

Robotic stereotactic body radiation therapy for liver-limited malignant tumors

Mariusz Frączek¹, Jacek Sobocki², Katarzyna Pędziwiatr³, Edward Skrocki³, Norbert Piotrkowicz³, Dobromira Tyc-Szczepaniak³, Elżbieta Korab-Chrzanowska³, Piotr Hevelke³, Maciej Krasnodębski¹, Waldemar Koszewski³

¹Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland

²Department of General, Oncology and Gastrointestinal Surgery, St. Anna Memorial Hospital, Warsaw, Poland

³Institute of CyberSurgery, Wieliszew, Poland

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Abstract

Introduction: Stereotactic body radiotherapy (SBRT) is rapidly gaining favor as a new treatment modality for malignant liver tumors. Most of the studies have recruited patients with disseminated disease originating from the liver. This study focuses on disease limited to the liver.

Aim: To perform a retrospective analysis of all patients with liver tumors treated by robotic stereotactic body radiation therapy in a single center.

Material and methods: The study included 13 patients with 22 lesions. The inclusion criteria were: patients with 1–4 inoperable liver lesions and absence of any extrahepatic disease. All but 3 patients received 3 fractions delivered by the Cyberknife system of a total of 45 grey (Gy). The other 3 patients received 30 Gy.

Results: The median follow-up time was 10.8 months (range: 7–16). The median dose was 41.5 Gy (range: 30–45). One lesion regressed (8%). In 5 patients, the disease was locally stabilized (38%), and in 7 other patients progression occurred (54%). Twelve patients (92%) are still alive, and 1 patient (8%) died. In 1 patient a new cancer (leukemia) was diagnosed.

Conclusions: The SBRT is well tolerated and effective for local control of most liver malignant tumors. It appears that SBRT is best suited for those patients in whom systemic recurrence can be controlled by chemotherapy. Further studies are mandatory to elucidate these effects on tumors of varying histology and to elaborate upon criteria used to select patients who can benefit most from this treatment.

Key words: cyberknife, liver tumors, stereotactic body radiotherapy.

Introduction

Liver surgery is a broadly accepted radical treatment of primary liver tumors and several metastatic cancers. These include colorectal cancer and neuroendocrine tumors [1]; however, the size and location of the tumor, as well as patient condition, limit the use of this method in a large group of patients [2].

The former group has been treated with some success by radiofrequency ablation (RFA) [3]. The RFA is also limited by size, location of a tumor (for example, proximity to the liver surface or to large vessels) and breathing motion. Implementation of the automated registration of breathing motion can be applied to compensate only for the former problem [4]. Several patients were beyond the reach of local treatment.

Address for correspondence

Mariusz Frączek MD, PhD, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, 16/20 Barska St, 02-315 Warsaw, Poland, phone: +48 601 329 250, e-mail: mariusz.fracz@gmail.com

Robotic stereotactic body radiation therapy (SBRT) was proposed for the treatment of liver metastases of different origin [5] and primary tumors [6]. The data from the literature suggest that local control is achieved in 90% and 86% of cases, effective for 1 and 2 years, respectively [7]. A complete response was achieved in 66% of patients, and a partial response in 13% of lesions treated. It has been reported that 1- and 2-year survival reaches 94% and 48%, respectively.

Aim

The aim of this study was to perform a retrospective analysis of all patients with liver tumors treated by robotic stereotactic body radiation therapy in a single center.

Material and methods

The retrospective analysis covered all patients treated for malignant liver tumors between July 2012 and January 2013. The indication for SBRT was determined by a multidisciplinary team which consisted of a hepatic surgeon, oncologist, radiotherapist and radiologist. Inclusion criteria comprised the following: 1 to 4 lesions located close enough to one another to enable simultaneous

irradiation, diameter of the greatest lesion less than 100 mm, and no evidence of dissemination of the disease outside of the liver. Thirteen patients with 22 lesions were treated. The mean age of the patient was 64 years old (range: 48–86), and the mean time from surgery to the SBRT was 16.6 months. Demographics of the patients and origin of the tumor are shown in Table I. Exclusion criteria are presented in Table II. Presence or suspicion of extrahepatic disease was considered an exclusion criterion. For this purpose all patients underwent a positron emission tomography-computed tomography (CT-PET) study. Mean follow-up was 10.8 months (range: 7–16 months).

