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Frameless single-session robotic radiosurgery of liver metastases in colorectal cancer patients

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ABSTRACT

Introduction: Due to advanced chemotherapy regimens, patients presenting with residual liver metastases of colorectal cancer (CRC) has increased. Surgery of residual metastases enhances overall survival, but surgical resection is often limited. Less invasive techniques have been invented to enhance local disease control. We investigated in a selected patient cohort local control of liver metastasis from CRC using robotic radiosurgery.

Methods and materials: In this study patients with colorectal liver metastases were prospectively followed after having been treated with single-session radiosurgery using a robotic image-guided device and real-time tumour tracking. The primary end-point was local control (LC); secondary end-points were toxicity, progression-free survival (PFS) and overall survival (OS). Extrahepatic metastases were excluded using a whole body (PET-CT: positron emission tomography computed tomography). Follow up was done by liver MRI every 3 months post-treatment.

Results: Fourteen patients (median age 65 years), with a total of 19 colorectal liver metastases were treated with 24 Gy in one fraction. Median follow up was 16.8 months. A one-year LC rate of 87% and a median PFS of 9.2 months were reached.

Discussion: Frameless robotic image-guided radiosurgery with real-time tumour tracking as an effective treatment for patients with colorectal liver metastases. This technique enhances the possibilities of multidisciplinary oncological concepts.

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1. Introduction

Colorectal carcinoma (CRC) is among the most prevalent and deadly cancers in the industrialised world.¹ About 50–60% of patients with CRC develop metastatic disease (mCRC), and one third of these are solitary metastases localised to the liver.² Surgical excision of liver metastases is currently the only means to achieve a cure and long-term survival for those patients. Unfortunately, only 10–25% of patients suffering from liver metastases are eligible for radical liver surgery,² either because the lesion is unresectable or the patient is inoperable

due to advanced age or comorbidities. Neoadjuvant chemotherapeutic regimens including 5-FU, oxaliplatin and/or irinotecan have achieved remission rates between 40% and 60%,^{3,4} which made secondary resectability possible in some patients. The addition of targeted treatment with antibodies to vascular endothelial growth factor, or VEGF (bevacizumab) and epidermal growth factor receptor, or EGFR (cetuximab, panitumumab) has increased remission rates further.^{3,4} Thus, the number of patients with stable disease or only residual disease grows and surgical resection of residual liver metastases in these patients leads to prolonged survival.¹

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Less invasive techniques have been introduced during the last two decades to support or even replace radical liver surgery in patients with co-morbidities. Among these there are CT- or ultrasound-guided radiofrequency thermal ablation (RFA),^{5–7} laser induced thermal therapy (LITT), cryosurgery, brachytherapy, and several external beam radiation therapies (EBRTs).⁸ The most established local ablative method is radiofrequency thermal ablation (RFA). Especially in metastases smaller than 3 cm in diameter it has shown good efficacy.⁹ However, adequately powered, randomised studies proving the equivalent efficacy of RFA and surgery are not yet available.⁹ The reported local recurrences of mCRC in the liver after RFA depend on the size of the metastasis and range between 10%¹⁰ and 29–37%.^{11,12}

New radiotherapy techniques such as stereotactic body radiation therapy (SBRT),¹³ hyperfractionated high-dose irradiation, three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT) allow treatment of intrahepatic metastases by external radiation (EBRT). Again, radiation and surgery of liver metastases have not been formally compared.⁸ The development of customised immobilisation devices improved the possibilities and accuracy of stereotactic body radiation to liver metastases at the expense of patient convenience as those devices restrict the breathing motion during radiation. IMRT may increase local control of irradiated colorectal liver metastases by enhancing the applied dose of radiation without harm to other organs,¹⁴ but data on this topic are still scarce. With the development of an image-guided stereotactic robotic radiosurgery technique that tracks respiratory motion of the irradiated volume,¹⁵ it is now possible to treat metastases in moving organs in one session with high accuracy and minimal radiation exposure to surrounding healthy tissue.¹⁶ Here we describe for the first time the application of Cyberknife radiosurgery for metastatic liver tumours of colorectal cancer.

