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ORIGINAL ARTICLE – RADIATION ONCOLOGY

Radiosurgery of Liver Tumors: Value of Robotic Radiosurgical Device to Treat Liver Tumors

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ABSTRACT

Background. The treatment of isolated liver metastases has become a rapidly developing field with many new, technically advanced methods. Here we present the therapeutic efficacy of a robotic radiosurgery for local control of liver metastases from solid tumors.

Methods. Patients with tumorous lesions to the liver, not qualifying for surgery, were treated with single-session radiosurgery (24 Gy) that used robotic image-guided real-time tumor tracking. All detectable lesions had to be irradiated. In a prospective analysis, follow-up was performed by magnetic resonance imaging scanning 2 months after the treatment, and subsequently at 3-month intervals to evaluate local control. For inclusion into the radiosurgery treatment protocol, tumor volumes had to be <90 ml.

Results. Thirty-six patients (median age, 65 years) with a total of 54 target lesions were evaluated. Single lesions were treated in 23 patients and multiple targets in 13 patients. Metastases originated from colon cancer ($n = 19$), ovarian cancer ($n = 3$), pancreatic cancer ($n = 2$), breast cancer ($n = 2$), and others ($n = 6$). Four lesions were of primary liver origin (hepatocellular carcinoma and cholangiocellular carcinoma). Median tumor volume was 18 ml (range, 2.2–90 ml). The median follow-up was 21.3 months. The disease of 25 patients (69.4%) showed complete or partial local response, 6 patients (16.7%) had stable lesions, and 5 patients (14%) experienced local recurrence. Grade 2–4 adverse events due to radiation treatment were not observed.

Conclusions. Robotic radiosurgery with image-guided real-time tumor tracking of liver neoplasm is a new and promising approach for patients with disease that is not eligible for surgical resection and might enhance the possibilities of multidisciplinary oncological treatment concepts.

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Patients with limited liver metastasis may benefit from aggressive locoregional treatment. In metastatic colorectal cancer, surgical resection may offer long-term survival and cure in a clinically relevant fraction of patients.[1] Accordingly, surgical resection is presently the accepted standard for treatment of solitary liver metastases.[2,3] For various reasons, surgery is applicable in only 10 to 20% of patients.[4] Technical reasons such as the size and localization of metastases, but also performance score and comorbidities, are known limiting factors. The development of new radiotherapies and sophisticated radiation devices promises a safe and effective approach to solitary liver metastases.[5] Among these there are hypofractionated stereotactic body radiotherapy (SBRT) and radiosurgical treatment.[6–10] These techniques compete with other local therapies such as radiofrequency ablation (RFA) and laser-induced interstitial thermal therapy.[11–14]

The most accepted and widely used procedure is RFA, although its efficacy has not been formally compared to surgery in a prospective randomized trial. External-beam radiotherapy to the liver has been limited by liver motion during breathing, and because a dose of more than 30–35 Gy applied to the whole liver may induce radiation-induced liver disease through veno-occlusive disease and subsequent liver failure.[15] Selective internal radiotherapy is another approach to treat liver neoplasm by radiation. By applying small yttrium-90-labeled biocomparable beads through the hepatic artery, it is possible to deposit more than 120 Gy selectively to the tumorous lesions as the beads get caught in the capillaries of the metastases. The healthy liver parenchyma is estimated to get a dose of approximately 20–25 Gy.[16] But because of arterio-arterio or arterio-venous shunting to the stomach or the lungs, the selective internal radiotherapy technique is not feasible in all patients.