Gross tumor volume (GTV) was estimated using contrast-enhanced tomography scans. Gold seed markers (fiducials) were placed around the tumor. Care was taken not to put markers in the same transversal plane to each other, nor to place them inside the tumor, so as to prevent interference with the measurements of the lesion in the control CT study.

Treatment was planned at least 7 days after implantation of the fiducials. The irradiation field was determined using CT scans in the treatment position, while the patient was immobilized using a customized mattress. According to the protocol used in

Table I. Demographic data and origin of the tumor

No.	Age [years]	Gender	Origin of cancer	Previous surgery	Time from surgery to SBRT [months]
1	66	Male	CRC	Left hemicolectomy	10
2	85	Male	CRC	Left hemicolectomy	14
3	77	Male	HCC	None	6 ^a
4	59	Male	CRC	Anterior rectal resection	3
5	79	Female	CRC	Anterior rectal resection	60
6	70	Female	HCC	None	4 ^a
7	57	Female	GC	Gastrectomy	24
8	70	Male	CRC	Left hemicolectomy	10
9	54	Female	AC	Adrenalectomy	18
10	47	Male	CRC	Left hemicolectomy	14
11	46	Female	GC	Gastrectomy	2
12	71	Male	CRC	Anterior rectal resection	14
13	48	Male	LS	Tumorectomy	13

CRC – colorectal cancer, HCC – hepatic cell cancer, GC – gastric cancer, LS – retroperitoneal liposarcoma AC – adrenal gland cancer, ^atime from diagnosis

other centers, GTV was calculated for contrast-enhancing disease visible on the CT scan in 1.25-mm slice thickness (Photo 1). The clinical target volume (CTV) was contoured by adding a 5 mm margin to cover possible microscopic spread. Finally, the planning target volume (PTV) was determined adding an additional 3 mm margin for targeting uncertainty of movement.

The treatment was performed using the CyberKnife (Accuray, USA). Ten patients received 3 fractions of 15 Gy, 2 received 3 fractions of 10 Gy, and 1 received 6 fractions of 5 Gy. A control contrast-enhanced tomography study was performed after 3 and 6 months.

Regression of tumors was assessed according to mRECIST criteria.

Results

The average total dose per patient was 40.8 Gy, with maximum 45 Gy, minimum 30 Gy and median

Table II. Exclusion criteria

No	Criteria
1	Size of lesion > 100 mm
2	Number of lesions > 4
3	Extra-hepatic disease
4	ECOG > 3
5	18 < Age < 85
6	Direct contact of lesion with the bowel

45 Gy. Total dose, number of fractions, size of tumor, and gross tumor volume, before and after treatment, in consecutive patients, are presented in Table III. In 1 patient migration of the gold fiducial was observed outside of the hepatic capsule, requiring subsequent re-implantation.

We observed limited toxicity associated with the treatment. One patient (no. 3 in Tables I and III) with hepatocellular carcinoma complained of nausea and