2. Materials and methods

2.1. Study design

Prospectively followed single arm study to evaluate the effectiveness of single-session robotic radiotherapy of colorectal liver metastases. Primary end-point was local control (LC); secondary end-points were toxicity, progression-free survival (PFS) and overall survival (OS).

2.2. Patients

Patients suffering from non-resectable liver metastases of colorectal carcinomas were included. To evaluate the possibility of surgical resection most patients were reviewed by the multidisciplinary gastro-intestinal tumour board of the University Hospital Grosshadern prior to cyberknife treatment or were seen by an experienced hepato-biliary surgeon. Patients refusing surgery in the first place were treated without tumour board decision. Pre-treatment with chemotherapy was preferred but not required. The maximum diameter of the malignancy had to be less than 5 cm, and no more than 2 metastases should be detectable on SPIO- (small particles of iron oxide) and gadolinium-enhanced liver MRI scans.

The total irradiated volume had to be smaller than 80 cc. To exclude metastases outside the liver all patients had a whole body fluorodesoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) scan prior to radiation therapy and only patients with surgically removed, and thereby histological proven, primary adenocarcinomas of the colon or the rectum were treated.

All patients gave informed consent to data evaluation prior to therapy. The study was performed in accordance with the guidelines of the local research ethics committee (# 383-08).

2.3. Marker placement

All patients underwent CT fluoroscopically guided percutaneous placement of one or two cylindrical gold fiducials (AB Medica, Milan, Italy), 5 mm long and 0.5 mm in diameter, directly into the metastasis prior to radiation. This was done under local anaesthesia.

2.4. Radiation

The 3-D target volume was identified in both contrast-enhanced CT and in MRI scans. Comparable to surgery, a safety margin of at least 7 mm was added to the tumour diameter in all three dimensions to reduce the probability of local recurrence. All patients were treated with single-session radiosurgery to a dose of 24 Gy to the 70% isodose. The respiratory motion of the lesion was tracked continuously using a method that was described in detail recently.¹⁵ Therefore a 6-MV compact linear accelerator (LINAC) is mounted on a six-axis robotic manipulator (CyberKnife, Accuray Incorporated, Sunnyvale, CA). The position of the linear accelerator is real-time corrected during the treatment based on 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. Thereby, changes in the position of the irradiated volume caused by breathing are compensated. The radiation beam itself can be directed from a multitude of angles around the patient. The whole procedure lasts about 1.5 h and patients are discharged from the institute immediately at the end of treatment.

2.5. Evaluation of response to treatment

The response of irradiated liver metastases was done according to the RECIST-criteria. Caused by remaining detectable tissue and the difficulties of differentiation between tumour re-growth versus radiogenic inflammation in a contrast enhancing margin the RECIST-criteria are difficult to apply.¹⁷ Therefore the follow-up exams included gadolinium-enhanced MRI scans of the liver that were performed 2 months after cyberknife irradiation and after that at 3-month intervals. As done before by others,¹⁷ local control was defined as tumour shrinkage or no tumour progress as evaluated by contrast-enhanced MRI scans. A local recurrence was defined as an increase of the tumour volume compared to pre-therapeutic dimension 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 an extrahepatic recurrence.

Table 1 – Patient characteristics.