To treat oligometastasis of the liver with external-beam radiation, newer magnetic resonance imaging (MRI) and computed tomographic (CT) scan-based planning procedures as far as new developments of stereotactic radiation procedures in combination with immobilization devices made it possible to treat solitary liver malignancies by radiation with only few adverse effects and reasonable efficacy.[5,17] In addition to SBRT, where the target is treated from several axes, a modality known as intensity-modulated radiotherapy has been established. With this technique, the intensity of the radiation beam is modulated by customized accelerators to shape the radiation field even more exactly to spare the healthy surrounding tissue and to maximize dose to the tumor. In this context, the Cyber-Knife technique represents a linear accelerator (LINAC) that is mounted on a six-axis robotic manipulator that makes it possible to track and adjust the beam to the target in real time. Therefore, single-session radiation of targets in moving organs has been made possible with high accuracy without requiring the use of immobilizing devices.

In this prospective cohort study, we investigated the efficacy (local control, overall survival, time to progression of disease) and safety of single-session robotic radiosurgery of liver metastases.

METHODS

Patients with up to four tumorous lesions limited to the liver who had received a total radiation volume of <90 ml were prospectively followed. Inclusion criteria were as follows: all detectable metastases had to be treated; extrahepatic metastasis had to be excluded by positron emission tomography CT scan; liver function had to be normal (serum bilirubin <2.0 mg/dl; normal coagulation values); and an Eastern Cooperative Oncology Group performance status of <3 was required. All patient signed informed consent forms before they were observed.

Decisions of the multidisciplinary gastrointestinal tumor board of the University Hospital Grosshadern, University of Munich, were used as a basis for radiosurgical treatment where possible. This board includes experienced hepatobiliary surgeons, radiation oncologists, medical oncologists, and interventional radiologists. For patients receiving chemotherapy, treatment had to be discontinued 2 weeks before irradiation. Data evaluation was performed according to the requirements of the local ethics committee (#383-08).

Treatment

Treatment was performed with a radiosurgical system (Accuray, Sunnyvale, CA) with real-time tumor tracking. Therefore, we needed to place at least one, or at most two, markers next to or into the metastases. Marker placement was carried out by CT fluoroscopically guided percutaneous placement of cylindrical gold fiducials (AB Medica, Milan, Italy), 5 mm long and 0.5 mm in diameter, directly into the metastasis before radiation.

The 3-D target volume was identified in both contrast-enhanced CT and MRI scans. A safety margin of at least 7 mm was added to the tumor diameter in all three dimensions to reduce the probability of local recurrence. In analogy to the phase I/II studies by Herfarth and colleagues.[18,19] testing single-fraction SBRT for liver metastases, we decided to apply 24 Gy in one fraction to the 70% isodose. This is in the upper range of the Herfarth studies using doses of 14 to 26 Gy, which demonstrated that the group receiving higher doses (22–26 Gy) had far better tumor control without a higher incidence of side effects.

Respiratory motion of the lesions was tracked continuously by means of a method described in detail elsewhere.[10] Radiation was performed with a 6 MV compact LINAC mounted on a six-axis robotic manipulator. The position of the LINAC was corrected in real time during the treatment on the basis of the correlation between the position of fiducials detected by two orthogonally positioned X-ray detectors and infrared markers on the patient's chest tracked continuously with external cameras. This allowed compensation of changes in the position of the irradiated volume caused by breathing without the use of an immobilization device. The radiation beam itself could be directed from a multitude of angles around the patient (>1500 directions). Treatment was performed on an outpatient basis. The whole procedure lasted approximately 1.5 h, and patients were discharged from the institute immediately after the treatment.

Study End Points and Statistics

Follow-up examinations included physical examination, toxicity examination, gadolinium-enhanced MRI scans, or contrast-enhanced CT scans of the liver, which were performed 2 months after radiation and then at 3-month intervals until disease progression was noted. Primary end point was local tumor control, defined as tumor shrinkage or no tumor progress as used before by others.[7–9] Within the first months after irradiation, it was difficult to define a response to treatment as a result of transient radiographic changes inside the treated volume. The modified Response Evaluation Criteria in Solid Tumors were applied to describe response. To assess the efficacy of the radiation, a by-lesion analysis was carried out. A local recurrence was defined as an increase of the tumor volume compared to pretherapeutic dimensions, or recurrence within the irradiated area of the liver—or, rather, in the same liver segments. Distant recurrence was defined as recurrence in another liver segment (intrahepatic) or as extrahepatic recurrence. For the calculation of progression-free survival and overall survival, a by-patient analysis was performed.

