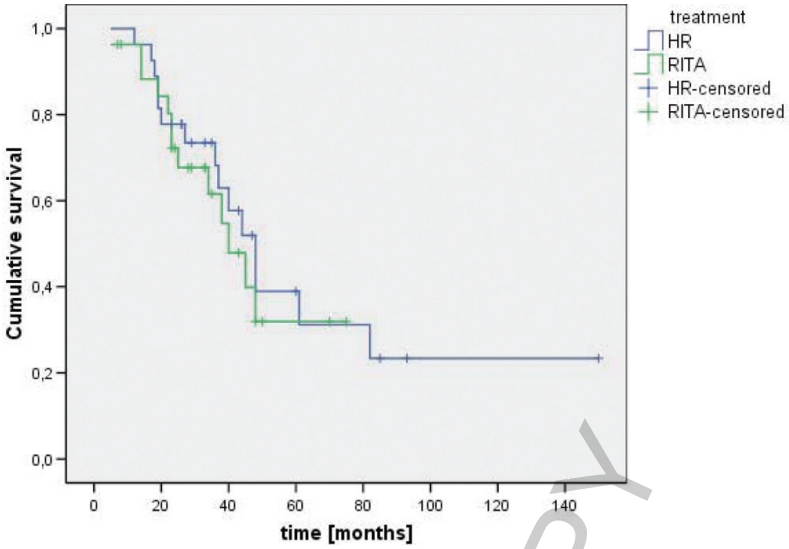


Fig. 1. Overall survival of patients with recurrent hepatocellular carcinoma treated by means of hepatic resection (HR) or radiofrequency ablation (RFA) [Kaplan-Meier estimation, $p = 0.641$ (logRank-test)]. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/THC-120705)

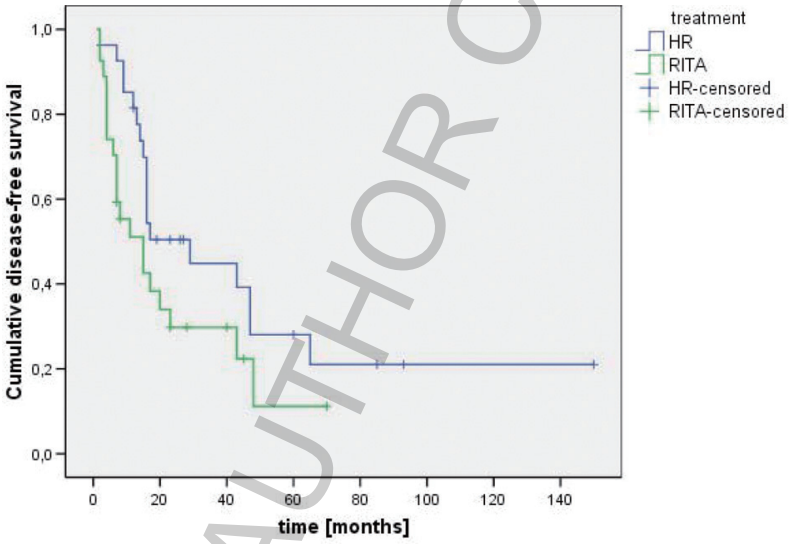




Fig. 2. Disease-free survival of patients with recurrent hepatocellular carcinoma treated by means of hepatic resection (HR) or radiofrequency ablation (RFA) [Kaplan-Meier estimation, $p = 0.07$ (logRank-test)]. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/THC-120705)

in four cases, three right hemihepatectomies in non-cirrhotic patients after wedge-resections and one left hemihepatectomy after initial wedge-resection in a patient with a Child A-stage cirrhosis. The minor procedures were eight bisegmentectomies, seven anatomical segmentectomies and 10 atypical wedge-resections; in two patients, wedge-resections were combined with anatomical resections (one segmentectomy and one bisegmentectomy). All available histopathological specimens confirmed the