Patient	Age (years)	Sex	KPS%	Primary	Metastases DFS (months)	Liver segment of metastases	Irradiated volume (cc)	Local response	Prior chemotherapy	Prior local therapy	Follow up (months)	Recurrence	Death
1	55	m	100	Colon	Metachronous 17.9	VI/VII	20.55	PR	No	None	29.4	intrahepatic (seg. II/III)	No
2	51	m	100	Rectum	Synchronous	VIII	43.22	PD	FOLFOX	Surgery	14.7	Local (seg. VIII)	Due to tumour progression
3	76	m	80	Colon	Metachronous	I/IVb	14.33	PR	FOLFOX	Surgery	17.0	Extrahepatic (lung, lymph nodes)	Due to tumour progression
4	67	m	100	Colon	18.5 Synchronous	V/VIII I	16.37 30.28	PR NC	No	Surgery	19.5	Extrahepatic (lung)	No
5	51	f	100	Rectum	Synchronous 5.5	I IVb V/VI	79.26 25.00 2.23	NC CR CR	No	None	27.2	No	No
6	67	m	100	Sigma	Metachronous	IV	39.69	CR	5-FU + folinic acid	Surgery	13.5	Intrahepatic (seg. VII/VIII)	No
7	66	m	90	Cecum	15.7 Synchronous	IV	14.26	PD	FOLFIRI	RFA	20.7	Local (IV)	No
8	63	m	100	Colon	41.2 Metachronous	IVb/VII	29.60	PR	No	Surgery	15.1	No	No
9	63	m	100	Sigma	31.5 Metachronous	III/IV	12.23	PD	No	Surgery	25.3	Local (seg. III)	No
10	58	f	100	Rectum	Synchronous	VIII	75.32	PR	5-FU + folinic acid	Surgery	18.1	Extrahepatic (lung)	No
11	73	m	90	Sigma	Metachronous 13.0	VIII	25.09 17.77	PD PD	No	None	16.7	Local (seg VIII)	No
12	72	m	100	Sigma	Metachronous	VI	12.57	CR	No	Surgery	11.6	Extrahepatic (lymph nodes)	No
13	72	f	80	Colon	85.1 Synchronous	IV	35.33	NC	FOLFOX → FOLFIRI + bevacizumab	Surgery	8	Extrahepatic (lung)	No
14	33	f	100	Cecum	Synchronous	VI	6.86	NC	No	Chemo-embolisation	7.4	No	No
						VII	25.47	NC					

f: female; m: male; cc: cubic centimeter; KPS: Karnofsky performance status, 5-FU: 5-fluorouracil; FOLFOX: 5-FU + folinic acid + oxaliplatin; FOLFIRI: 5-FU + folinic acid + irinotecan, RFA: radiofrequency thermal ablation; DFS: disease free interval, NC = no change; PR = partial response, CR = complete response.

2.6. Evaluation of toxicity

Before and at first follow up appointment liver toxicity was evaluated by measuring total bilirubin, AST (aspartate transaminase), ALT (alanine transferase) and INR. All patients were questioned for gastrointestinal symptoms like nausea or heart burn. In case of any noticeable problem an upper GI-endoscopy had to be scheduled.

Morbidity was evaluated separately for morbidity due to marker placement (bleeding, pain) and morbidity due to radiation treatment.

2.7. Statistics

Statistical analysis was done using STATA 10.1 for Macintosh (Stata Corporation, USA). Progression-free survival (PFS) was calculated using the 'Kaplan–Meier' method and was measured from the day of radiation to the date of progression or death.

3. Results

Nineteen metastases derived from colorectal cancer in 14 patients (male 10, female 4) aged 33–76 years (median 65 years) each were treated in one session with 24 Gy to the 70% isodose (patient characteristics and outcomes are detailed in Tables 1 and 2). The patients had several concomitant diagnoses such as coronary heart disease, post-myocardial infarction, hypertension, diabetes mellitus or obesity. Because of co-morbidities some patients got irradiated although they had technically resectable metastases (see patient #5 in Fig. 1). Other reasons for surgical non-resectability were mostly technical, such as prior hepatic surgery, prior RFA treatment, or the difficult localisation of the metastases. No patient reported any side-effects of either fiducial placement or the radiation therapy. In particular, gastrointestinal side-effects such as bleeding, ulcers or strictures have not been detected. This might be due to the high accuracy of the cyberknife treatment as shown before.¹⁵ The median Karnofsky Performance Status was 90% with a range of 80–100%. The median irradiated volume was 25.0 cc (range = 2.2–79.3 cc). In most patients, MRI of the liver performed 3 months after radiation showed contrast

enhancement at the margin of irradiated lesions. Since follow-up MRI analyses indicated a decrease of margin enhancement we suggest that initial findings reflected local inflammation and enhanced perfusion of the border of the irradiated volume, comparable to changes after RFA.