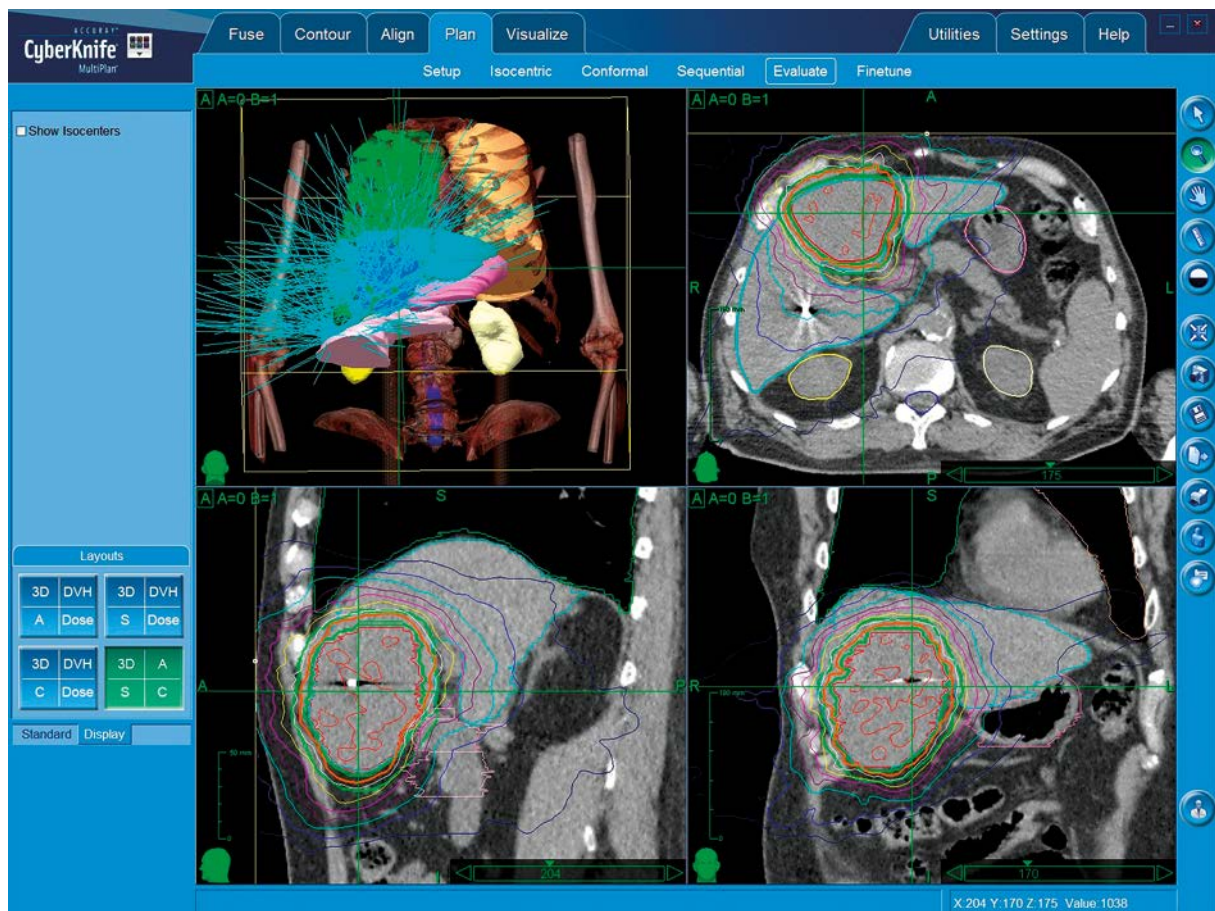


Photo 1. Planning of treatment

Table III. Total dose, number of fractions and size of tumor before and after treatment

No.	Origin of cancer	GTV [ccm]	Total dose [Gy]	Fractions	Lesion/lesions size, max size [mm]			Outcome
					Initial	After 3 months	After 6 months	
1	CRC	5.2/4.8/7.0/3.0	45	3	18/12/17/10	12/14/18/14	-	Dissemination
2	CRC	18.9	45	3	29	29 S	3 new meta	Died
3	HCC	7.8/225.0	30	6	29/92	20/27 R	1 new meta	Regression
4	CRC	4.5/2.4	45	3	44/12	25/8 R	1 new meta	Dissemination
5	CRC	430.0	30	3	70	46 R	33	Regression
6	HCC	3.3/11.3/3.5/8.1	30	3	6/24/30/15	4/17/1/1 R	4 new meta	Dissemination
7	GC	23.3	45	3	25	9 R	9	Leukemia
8	CRC	59.9	45	3	4	2 R	3 new meta	Dissemination
9	AC	2.3/1.3	45	3	8/10	8/13 P	Numerous meta	Dissemination
10	CRC	45.0	45	3	38	41 P	-	Progression
11	GC	7.1/2.0	45	3	6/7	16/4 R	9/0	Regression
12	CRC	23.1	45	3	45	32 R	-	Regression
13	LS	123.7	45	3	72	49 R	Numerous meta	Dissemination

R – regression, S – stabilization, P – progression, GTV – gross tumor volume

vomiting after the second course of radiation. There were no other complaints regarding toxicity-associated symptoms.

We observed an objective tumor response in 16 of 22 metastases (72%: 1 complete, 15 partial responses) and stable disease in 1 patient (5%). Five lesions (23%) progressed within 3 months of receiving treatment. The regression in 1 patient was visualized in magnetic resonance imaging before and after treatment (Photos 2 and 3 respectively).



Photo 2. Magnetic resonance images showing tumor before treatment



Photo 3. Regression of tumor

Seven patients developed new metastases in the liver within 3 months. Similarly to other papers, we observed the best response, complete regression, in 1 of 2 gastric cancer patients. One patient died, 1 developed a new cancer (leukemia), and 7 developed dissemination of the disease to other organs within 6 months. Only 4 patients demonstrated a clear benefit from the treatment in the observation period, defined as local control of disease without any signs of loco-regional recurrence or distant metastases. In 2 of 7 patients with colorectal cancer metastases, we observed moderate regression of lesions. This was defined as a reduction in their dimensions. One case of liposarcoma was treated. The objective local response was partial, but numerous metastases in other locations reduced the enthusiasm for continuing with this patient's radiotherapy plan. Table IV presents the type of chemotherapy concomitant to SBRT introduced in respective patients.