Toxicity analyses distinguished between morbidity due to marker placement such as pneumothorax, bleeding, and pain, requiring intravenous pain medication within 24 h after placement, and adverse effects associated with irradiation such as liver failure, gastrointestinal toxicity (vomiting, ulcers, bleeding, and strictures), or renal impairment.

Statistical analysis was performed by Stata software, version 10.1 for Macintosh (StataCorp, College Station, TX). Duration of local control, progression-free survival, and overall survival were calculated by the Kaplan–Meier method. Time intervals were measured from the day of radiation to the date of progression or death.

RESULTS

Patients

A total of 36 patients with 54 metastases of the liver were treated between August 2006 and August 2009. The median beam number per treatment was 149 (range, 136–158). Detailed patient and tumor characteristics are listed in Table 1. More than half of all lesions were associated with colorectal primary disease. More than two-thirds of all patients received palliative chemotherapy before stereotactic radiotherapy was administered.

Local Control, Progression-Free Survival, and Overall Survival

A total of five lesions recurred during follow-up (Fig. 1), with a median time to local failure of 14.5 months (range, 9.3–17.5 months). The actuarial 12-month local control rate was 95%. Most of the patients had recurrent disease outside the radiated area. The median time to progression was 11.6 months (95% confidence interval, 6.8–14.9). Twenty patients died during surveillance. The median overall survival was 25.1 months. The actuarial 1- and 2-year survival was 83% and 62%, respectively (Table 2).

TABLE 1 Baseline characteristics

Characteristic	Value
Total no. of patients	36
Sex	
Male	18 (50%)
Female	18 (50%)
Total no. of lesions evaluated	54
No. of treatments	43
Follow-up (months)	
Median	21.3
Range	2.8–44
Age (years)	
Median	65.3
Range	33–87
Primary tumor of metastases, *n* (%)	32 (88.9)
Colorectal	19 (52.8)
Ovary	3 (8.3)
Pancreas	2 (5.6)
Breast	2 (5.6)
Lung	1 (2.8)
Bladder	1 (2.8)
Gallbladder	1 (2.8)
Malignant Melanoma	1 (2.8)
Esophagus	1 (2.8)
CUP	1 (2.8)
Primary liver tumors, *n* (%)	4 (11)
Hepatocellular carcinoma	3 (8.3)
Cholangiocellular carcinoma	1 (2.8)
Time since primary diagnosis (years)	
Median	2.8
Range	0.27–8.8
Systemic treatment before CyberKnife treatment, *n* (%)	25 (69.4)
Previous local therapy for liver metastases, *n* (%)	
No	9 (25)
Yes	27 (75)
Surgery	17 (47.8)
RFA	5 (13.9)
Chemoebolisation	5 (13.9)
Selective internal radiotherapy	1 (2.8)
Laser-induced thermal therapy	1 (2.8)
Lesion volume (ml) ($n = 54$)	
Median	17.9
Range	2.2–90
No. of lesions per patient treated, *n* (%)	
1	23 (63.9)
2	10 (27.8)
>2	3 (8.3)

