

ORIGINAL ARTICLE

Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases

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Abstract

Background. Stereotactic radiation therapy is an evolving modality to treat otherwise unresectable liver metastases. In this analysis, two local therapies: 1) single session robotic radiosurgery (RRS) and 2) percutaneous radiofrequency ablation (RFA) were compared in a total of 60 heavily pretreated colorectal cancer patients. **Methods.** Thirty patients with a total of 35 colorectal liver metastases not qualifying for surgery that were treated in curative intent with RRS were prospectively followed. To compare efficacy of both treatment modalities, patients treated with RFA during the same period of time were matched according to number and size of the treated lesions. Local tumor control, local disease free survival (DFS), and freedom from distant recurrence (FFDR) were analyzed for efficacy. Treatment-related side effects were recorded for comparison. **Results.** The median diameter of the treated lesions was 33 mm (7–53 mm). Baseline characteristics did not differ significantly between the groups. One- and two-year local control rates showed no significant difference but favored RRS (85% vs. 65% and 80% vs. 61%, respectively). A significantly longer local DFS of patients treated with RRS compared to RFA (34.4 months vs. 6.0 months; $p < 0.001$) was found. Both, median FFDR (11.4 months for RRS vs. 7.1 months for RFA $p = 0.25$) and the recurrence rate (67% for RRS and 63% for RFA, $p > 0.99$) were comparable. **Conclusion.** Single session RRS is a safe and effective method to treat colorectal liver metastases. In this analysis, a trend towards longer DFS was seen in patients treated with RRS when compared to RFA.

Stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) to treat liver metastasis are new and rapidly evolving techniques to extent the multidisciplinary treatment options of colorectal liver metastasis [1]. Although not formally tested in a head to head design with local therapies, surgery is accepted to be the gold standard in the treatment of single or oligo-colorectal liver metastases [2,3]. Patients not qualifying for surgical procedures are offered local treatment options. Among those there are thermal ablation techniques like radiofrequency ablation (RFA) [2,4], microwave ablation or laser-induced thermal treatment (LITT)

[5] and different radiation therapies [1]. Among the non-surgical therapies, RFA has superseded during the last decade other ablative therapies in the treatment of colorectal liver metastases [6]. Next to RFA, radiation therapy to treat liver and lung metastases with SBRT or RRS is a comparatively new field in radiation oncology and is still in the process of evaluation of treatment effects and long-term outcome. Robotic radiosurgery (RRS) using real time tumor tracking is able to apply high local ablative radiation doses in a single treatment session and therefore can compete with other local therapies such as RFA and microwave ablation [7,8].

Here we compare treatment efficacy and toxicity of the widely used percutaneous, computed tomography (CT)-guided, RFA and RRS for salvage treatment of colorectal liver metastases.

Methods

This analysis included patients that were treated either with percutaneous RFA or RRS therapy for colorectal liver metastases. Hepatic lesions had to be deemed surgical unresectable by the multidisciplinary gastrointestinal tumor board of the University Hospital Grosshadern, University of Munich. This board includes experienced hepatobiliary surgeons, radiation oncologists, medical oncologists and interventional radiologists. All metastases had to be treated in curative intent. Therefore, no extrahepatic disease and no other lesions to the liver than those to be treated with local therapy had to be detectable prior to therapy. The decision if percutaneous RFA or RRS should be applied was based on the following algorithm: the standard procedure to treat unresectable colorectal liver metastases was RFA. RRS was preferred if one of the following reasons were present: vicinity of the metastasis to great vessels, as those might cause a heat sink effect, location close to the liver capsule, as RFA is more painful to those patients and patient wish. A maximum diameter of the lesion exceeding 30 mm has been a factor favorable for the use of RRS during the last two years of the study [9].