Discussion

The SBRT is a relatively novel, minimally invasive technique adapted for the treatment of liver malignant lesions. Its advantage is local ablation of tumors using precise and hypofractionated irradiation. We observed regression in 9 of 13 patients, in 1 patient the tumor size was stabilized, and in 3 patients tumor progression was found.

Histology-related response

We have treated 7 patients with colorectal metastases and 6 patients with other histological type tumors. Lee *et al.* suggest that colorectal liver metastases appear to have weakened local control in comparison with others, but these results are not significant due to the small number of observed cases [7]. In our study metastases regressed in 4 of 7 patients with colorectal cancer. The best response was observed in patients suffering from gastric cancer. All metastases in this group regressed while one disappeared. This is in concordance with results published by other authors [8]. Several papers have been published on the treatment of hepatocellular carcinoma by SBRT [9–11]. We have treated 2 patients with this type of tumor. Similarly to most papers, in both cases we observed regression of the primary tumor. Unfortunately, metastases out of the irradiated field developed in both patients.

Table IV. Chemotherapy concomitant to SBRT

No.	Concomitant chemotherapy
1	FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) 12 cycles
2	Oxaliplatin + capecytabine 8 cycles
3	No concomitant chemotherapy
4	FOLFOX (oxaliplatin, 5-fluorouracil, leucovorin) + Erbitox (cetuximab) 4 cycles
5	5Fu + LV (5-fluorouracil z leucovorin) 6 cycles
6	Interferon
7	No concomitant chemotherapy
8	Disqualified from chemotherapy
9	Mitotane
10	No concomitant chemotherapy
11	No concomitant chemotherapy
12	Disqualified from chemotherapy
13	No concomitant chemotherapy

Stereotactic body radiation therapy-induced tumor regression

Fifteen of 22 tumors regressed in our group of patients, a 68% response. This is a much weaker response than reported local control rates published by other authors. One-year response rates from different studies range from 71% to 95% [12–20]. The impact of tumor size on outcome remains unclear in the literature. Vautravers-Dewas *et al.* did not observe any statistical difference in degree of regression between tumors larger or smaller than 25 mm [12]. Similar results have been published by Herfarth *et al.* [13]. In contrast to these data, Rusthoven *et al.* suggest that lesions with a maximum diameter of < 3 cm had a 2-year local control rate of 100% compared with 77% for lesion diameters of > 3 cm ($p = 0.015$) [14]. The SBRT-induced regression was observed in most studies [15–20]; however, the principal problem in the comparative analysis of the published data is the variation in response criteria.

Toxicity of therapy

We observed only a mild adverse event in 1 patient. This was nausea and vomiting at the beginning of irradiation which resolved spontaneously and never returned. This means that only 7.6% of the group studied complained of symptoms associated with

mild toxicity. There were no adverse events reported in this investigation. Vautravers-Dewas *et al.* observed a greater incidence of adverse events of the therapy, including nausea, vomiting, gastritis, gastric ulceration, esophagitis, anorexia, diarrhea/constipation, hepatic pain, cirrhotic decompensation, asthenia and pericardial effusion. Of these, nausea was most frequent and occurred in 27.6% and 25% of cases for 40 and 45 Gy, respectively [12].

Survival

All but 1 patient survived 1 year, accounting for 93% of our group. Similar results are published by Vautravers-Dewas *et al.* [12]. The same author published a 2-year survival rate of 48%. In contrast to our study, patients were included with metastatic disease not confined to the liver (35.7% at the time of SBRT). One-year survival counted for specific cancers was as follows: colorectal cancer 6 of 7, hepatocellular carcinoma 2 of 2, gastric cancer 2 of 2, liposarcoma 1 of 1, and adrenal cancer 1 death of 1 treated patient.

Conclusions

The SBRT is a well-tolerated method and is effective for local control of some subgroups of malignant liver tumors. It appears that SBRT is most appropriate for use in those patients in whom systemic recurrence can be controlled by adjuvant chemotherapy. Further studies are mandatory to elucidate the effect on tumors of various histology and to elaborate criteria to select patients who can profit from the treatment.

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