Table 2
Synopsis of reports on the comparison of radiofrequency ablation (RFA) to hepatic resection (HR) for the treatment of primary hepatocellular carcinoma

| Source | | Vivarelli 2004 | Maluccio 2005 | Montorsi 2005 | Hong 2005 | Abu-Hilal 2006 | Chen 2006 | Wakai 2006 | Hiraoka 2008 | Guglielmi 2008 | Yamakado 2008 | Santambrogio 2009 | Ueno 2009 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | | 158 | 73 | 98 | 148 | 68 | 159 | 149 | 164 | 200 | 166 | 152 | 278 |
| n | HR | 79 | 40 | 40 | 93 | 34 | 88 | 85 | 59 | 91 | 62 | 78 | 123 |
| | RFA | 79 | 33 | 58 | 55 | 34 | 71 | 64 | 105 | 109 | 104 | 74 | 155 |
| Follow-up (months) | | 22 | 23 | 24 | 35 | 32 | 28 | 69 | n.a. | 27 | 37 | 37 | 36 |
| LTR (%) | RFA | 26 | 42* | 19 | 18 | 30 | 30 | 28 | n.a | n.a. | 13 | 24 | 23 |
| | HR | n.a. | 35* | n.a. | 2 | 4 | 2 | 3 | n.a. | n.a. | 0 | 6 | n.a. |
| Survival | HR | 65%/3y | 58%/5y | 61%/4y | 84%/3y | 56%/5y | 64%/4y | 53%/10y | 59%/5y | 48%/5y | 81%/5y | 54%/5y | 80%/5y |
| | RFA | 33%/3y | 56%/5y | 45%/4y | 73%/3y | 57%/5y | 68%/4y | 31%/10y | 59%/5y | 20%/5y | 75%/5y | 41%/5y | 63%/5y |
| p | | 0.002 | 0.200 | 0.139 | 0.240 | 0.302 | n.s. | 0.013 | n.s. | 0.001 | 0.870 | 0.163 | 0.06 |
| Type of trial | | Match2 | Retrosp. | Prospect. | Retrosp. | Match2 | RCT | Retrosp. | Retrosp. | Retrosp. | Retrosp. | Cohort | Cohort |

* All intrahepatic recurrencies counted, n.a. – not assessed, LTR – local tumor recurrence, Match2 – matched-pair analysis, Retrosp. – retrospective trial, Prospect. – prospective trial, RCT – randomized controlled trial, Cohort – cohort analysis.

Table 3
Synopsis of reports on repeated hepatic resection for recurrence of hepatocellular carcinoma

| Source | Itamoto 2007 | Tralhão 2007 | Minagawa 2003 | Sugimachi 2001 | Nakajima 2001 | Neeleman 1996 |
|---|---|---|---|---|---|---|
| n | 84 | 16 | 67 | 78 | 12 | 128 |
| Complications | 23% | 28% | n.a. | – | 25% | 13% |
| Mortality | 1% | 6% | 0% | 0% | 0% | 2% |
| Survival | 88%/1y | 89%/1y | 83%/1y | n.a. | 90%/1y | 82%/1y |
| | 67%/3y | 46%/3y | 70%/3y | 83%/3y | 72%/3y | 40%/3y |
| | 50%/5y | 31%/5y | 56%/5y | 48%/5y | n.a. | 40%/5y |
| Time since prev. surg. | 29 months | 17 months | 21 months | 26 months | 31 months | 19 months |

(n.a. – not assessed, prev. surg. – previous surgery).

Table 4
Synopsis of reports on radiofrequency ablation for recurrent hepatocellular carcinoma following hepatic resection

| Source | Nicoli 2001 | Choi 2004 | Lu 2005 | Yang 2006 | Taura 2006 | Choi 2007 |
|---|---|---|---|---|---|---|
| n | 5 | 45 | 72 | 41 | 48 | 102 |
| Complications | 0% | 0% | 4% | n.a. | n.a. | 5% |
| Local recurr. | n.a. | 21% | 14% | 9% | n.a. | 12% |
| Survival | 60%/3y | 54%/3y | 43%/3y | 72%/3y | 22%/5y | 66%/3y |
| Progression | 80% | 60% | 85% | 37% | 75% | 84% |
| Time since prev. surg. | 26 months | 18 months | n.a. | 25 months | 14 months | 15 months |

(recurr. – recurrence, n.a. – not assessed, prev. surg. – previous surgery)



presence of non-fibrolamellar HCC.