Robotic radiosurgery (RRS)

Thirty consecutive patients with one to three liver metastases from colorectal cancer were treated in curative intent with single session RRS at the European Cyberknife Center Munich as described before [8,10] from May 2005 to May 2011. In short, a radiosurgical device (CyberknifeTM, Accuray Inc. CA, USA) with real time tumor tracking was used. Prior to radiation, one or two gold fiducials (CP Medical Inc., Portland, OR, USA) were placed inside or next to the metastases via an 18G needle under local anesthesia and CT fluoroscopy guidance in the interventional radiology unit. Contrast enhanced dynamic CT (arterial and portalvenous phase) or magnetic resonance imaging (MRI) (using liver-specific contrast agents) was used to exclude additional intrahepatic tumors. A dedicated liver MRI examination either performed with a Gadolinium-based extracellular [Magnevist[®] (Gadopentetate Dimeglumine) or Gadovist[®] (Gadobutrol), Bayer HealthCare Pharmaceuticals Diagnostic Imaging, Germany] or a liver cell-specific [Primovist[®] (Gadoxetic Acid), Bayer HealthCare Pharmaceuticals Diagnostic

Imaging, Germany] contrast agent, and characterized by dynamic contrast-enhanced T1 weighted 3D FLASH sequences (Volumetric Interpolated Breath-hold Examination; VIBE; Siemens Healthcare, Erlangen, Germany) with a slice thickness of 3 mm was fused to the planning CT in all cases by means of rigid image registration provided by the system software (Multiplan, Accuray Inc.). It was aimed to scan the patient in the same breathing phase during CT and MRI to get a fusion result as good as possible. In difficult cases the fusion was directed to the lesion itself and not to the outer margins of the liver. Additionally, a margin of 6 mm was added to the tumor diameter in all three dimensions to accommodate for tumor cell spread around the tumor. The set-up inaccuracy for the RRS system used in this analyses is <1 mm [11]. In a single session treatment, a total of 24–26 Gy to the 70% isodose (dose maximum 34–37 Gy) were administered to the target volume, using a 6 MV compact linear accelerator (LINAC) mounted on a six-axis robotic manipulator. All patients were pretreated with ondansetron on the day of treatment to prevent radiation-induced nausea.

During treatment, respiratory motion tracking of the target volume was done as previously described [12]. The whole procedure lasted about one hour, and patients were discharged from the institute immediately after treatment.

Radiofrequency ablation (RFA)

RFA treatment was performed by interventional radiologists with at least five years of experience under single-shot antibiotics, pulse oximetry and conscious sedation using midazolam, dipyrone and pethidine or piritramide, respectively. All RFA procedures were done on a 4-, 16-, or 128-row CT scanner (Siemens Healthcare, Erlangen, Germany) under CT fluoroscopy guidance with angular beam modulation (tube voltage, 120 kV; tube current–time product per reconstructed image, 15–25 mAs). The lesions were to be treated in a single session. If tumor size was too big, a second treatment was planned for the following day. The subsequent RFA systems were used: 1) AngioDynamics/RITA Medical Systems (Queensbury, NY, USA): 1500X RF Generator (max. 250W of power) with StarBurst[®] XL RF electrode (umbrella diameter: 5 cm) and 2) Boston Scientific (Natick, MA, USA): RF3000[®] Radiofrequency Ablation System (max. 200W of power) with LeVeen[®] RF electrodes (umbrella diameter: 2–5 cm). After RFA treatment, patients were sent back to the ward for further pain management and clinical monitoring, and usually discharged from the hospital after CT follow-up 24 hours later.

RRS patients were matched to patients who underwent RFA treatment at the Institute of Clinical Radiology, University Hospital Munich.

Patients were matched according to the following strata: 1) number of colorectal cancer metastases and 2) size of lesions [13]. To minimize bias, patients were excluded from the analysis when both methods (RFA and RRS) were applied in the same patient.

Ethical considerations

Following the RRS patients has been approved by the local ethic committee (Ethic Committee of the University Hospital Großhadern, University of Munich project #383-08).

Determination of treatment efficacy

Contrast enhanced CT- or MRI scans were done in three-month intervals after treatment. After 12 months, intervals were switched to six-month intervals [14,15]. Local recurrence was defined as any sign of growth or progression of tumorous tissue within or adjunct the treated liver volume. A contrast enhancement at the rim of the treated volume as seen within the first staging after RFA or RRS was stated as treatment-related change and not as local treatment failure.