CUP carcinoma of unknown primary, *RFA* radiofrequency ablation

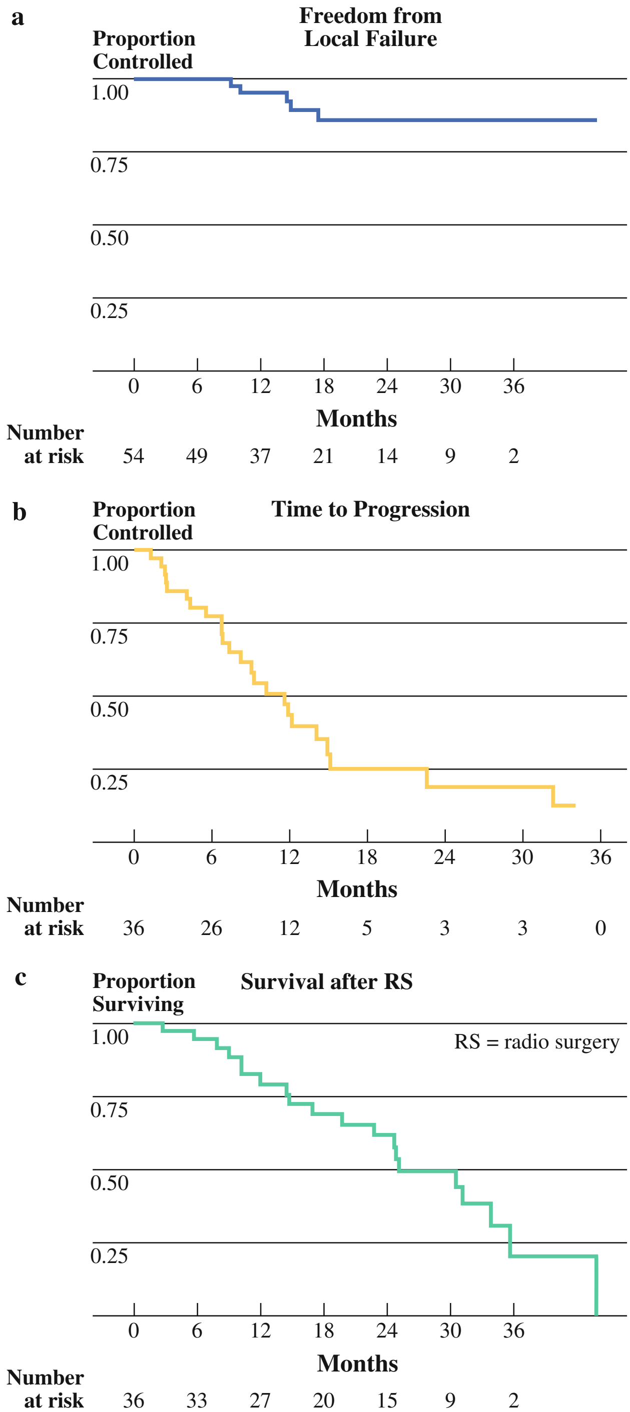

FIG. 1 Kaplan–Meier analyses of: (**a**) freedom from local failure (**b**) time to progression and (**c**) survival after radiosurgery (RS)

Because a tumor size of >3 cm in diameter (approximately a volume of 14.5 ml) was identified as a negative predictive factor for RFA therapy, we carried out the log rank test for lesions of >15 ml ($n = 32$) versus smaller lesions ($n = 22$) (Fig. 2).[20] In our analysis, there was no relationship between tumor size and recurrence (log rank test $P = 0.96$). Furthermore, we calculated the possibility for recurrence in dependence of histology (Fig. 2b). Metastases derived from colorectal cancer had a significantly higher probability of recurrence than other tumors (log rank test $P = 0.02$) (Table 3).

TABLE 2 Results

Characteristic	Value
Response according to RECIST 1.1 criteria, *n* (%)	
Complete response	14 (38.9%)
Partial response	11 (30.5%)
Stable disease	6 (16.7%)
Progressive disease	5 (13.9%)
Time to progression (months), median (95% CI)	11.6 (6.8–14.9)
Local control rate (actuarial) (%)	
6 months	100%
12 months	95%
18 months	86%
Survival (months), median (95% CI)	25.1 (17–35.6)
Overall survival rate (actuarial) (%)	
6 months	94%
12 months	83%
18 months	70%

RECIST Response Evaluation Criteria in Solid Tumors, *95% CI* 95% confidence interval

Toxicity

We could not detect any adverse events during marker placement such as blood loss, pneumothorax or pain. After radiation, none of the patients complained of severe (National Cancer Institute common toxicity criteria grade 2 to 4) adverse effects such as gastrointestinal discomfort or pain. No gastrointestinal ulceration occurred during observation time. Grade I fatigue was reported by 8 (22%) of 36 patients, and nausea immediately after radiation occurred in 5 of all patients (14%).