The 1-year local control rate was 87% (17/19) during a median follow-up of 16.8 months. Among the 19 treated lesions 9 metastases decreased in size (PR or CR), 5 remained unchanged and 5 increased in sizes (PD) after irradiation. The median progression-free survival (PFS) (Kaplan–Meier method) was 9.2 months (for both see Fig. 2). Local progression within the previously irradiated area occurred in patients #2, #7, #9 and #11 after 9.3, 17.5, 14.5 and 14.9 months. Distant recurrence outside the irradiated liver segments appeared in 7 patients. Intrahepatic progression, defined as tumour mass in another liver segment than the previously irradiated, was seen in patients #1 and #6 after 2.3 and 2.1 months. Extrahepatic progression was observed in patients #3, #4, #10, #12 and #13 after 2.5, 2.4, 11.9, 6.9, 11.6 and 4.0 months. Within our follow-up, 2 of 14 patients died at 14.7 and 17.0 months after radiation due to tumour progression. One of those had achieved local control but developed lung and lymph node metastases, the second one showed recurrence within the irradiated area.

4. Discussion

In the current study the progression-free survival (PFS) of 9.2 months and the 1-year local control rate of 87% is comparable to other studies investigating local ablative treatment applications for colorectal liver metastasis. For example, radiofrequency ablation is widely used as an alternative local treatment in surgically ineligible cases. The 1-year local control rates for RFA-treated colorectal liver metastases range between 63% and 88%^{10–12} and are mainly dependent on the size of the treated lesions. The median PFS after RFA differs widely among several studies and range between 7 and 13 months. Studies examining SBRT of colorectal liver metastases showed 1-year local control rates of 92–94%^{14,17}, also comparable to our results. The median time to progression was calculated in one study and achieved 6.5 months¹³ which is slightly below the 9.2 months obtained in our study.

Table 2 – Results.

Follow up (median)	16.8 months
Progression-free survival (Kaplan–Meier method)	9.2 months
Targets treated per patient	9 × 1 5 × 2
Volume irradiated (median)	25.0 cc (range 2.2–79.3 cc)
Radiation dose per target (to the 70% isodose)	24 Gy
Control rate (treated lesions)	
1-Year-local control rate	87%
Recurrence within irradiated liver segments (local)	5/19 (26%)
Recurrence outside the irradiated liver segment (distant)	9/19 (47%)
Intrahepatic recurrence	2/19 (11%)
Extrahepatic recurrence	7/19 (37%)
Death during surveillance (treated patients)	2/14 (14%)
Local controlled	1/14 (7%) after 17.0 months
Local recurrence	1/14 (7%) after 14.7 months