Local control rate was defined as no recurrence of tumor tissue within the site or at the margin of the treated metastases and therefore was deemed a

strong indicator of treatment efficacy. Local DFS was defined as the time of local control of the treated metastases. Freedom from distant recurrence (FFDR) was measured from the start of treatment until death or reappearance of any metastasis. Furthermore, overall recurrence rate, as the rate of recurrence of any metastases independent of the localization and overall survival as the time span between treatment and death were evaluated.

Statistical analyses

Statistical analysis was performed using SPSS PASW 18.0 (SPSS Inc., Chicago, IL, USA) software. Differences were calculated using two-sided Fisher's exact test or Spearman correlation index. Survival times were tested using the Kaplan-Meier method and the log-rank test. Time intervals were measured from the day of treatment to the date of progression or death. A p-value < 0.05 was regarded as statistical significant.

Results

A total of 60 patients with 70 hepatic lesions were treated between 2005 and 2011. Number and size of the lesions fitted well between the matched patients with a maximum difference of 5% in diameter. Both patient groups were heavily pretreated with palliative chemotherapy (72%) and liver surgery (57%) prior to local treatment (Table I). The median follow-up

Table I. Baseline characteristics.

	RRS (n = 30)	RFA (n = 30)	p
Gender			
- male	21	17	0.42*
- female	9	13	
Age, median (years)	67.6	64.5	0.82 ⁺
- range (years)	33–84	39–80	
Total number of lesions evaluated (n)	35	35	
Number of lesions per patient treated (n)			
- 1	26	26	0.38 [#]
- 2	3	3	
- > 2	1	1	
Number of treatments	30	38	0.005*
- second treatment of the same lesion	0	8	
Mean maximum diameter of lesions (mm) (range)	34 (7–53)	33 (8–53)	0.64 ⁺
Palliative chemotherapy prior to local therapy n (%)	20 (67)	23 (77)	0.57*
Previous local therapy for liver metastases (other than RFA or RRS) n (%)	10 (33)	14 (47)	0.19*
- no	20 (67)	16 (53)	0.61*
- yes	20 (67)	14 (47)	
surgery	1 (3)	3 (10)	
SIRT/embolization/LITT			
Median Time Since	35.0	24.8	0.88°
Diagnosis (Months, Range)	(6–96)	(2–138)	

*Fisher's exact test; ⁺Mann-Whitney U-test; [#] χ^2 -test; [°]log-rank test significant p-values are bold typed.

time was 23.3 months. A significantly higher percentage of patients in the RFA group underwent additional treatments for the same lesion.

Both treatment strategies were feasible and well-tolerated (Table II). Due to technical reasons, patients undergoing RFA treatment needed analgesic sedation during the procedure. All other toxicities were within the expected range [16] and showed no differences between both groups.

The 12- and 24-months actuarial local control rate was higher in RRS treated metastases than in RFA treated metastases (85% vs. 65% and 80% vs. 61%, respectively) but did not reach level of significance. Local DFS differed significantly between the two treatment groups with a median of 34.4 months in the RRS group and a median of 6.0 months in the RFA group ($p < 0.001$) (Figure 1). The recurrence rate showed no significant difference between both treatment groups and reached 67% in the RRS group and 63% in the RFA group ($p > 0.99$) (Table III). There was no statistical significant difference in the median FFDR, which reached 11.4 months in the RFA group and 7.1 months in the RRS cohort (log-rank $p = 0.25$) (Figure 2).

There was a trend towards shorter median OS of the RRS treated patients with 34.4 months compared to 52.3 months of the RFA group ($p = 0.06$).

Discussion

Colorectal cancer patients with oligometastases benefit from removal of metastases of the liver. Surgical resection of metastases to the liver or lung is one of the most evident predictors for long-term survival [3,17] and is presently the accepted gold standard in the treatment of hepatic metastasis from colon cancer [18,19]. For many reasons only a small percent-