DISCUSSION

Extracranial stereotactic radiation is an important treatment option in oligometastatic disease. Exact planning methods that used MRI and CT scans and the implementation of hypofractionated SBRT in combination with immobilization devices made it possible to treat liver metastases by conventional irradiation.[7,10] One main difficulty that had to be overcome was the motion of the target volume due to breathing, resulting in inaccurate irradiation and irradiation of nearby organs. In this study, a real-time tumor tracking system in combination with a robotic radiation device enables irradiation of moving volumes with high accuracy, without immobilization devices, making irradiation more convenient for the patients.[21]

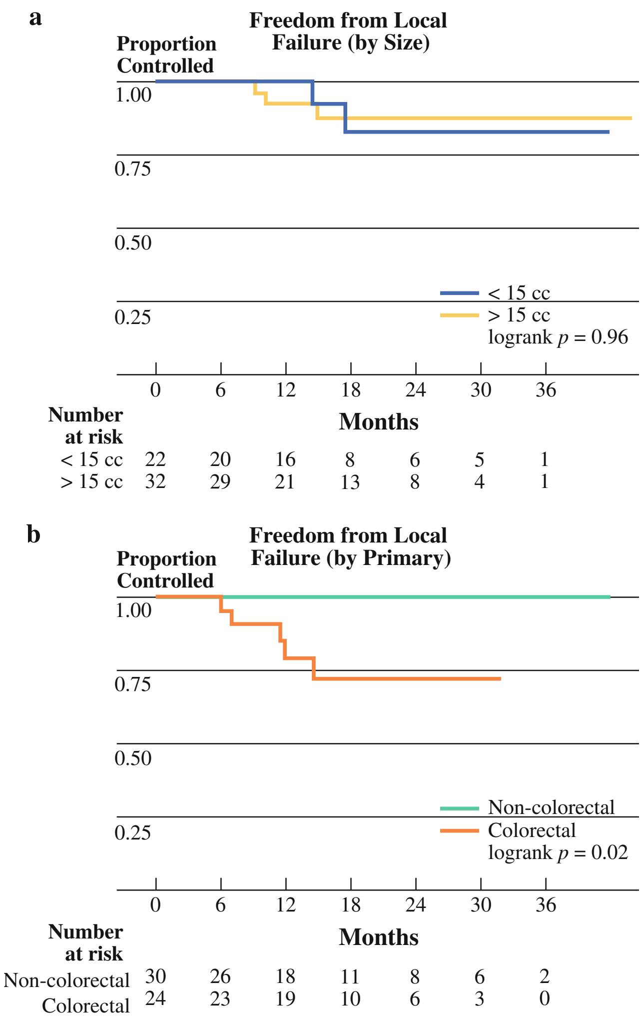

FIG. 2 Kaplan–Meier analyses of: freedom from local failure by (**a**) size and (**b**) primary

In contrast to conventional SBRT that used hypofractioned radiation (1 × 14 Gy to 3 × 20 Gy), in this study, the whole radiation dose of 24 Gy to the 70% isodose was applied in a single session.[6,7,9,18,22,23] Radiobiological considerations dealing with dose finding for SBRT are difficult because the linear-quadratic model describes the radiation effects for low dose per fraction scheme used in conformal fractionated radiotherapy and is controversially debated for ablative dose ranges used in the current study.[24] To overcome this problem, the single-fraction equivalent dose methodology has been proposed by Park and colleagues as a way to compare the relative biologic potency of hypofractionated radiotherapy schedules.[25] Within this model approach, we contribute data for an single-fraction equivalent dose of 24 Gy. Sophisticated survival curve models have been described to better understand tissue responses in SBRT to different dose fractionation schemes.[23]