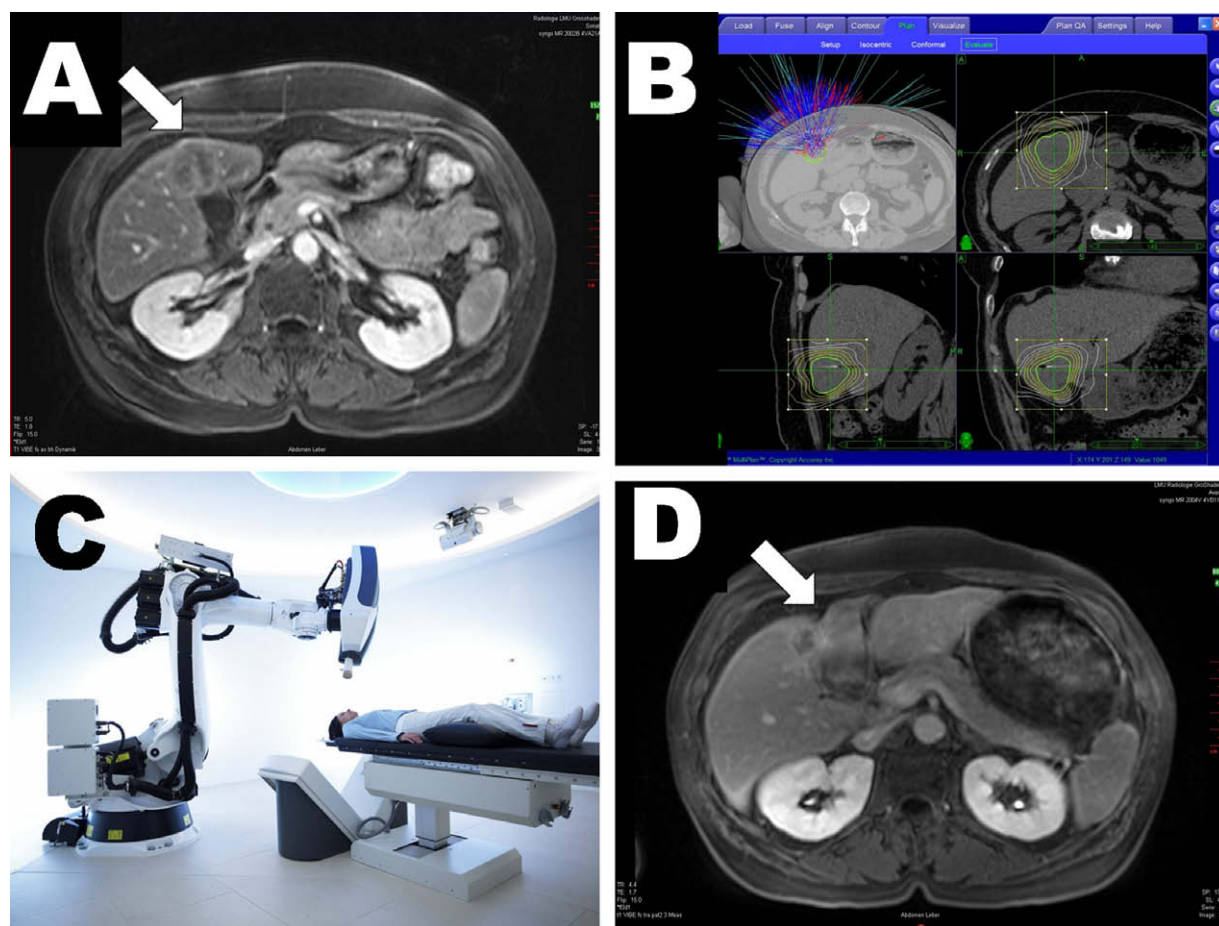


Fig. 1 – All four pictures are from the same patient. (A) Pre-treatment MRI scan showing the metastases (white arrow). (B) Beam arrangement and dose distribution. (C) Robotic radiosurgery device. (D) 8 months after treatment the MRI scan shows the typical reaction of the irradiated metastases.