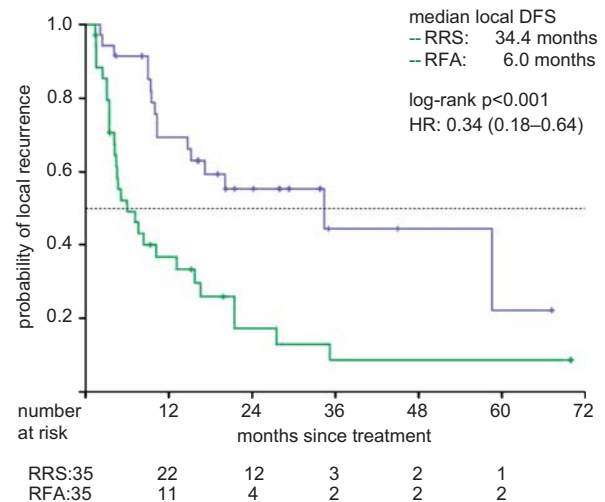


Figure 1. Median local disease free survival (DFS) since treatment of liver metastases.

age of patients qualify for surgical procedures [3]. CT-guided, percutaneous RFA is the most common local treatment option to be offered to such patients [15]. Although it has not been formally compared to surgical resection of liver metastases in a randomized setting [17,18], it is feasible, easy accessible and effective. RRS and other SBRT modalities are newer methods of local treatment for liver metastases that have shown safety and feasibility in recently published studies [8,10,20–26]. In this analysis two local methods with a singular treatment application (RFA and RRS) were compared in a matched pair design.

This study is clearly limited by its retrospective nature as selection bias cannot be excluded and therefore results have to be interpreted with caution. However, size and number of metastases as the main predictors of outcome [13] match perfectly well.

Therefore, local control rate and local DFS were assumed to be valid indicators of local effectiveness induced by the investigated procedures. Our cohort consisted of heavily pretreated patients most of whom had received palliative chemotherapy and liver directed surgical procedures prior to local therapy.

In the current analysis all RRS treatments were done in one single fraction using a high irradiation dose of 24–26 Gy to a prescription isodose of 70%. The dose level was selected according of the favorable early results of SBRT for liver tumor treatments [22,27–29]. Herfarth et al. performed a phase I/II dose escalation trial of 37 patients with 60 liver lesions, the majority of which were metastases [29]. The dose was escalated from 14 to 26 Gy. Similar to the findings in our analysis all patients tolerated the treatment well without any major side effects or clinically detectable RILD. The results of Herfarth et al.

Table II. Toxicity per treatment.

	RRS (n = 30)	RFA (n = 38)	p*
Bleeding (liver capsule)#	1 (3)	2 (5)	0.84
Blood bilirubin increased	1 (3)	2 (5)	0.84
- due to procedure§	1 (3)	1 (2.5)	0.99
- due to tumor progression§	2 (6.5)	1 (2.5)	0.45
Nausea (any)	0	5 (13)	
- required treatment§	0	3 (7.5)	
Pain (required i.v. pain medication)		2 (5)	
Treatment required			
- analgesic sedation	0	34 (89)	
- general anaesthesia	0	4 (11)	

All toxicities were graded according to the NCI CTCEA criteria version 3.0.

*Fisher's exact test; #all bleedings were minor bleedings to the liver capsule (NCI CTCAE 3.0 grade 1) requiring no further treatment; §grade 1; §grade 2.

Table III. Treatment efficacy and survival times.

Lesions	RRS (n = 35)	RFA (n = 35)	p*
12-month local control rate (actuary)	85%	65%	0.09
24-month local control rate (actuary)	80%	61%	0.20

Patients	RRS (n = 30)	RFA (n = 30)	p
Recurrence rate n (%)	20 (67)	19 (63)	0.99*
Local PFS months	34.4	6.0	<0.001°
95% CI	3.4–65.4	1.9–10.0	
FFDR months	11.4	7.1	0.25°
95% CI	7.9–14.9	1.8–12.4	
OS	34.4	52.3	0.06*
95% CI	19.9–48.9	31.1–73.6	

°log-rank test; *Fisher's exact test. FFDR, freedom from distant recurrence significant p-values are bold typed.

could be confirmed in a recent publication by Goodman et al. [27]. These authors have reported on their dose escalation trial with single fraction SBRT for liver malignancies with a prescribed radiation dose from 18 to 30 Gy at 4-Gy increments. All patients tolerated the single fraction SBRT well without developing a dose limiting toxicity.

