

Stereotactic Body Radiation Therapy for Colorectal Cancer Liver Metastases; Early Results

Stereotaktická radioterapie jaterních metastáz kolorektálního karcinomu; časně výsledky

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Summary

Background: Stereotactic body radiation therapy (SBRT) is well feasible and effective method for treatment of colorectal cancer liver metastases. **Materials and Methods:** From September 2009 to December 2011, 11 patients with 15 inoperable liver metastases of colorectal cancer were treated by SBRT using Varian Clinac iX linear accelerator. We treated 6 men and 5 women of age from 51 to 81 years (median 68). SBRT doses ranged from 40 to 56 Gy (median 54 Gy) and were administered in 3 to 8 fractions. **Results:** Local control rates at 2, 4, 6, 9 and 12 months after completion of SBRT were 100%, 91%, 91%, 67% and 50%, respectively. Disease progression-free survival rates at 2, 4, 6, 9 and 12 months were 82%, 82%, 64%, 50% and 50%, respectively. Median follow-up was 15 months. No severe side effects were attributed to the therapy. **Conclusion:** Our study assessed the feasibility of SBRT in selected group of patients with 1 to 3 colorectal cancer liver metastases with no other treatment option. We achieved excellent local control and very moderate acute and late side effects. Distant metastases were the most common recurrence form after SBRT. SBRT demonstrated excellent local control and resulted in occasional long-term survivors without any serious side effects of therapy.

Key words

colorectal neoplasms – neoplasm metastasis – liver – radiation therapy – stereotactic body radiotherapy

Souhrn

Východiska: Extrakraniální stereotaktická radioterapie (SBRT) je dobře proveditelná a účinná metoda léčby jaterních metastáz kolorektálního karcinomu. **Materiál a metody:** Od září 2009 do prosince 2011 bylo extrakraniální stereotaktickou radioterapií pomocí lineárního urychlovače Varian Clinac iX léčeno 11 pacientů s 15 inoperabilními jaterními metastázami. Jednalo se o 6 mužů a 5 žen ve věku od 51 do 81 let (medián 68 let). Použité dávky záření v rozmezí od 40 do 56 Gy (medián 54 Gy) byly aplikovány ve třech až osmi frakcích. **Výsledky:** Lokální kontrola ve 2, 4, 6, 9 a 12 měsících od ukončení SBRT byla 100 %, 91 %, 91 %, 67 % a 50 %. Bez progresse onemocnění přeživalo ve 2, 4, 6, 9 a 12 měsících 82 %, 82 %, 64 %, 50 % a 50 % pacientů. Medián sledování byl 15 měsíců. Žádné závažné nežádoucí účinky léčby nebyly pozorovány. **Závěr:** Naše studie hodnotila proveditelnost SBRT ve vybraném souboru pacientů s 1–3 jaterními metastázami kolorektálního karcinomu neřešitelnými jinými metodami léčby. Dosáhli jsme vynikající lokální kontroly za současných velmi mírných akutních i pozdních nežádoucích účinků léčby. Nejčastější příčinou relapsu onemocnění po provedené SBRT se staly vzdálené metastázy. SBRT vykazuje vynikající lokální kontrolu a umožňuje u vybraných pacientů dlouhodobé přežití bez vážných nežádoucích účinků léčby.

Klíčová slova

kolorektální karcinom – metastázy – játra – radioterapie – extrakraniální stereotaktická terapie

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Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

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Tab. 1. SBRT of colorectal liver metastases, recent publications.

Author (year of publication)	Number of patients	Fractionation	Follow-up (median; month)	Local control (%) (1 year; 2 years)	Survival (%) (1 year; 2 years)
Hoyer et al (2006) [9]	44	15 Gy × 3 (isocenter)	51.6	?; 78	67; 38
Mendez Romero et al (2006) [10]	17	10–12.5 Gy × 3 (65% isodose)	12.9	100; 86	85; 62
Katz et al (2007) [11]	69	30–55 Gy × 7–20 (100% isodose)	14.5	76; 57	?
Rusthoven et al (2009) [12]	47	12–20 Gy × 3 (80–90% isodose)	16	95; 92	77; 30
Lee et al (2009) [13]	68	4.6–10 Gy × 6	10.8	71; ?	60; 39
Ambrosino et al (2009) [14]	27	8.3–20 Gy × 3	13	74 (crude)	?
Goodman et al (2010) [15]	19	18–30 Gy × 1	17.3	77; 75	62; 49
Rule et al (2011) [16]	27	10 Gy × 3	20	56; 56	90; 50
		10 Gy × 5		100; 89	78; 67
		12 Gy × 5		100; 100	75; 56

Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Europe, with an annual incidence of 400.000 cases and an annual mortality of more than 200.000 patients [1]. The incidence in the Czech Republic is one of the highest worldwide. The most frequent site of metastases of CRC is the liver. Almost 70% of CRC patients develop liver metastases during the course of disease [2]. However, although the median survival of patients with untreated disease ranges from 6 to 12 months, the addition of an optimal chemotherapy regimen improves median survival only to 20 months. Further improvement is achieved by implementation of molecular targeted therapy into the treatment [3–6].