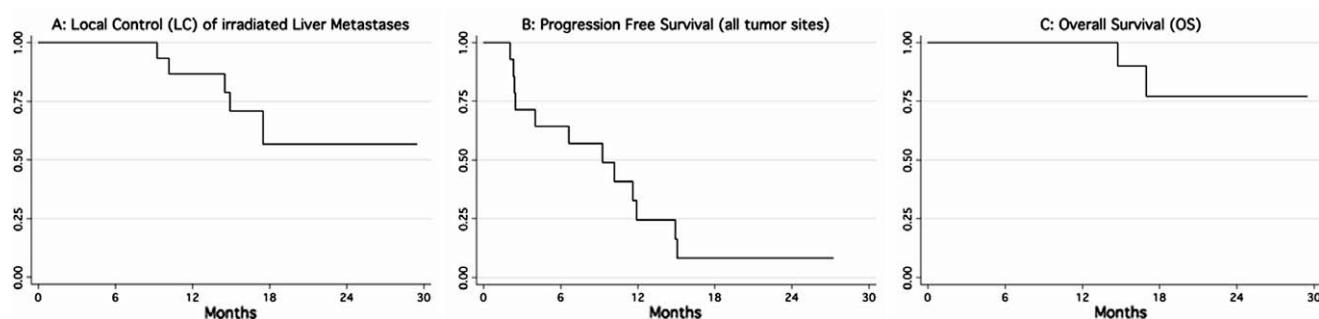


Fig. 2 – Kaplan–Meier–survival analyses for: local control rate (A), progression-free survival (B) and overall survival (C).

Short-term survival (OS) in this group of 14 patients was 87% after a median follow-up of 16.8 months. Two patients died at 14.7 and 17 months after cyberknife irradiation due to tumour progression. Presently, surgery is the treatment of choice in resectable liver metastasis. Nevertheless, recurrence rates (intra- and extrahepatic) of 60–70% have been observed after complete resection of liver metastases.¹ One-, 3-, and 5-year survival rates after RFA of colorectal liver metastases are 71–88%,^{9,10} 14.3–54%^{11,18} and 27–33%.^{12,18} and are dependent

on patient selection, size of the treated metastasis and other factors such as CEA levels. For that reason, metastases smaller than 3 cm treated with RFA have 1-, 2- and 3-year survival rates that are comparable to the outcome after surgical resection.^{10,18}

Data on survival after SBRT of colorectal liver metastases range widely due to patient selection and radiation modality. Older studies reported 1- and 3-year survival rates of 65% and 34%, respectively.¹⁹ Newer studies using immobilisation

devices and newer planning methods achieve 1-year survival rates of 67–85% and 2-year survival rates of 32–54%^{13,14,17} that are in line with our observations.

Survival rates after surgical resection as the gold-standard of treatment of colorectal liver metastases, were 71–93% (1-year) and 35–73% (3-year).¹ These data are not strictly comparable; all studies encounter severe selection biases as patients with no or minor co-morbidities and resectable liver metastases are almost always admitted to surgery. This selection bias suggests that the efficacy of local ablative techniques will likely be inferior to surgery when it comes to long-term survival.

The major dose-limiting concern in the use of radiation for liver tumours is the risk of radiation-induced liver disease (RILD). The liver tolerance to external beam irradiation depends on the volume treated and the fractionation schedule. Lawrence and colleagues found that patients who developed grade III or IV radiation-induced liver disease (RILD) tended to receive a higher mean dose and have less sparing of normal liver than those who did not.²⁰ It is suggested that by using modern conformal radiation planning it is possible to deliver tumouricidal doses of radiation with a potential curative intent. Nevertheless, up to now, stereotactic irradiation in the setting of liver metastases is unlikely to be curative, but may provide durable local tumour control. The study by Dawson and colleagues helped to understand the relationship between dose, volume of liver irradiated and RILD, based on an analysis of over 200 patients with hepatic malignancies.²¹ This analysis demonstrates that for a small effective liver volume irradiated, far higher doses of radiation can be prescribed than estimated previously. We here describe a single fraction regimen using a high dose to mimic classical radiosurgical approaches well-known for brain tumours.²² It is essential to note that in our series mostly small tumour volumes were treated in these highly selected cases of SBRT. None of our patients developed signs of liver failure or jaundice. Neither ulcers nor fistulas in adjacent organs were found in the follow-up period. This is in line with previous published data where no grades 3–4 toxicities after extracranial CyberKnife® therapy could be observed.²³ In RFA-treated patients (external and intra-operative) the reported morbidity rate is between 5% and 10%.^{11,18,24} But in most of the cases only minor complications occur. The rate of major complications, including pneumothorax, bleeding, urinary retention, reoperation for colonic perforation, intrahepatic abscess and ileus, is as low as 2.4%.²⁴ One study dealing with stereotactic radiation therapy of colorectal metastases showed low toxicity rates,¹³ but grade 2–4 toxicities were reported in 28%. Although customised immobilisation frames were used to reduce radiation of adjacent organs a total of 5% (3 of 61 patients) suffered from intestinal perforations due to radiotherapy.