The 12-month actuarial local control rate after RRS of 85% was in the range (61–100%) of what has been achieved in other SBRT series [21,23,25,28,29]. Therefore an inferiority of single session RRS to hypofractionated radiation therapy as most other studies have applied cannot be stated. The actuary local control rate at 12 months of percutaneous RFA reached 65% and therefore was within the expected range [17], although median maximum diameter of the treated lesions was 33 mm and therefore was above the 30 mm in diameter that

is presently discussed as the upper size where RFA is feasible for colorectal metastases [9,30]. Several studies have shown that local recurrence rates rise significantly when the RFA treated lesion is larger than 30 mm in diameter. In our RFA group with a limited number of patients, there was, with regard to the outcome measurements local recurrence, DFS or OS, no significant difference between lesions larger or smaller than 30 mm (data not shown). In a recent report on RRS, size of the lesion was reported to be a predictor for local recurrence when lesions get bigger than 50 mm in diameter [21]. In this analysis only four lesions in the RRS treated group reached a maximal diameter greater than 50 mm. Therefore no valid data on lesions greater than 50 mm in diameter can be stated. The higher local control rate in the RRS treated patient group is reflected in a significantly longer local DFS time. However, this finding has to be interpreted with caution. To assess, whether RRS is the better way to treat colorectal liver metastases further prospective and randomized studies are needed to eliminate pretreatment and patient-specific bias.

Considering all patients treated in this study, the recurrence rate observed during a median follow-up time of about two years was 75%, and therefore within the expected range [31] for local therapeutic approaches. As there was no significant difference between RRS and RFA in this study, this might reflect the similarity in patient selection, as recurrence of the disease outside the treated region is rather an indicator of the biology of the disease than the efficacy of a local therapy. This similarity again is expressed by the equality in the freedom from distant recurrence of both treatment groups. Median disease free survival times of 6–18 months is what is expected in the local treatment of colorectal liver metastases [17,32].

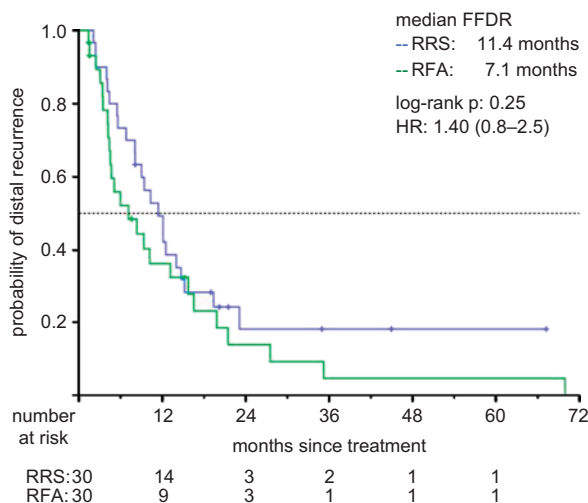


Figure 2. Median freedom from distant recurrence (FFDR) since treatment of liver metastases.

A median OS of 52 months after RFA treatment of colorectal cancer metastases is in the higher range of what has been reported in previous studies, where median OS ranged from 39 to 59 months [4,13,30,33,34]. Reasons for this large variety of OS times may be patient selection, number and types of treatments used before RFA. Overall survival time of 34.4 months after RRS was somewhat longer than what has been published before in SBRT treated cohorts [24].

Side effects were rare, did not differ significantly between both treatment entities and were within the published range [8,35,36]. It is noteworthy that due to size reasons eight patients of the RFA group needed a second treatment for the same metastasis. As a size of more than 30 mm is associated with a higher frequency of a second RFA treatment to the same lesions which is then quite uncomfortable for the patient, RRS treatment might be the better solution for treating larger colorectal cancer liver metastases.

Our data show that RFA and RRS are both feasible and effective methods to treat colorectal cancer liver metastases. In terms of local control, no significant difference between both cohorts could be established but local DFS differed significantly in favor of RRS. Prospective, randomized trials are needed to assess the effects of RRS, RFA and surgery in a comprehensive way on long-term survival in patients with oligometastases to the liver.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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