Among the RFA patients, 10 open surgical, 13 percutaneous and 4 laparoscopic procedures were performed. The laparoscopic RFAs were performed after initial percutaneous RFA treatments. Four out of the ten open surgical procedures were accompanied by simultaneous HR (3 wedge-resections and 1 left lateral bisegmentectomy), one further by a splenectomy. For the majority of all RFAs, a monopolar multi-pronge device (Starburst XL, RITAmedical, Mountain View, CA, USA) was used ($n = 17$). A cool-tip electrode (radionics, Burlington, CA, USA) was used in 8 cases. Two patients were treated using a novel bipolar RFA device (RFAmedical, Mountain View, CA, USA).

Major complications classified stage III or higher according to Clavien occurred after four HRs, one arterial bleeding requiring relaparotomy, one biliary leakage treated by interventional means, one lymphatic fistula and one occurrence of ascites. After RFA, only one case of ascites resembling a major complication defined like above occurred resulting in a prolonged hospital stay. Due to the low number of complications, no statistical analysis was performed.

Recurrence and survival data are provided by Table 1. Survival was 100%, 78%, 68%, 52% and 39% (HR) vs. 96%, 72%, 62%, 40% and 32% (RFA) at 1, 2, 3, 4 and 5 years, respectively, and tumor-free survival was 82%, 50%, 45%, 39% and 28% (HR) vs. 51%, 30%, 30%, 22% and 11% (RFA) at 1, 2, 3, 4 and 5 years, respectively. There were no statistical significances in the survival data of both groups; recurrence was also not significantly different in the comparison of both groups. Kaplan-Meier-estimations of the survival functions are shown in Figs 1 and 2. Since no autopsy was performed, the reason for death was occasionally difficult to assess. Approximately half of the patients (47%, $n = 7$ from a total of 15), who died after repeated resection, were known to have extrahepatic tumor burden at the date of their death, among them three lymph node positivities, two pulmonary metastases and one brain metastasis. In contrast, eight out of 13 confirmed deaths of the RFA patients (62%) can be traced to acute decompensation of the liver function with additional multi-organ failure, acute renal insufficiency and lethal pneumonia in one case each. A further death was caused by acute myocardial infarction,

whereas only four deaths (31%) were proven to be associated with intra- ($n = 1$) or extrahepatic ($n = 3$) metastatic tumor growth. These differences were however not found to be statistically significant.

## 4. Discussion

The presented data describe a single-center experience with patients treated by either repeat resection or RFA for HCC recurrence. Apparently, the heterogenous composition of the two groups precludes a direct comparison. It is however interesting to observe, that patients considered irresectable, and hence palliative, have comparable survival following RFA in comparison to the resected patients. The minority of all HCC recurrencies will be amenable to HR, consisting in non-cirrhotic patients with tumors limited to one distinct part of the liver remnant. The applicability of RFA is also restricted to no more than 4 nodules, none of them larger than 3 cm; most suitable are tumors deep in the parenchyma and distant to larger vessels. This is the reason why the case number in the presented trial is comparably low, and why randomized controlled trials are difficult to accomplish. Tranchart et al. confirm this observation in a recently published paper [8]. Only a small proportion of patients with HCC recurrence was amenable to surgical treatment such as liver transplantation (10%) and repeated resection (12%).