Selection of appropriate dose for stereotactic body radiotherapy is difficult as the LQ model describes the radiation effects for low dose-per-fraction schemes used in conformal fractionated radiotherapy, and was never intended to be applied to the ablative dose ranges used in the current study. To overcome this problem the single fraction equivalent dose (SFED) methodology has been proposed by Park and colleagues as a way to compare the relative biologic potency of hypofractionated radiotherapy schedules.²⁵ We used stringently one fraction with 24 Gy to the 70% isodose and treated

therefore in the lower range of published single and hypofractionated regimens. Our clinical results seem to be in line to the recently published results with similar approaches.^{13,14,26,27} For example, Rusthoven and colleagues²⁸ recently found in a multi-institutional phase I/II trial of SBRT for liver metastases that when higher, more intense doses were used, higher rates of local control were observed. For the 49 liver lesions treated with an escalating dose from 36 Gy to 60 Gy (3 x 20 Gy was the phase II dose), local control at 2 years was 92%. Grade 3 and higher toxicity occurred in only 2% of the patients. Dose fractionations published in phase II studies that use SBRT for the treatment of liver metastases range from 1 x 14 Gy up to 3 x 20 Gy.^{13,14,26–28}

Sophisticated survival curve models have been described to help to better understand tissue responses in SBRT to different dose fractionation schemes.²⁹ Although of definite significance, ultimately more prospective clinical data with longer follow-up is needed to add clinical knowledge to these mathematical calculations.^{25,29} We hope that our small prospective series with constantly applied treatment parameters adds some relevant clinical information to the fast-developing field of SBRT for liver metastases.

Today, 3D-CRT is the most frequently used radiation therapy to liver metastases. But even in the time of CT- and MRI-scan-based computer-assisted planning this relatively safe technique has restrictions¹⁹ relating to treatment accuracy and patient comfort; it is not recommended in patients with liver cirrhosis, with large tumour volumes, or in patients with metastases near other organs and the portal vein (where thrombosis may ensue). Furthermore, the use of immobilisation tools such as body frames with abdominal pressure devices causes significant discomfort for the patient during treatment. These immobilisation devices were until recently necessary to limit tumour movement caused by normal breathing. The robotic technology described here mostly overcomes these restrictions and enables highly precise (1 mm) local irradiation of liver tumours without immobilisation, as the robot tracks and corrects tumour movement in real-time.^{15,23} This allows using significantly lower margins for treatment planning and therefore lower toxicity to the surrounding healthy tissues and sensitive structures. In fact, in the current study we did not observe any relevant toxicity of the liver or the neighbouring structures during the reported follow-up time.

5. Conclusion

Frameless robotic radiosurgery is a new and convenient method to treat metastases of colorectal cancer. Despite the small number of patients and relatively short follow-up we can state that this method is a feasible and safe way to treat liver malignancies and achieve local tumour control. Particularly for patients with comorbidities or for technically unresectable metastases, this is a promising way to deal with residual disease after chemotherapy, and potentially to prolong life. Further examination of this technique, with more patients and longer follow-up is needed to confirm its effectiveness and to define the optimal dose and fractionation regimen. SBRT will have a substantial role in the treatment

of metastatic liver cancer to eradicate unresectable disease. Although other ablative techniques, such as radiofrequency ablation, compete with radiation therapy, they are invasive and cannot be applied everywhere in the liver (e.g. near large vessels or superficial locations). There is a need for improved local therapies for liver metastases. We are confident that the RTOG trial 0438³⁰ will bring more awareness and clinical evidence to SBRT for liver tumours.

Conflict of Interest statement

None declared.

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