Ultimately, more data from prospective clinical trials with longer follow-up are needed to add clinical knowledge to these mathematical models.[23,25] In this context, the ongoing Radiation Therapy Oncology Group trial 0438, exploring doses escalating up to 50 Gy to treat liver metastases with conformal SBRT, will generate more data regarding the kind of fraction and its dose to liver metastases.[26] Another aspect to be considered in single-fraction radiotherapy is that the higher the dose and the more hypofractionated the radiotherapy is, the greater the accuracy required to avoid necrosis of the adjacent tissue.[27,28] As shown before, the accuracy of the system used in this study is down to a precision of approximately 1 mm.[21] Moreover, to avoid damage to the adjacent tissue, the tumorous lesions were targeted by an average of 149 noncoplanar, nonisocentric beams, allowing conforming and distributing the dose in three dimensions. This is in contrast to conventional SBRT, which is limited to directions in the gantry's rotational plane.

Because of the accuracy of radiation, healthy tissue could effectively be spared, and adverse effects from the irradiation were not noted. This is in line with studies that used SBRT for liver metastases.[7] In addition, no adverse effects caused by fiducial placement could be observed. Because the placement of the fiducial is comparable with a needle biopsy of the liver, the expected complication rate is 2 to 4%, so we expected at most one adverse event.[29]

Our actuarial 1- and 2-year local control rate was 95% and 86%, which is in line with previously published data from trials that used SBRT to liver metastases where the 2-year local control rate was between 67 and 92%.[7,8,22] Therefore, the radiosurgical treatment of tumorous lesions to the liver seems to be as effective as SBRT with respect

TABLE 3 Characteristics of local failure[a]

Age (years)	Histology	Tumor volume (ml)	Time to local progression (months)	No. of liver metastases	Liver segment localization
51	Colorectal	43.22	9.3	1	VIII
64	Colorectal	12.22	14.5	1	III/IV
67	Colorectal	14.26	17.5	1	IV
67	Colorectal	30.28	10.2	2	I
74	Colorectal	25.09	14.9	2	VIII

[a] Median time to local failure was 14.5 months

to local control. Progression-free and overall survival depend on the underlying disease and therefore are only indirect measurements of the efficacy of a local therapy to the liver. Additional, negative patient selection is a problem for all studies investigating local therapies to liver. This is demonstrated by the fact that almost 70% of our patients received palliative systemic chemotherapy before radiotherapy, and 75% experienced other local therapies (e.g., surgery or RFA) before radiosurgical treatment. Most of our patients were extensively pretreated and did not qualify for surgery because of comorbidities. A relationship between the size of the lesions and the probability of local failure was not evident. This is in contrast to the study of Rusthoven et al. and many studies dealing with RFA.[7,20] But it is supported by other studies that used radiosurgery to treat liver metastases.[8] As seen in our patients, colorectal liver metastases had a statistically significantly higher risk of recurrence than metastases of other origins. One reason for this might be the exact radiation margins set by the radiosurgical device, because all of these recurrences were at the margin of the irradiated volume. Therefore, a wider safety margin might be advised specifically for treatment of colorectal metastases by a radiosurgical device.

In conclusion, our data show that single-session, frameless, image-guided robotic radiosurgery of tumorous lesions to the liver is a safe and efficient way to treat patients when liver surgery cannot be applied. With regard to treatment efficacy and adverse effects, the results of our study are comparable to other studies that used SBRT. Beyond that, radiosurgery seems to control tumorous lesions to the liver independent of size in a range up to 90 ml. Furthermore, it promises better patient comfort because no immobilization devices and only one irradiation session are needed.

CONFLICT OF INTEREST STATEMENT The authors state that they have no conflicts of interest with Accuray Inc.

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