RFA as well as HR play a major role in the treatment of HCC. So far, HR is considered the gold standard in HCC patients without cirrhosis and patients beyond the criteria for LT. However, the majority of HCC occurs in cirrhosis, and the impaired functional capability of cirrhotic livers represents occasionally a contraindication for performing a safe and secure HR. Moreover, HCC recurrence following HR is rather common [9–12]. Cumulative 3- and 5-year recurrence rates after curative partial hepatectomy reach up to 70 to 80%. Usual distinctive markers are late vs. early as well as multilocular vs. solitary recurrence. The latter is due to the development of intrahepatic metastases, whereas the former is thought to be caused by multicentric carcinogenesis. The same pattern of recurrence could be demonstrated in RFA patients, too [5,10]. The choice of the appropriate treatment seems however to be dependant rather on technical feasibility than on the entity of recurrence.

RFA is known to be valuable in the treatment of primary HCC [13,14]. At date there is only one randomized controlled trial published in the current literature comparing RFA and HR for HCC [15], which – although underpowered – reveals equivalence of RFA and resection in survival. A few data derived from retrospective analyses are available (Table 2 [3,4,16–18,18,20–24]). Three publications suggest a significant better survival for HR compared to RFA for primary HCC [16,18,22]. Only one of these is a controlled matched-pair analysis [16]. Wakai et al. included a major number of percutaneous ethanol instillations instead of thermoablative treatment modalities in their percutaneous ablation group [18]. The majority of all published data (9 papers), particularly the well-designed recently published works of Yamakado [23] and Ueno [4] with large numbers of patients, indicate no significantly increased survival after HR for small HCC in cirrhosis with well-preserved hepatic function in comparison to RFA. Even more promising results may be obtained by use of laparoscopic access for RFA of HCC [25].

Treatment of recurrent HCC is thought to be quite similar to that of primary HCC [26,27]. A general recommendation is to choose a surgical therapy of recurrent HCC, whenever feasible. Repeat HR for recurring colorectal liver metastases has previously been described [7], whereas repeat HR for HCC recurrence seems to be as common (Table 3 [28–33]). Recently, RFA was suggested for the treatment of recurrent HCC following previous HR (Table 4 [34–39]). Repeat RFA seems to provide a survival superior to transarterial chemoembolization in these patients [40]. A description of microwave ablation (MW) as well as HR for the treatment of HCC recurrence was provided by Matsuda, Fujii,

Kono and Matsumoto in 2001 [41]. They pointed out, that the number of recurrent tumor nodules is a significant prognostic factor for survival, and in case of multicentric occurrence, MW is as effective as HR. These findings are neither confirmed nor contradicted by our data, as we did not discern multicentric reoccurrence and intrahepatic metastases, and the number of tumors as measured by the proportion of patients with solitary tumors was not significantly different in the two treatment groups.

To our knowledge, only one report compares RFA to HR for the treatment of HCC recurrence [42]. The authors included only percutaneous procedures in the RFA group; the follow-up in the HR group was significantly longer (34 vs. 21 months). Survival was approximately 50% after 2 years in contrast to our own results with a better survival even in the RFA group with 72% after 2 years. This clearly underlines that RFA is as valuable as HR in the treatment of recurrent HCC confined to the liver. The shortcomings of the presented trial are however obvious: Due to different selection criteria for the particular treatment modality, no comparison of RFA to repeat HR is carried out. The comparison of two populations with HCC recurrence confined to the liver, treated by either RFA or repeat HR reveals however the surprising result of comparable survival for patients treated with either palliative (RFA) or curative (HR) intention. Obviously, repeated HR was the desired treatment in non-cirrhotic patients, in larger tumors and if recurrence occurred late after the first surgical treatment, since hypertrophy of a liver remnant was likely to occur. RFA instead was chosen in case of irresectability, in older patients, in early recurrence and in the presence of clinically significant liver cirrhosis. This analysis clearly describes the criteria of decision making for a particular treatment in case of HCC recurrence in a surgical department of a large volume hospital. There is probably no reason to perform a thermoablation, if surgical resection is feasible; it is however astonishing, how small the difference in survival was, comparing both populations.



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