In most cases local palliative treatment leads to both local tumour control and survival improvement. Surgical data show that local treatment of liver tumours – especially hepatocellular carcinoma and liver metastases – might be curative in up to 25–30% of patients if patient selection is appropriate [7]. Nevertheless a significant proportion of patients are not suitable for surgery because of age, medical comorbidities, or unfavourable intrahepatic localisation of the tumour (bilobar, adjacent to large vessels/portal structures). For these cases, SBRT might be a good treatment option [8].

Stereotactic Body Radiation Therapy (SBRT) is one of the most advanced methods of radiation treatment characterised by limited number of fractions using

highly focused ablative beams for treating cancer lesions outside of the skull. Recent results of clinical studies using SBRT in the treatment of liver metastases are emerging. Phase I and II studies have demonstrated excellent local control and occasional long-term survivors. These studies showed actuarial local control rates of at least 80% after 2 years (see Tab. 1) [9–16].

SBRT is a non-invasive short time treatment method, with no need of hospitalisation whereby meets the criteria of high-quality palliative care of patients with metastatic disease. Because of its' precision, SBRT delivers a higher dose to the tumour and causes less damage to surrounding normal tissues. Reported acute toxicity is moderate. Clinically relevant subacute or late toxicities are not reported, if organs at risk (OAR) are kept out of the high dose region. Radiation-induced liver disease (RILD) is rare after SBRT of liver metastases, while fibrosis of those portions of the liver included in the high dose volume is common, with subsequent compensatory hypertrophy of liver tissue spared from radiation. When dose limits to the adjacent organs are exceeded (oesophagus, stomach, duodenum or large bowel) possible late side effects might appear (e.g. gastrointestinal bleeding, small bowel obstruction, gastric outlet obstruction or fistula

Tab. 2. Possible acute and late toxicity listed in the literature.

Acute toxicity

- fatigue, nausea, vomiting, fever, chills, abdominal pain, erythema, elevation of liver enzymes

Late toxicity

- reduction in liver function
- RILD (*Radiation-Induced Liver Disease*)
- anicteric hepatomegaly, ascites, elevation of liver enzymes
- intermittent pain, rib fractures, colitis, gastrointestinal ulceration, perforation or obstruction

Tab. 3. Patients and treatment characteristics, response and survival.

No.	Sex/age	Primary site/ /grade	No. of MTS	Total ITV (ccm)	SBRT dose (Gray)	Response at 2–4 mo	Local recur- rence (mo)	Distant recurrence site (mo)	Follow- up (mo)	Survival status
1	M/70	coecum/G3	3	40.2	56	PR	yes (9)	liver outfield (2)	15	dead
2	M/51	coecum/G3	1	5.7	40	PR	no	no	18	ned
3	F/67	sigma/G3	1	16.9	54	PR	yes (12)	liver outfield (2) retroperitoneum (9)	16	dead
4	M/69	coecum/G2	1	1.9	54	CR	no	no	18	ned
5	F/61	rectum/G3	1	17.5	55	SD	yes (9)	lungs (6)	18	awd
6	F/62	colon/G2	2	34.7	55	PR	no	retroperitoneum (14)	18	awd
7	M/71	rectosigma/G2	1	42.7	55	CR	no	no	9	ned
8	F/81	coecum/G2	1	23.6	54	CR	no	lungs (6)	9	awd
9	F/59	colon/Gx	1	74.5	40	SD	yes (4)	no	6	awd
10	M/68	rectum/G2	2	23.4	40	CR	no	no	6	ned
11	M/68	rectosigma/G2	1	44	40	PR	no	no	6	ned

M – male, F – female, G – grade, ITV – internal target volume, mo – month, SD – stable disease, CR – complete response, PR – partial response, ned – no evidence of disease, awd – alive with disease

formation) [9,17]. The most common toxicities found in the literature are listed in Tab. 2.

In our present work, we focused on the feasibility and efficacy of SBRT in the treatment of colorectal cancer liver oligometastases. Even though the number of patients included is relatively small, we attempted to determine local control rate, disease free survival and failure patterns after SBRT retrospectively.

Materials and Methods

Patients' Characteristics

From September 2009 to December 2011, 11 patients with 15 liver metastases of colorectal cancer were treated with SBRT using the linear accelerator Varian Clinac iX (Varian Systems, USA) at our institution. Patient eligibility criteria for SBRT for liver metastases of colorectal cancer were as follows:

- 1) inoperable disease or refusal of surgery
- 2) progression after chemotherapy +/- targeted therapy
- 3) another local treatment modality (such as radiofrequency ablation) not indicated
- 4) fewer than four hepatic lesions, tumour not attached or close (< 3 mm) to the oesophagus, stomach or duodenum

- 5) good performance status (Karnofsky index > 70, life expectancy > 6 months, Child-Pugh score class A)
- 6) no extra-hepatic active lesion detected by positron emission tomography (PET) or PET/CT

Tab. 3 summarises patient and tumour characteristics. We treated 6 men and 5 women of age from 51 to 81 years (median 68 years). Primary tumours were located in the colon

in 7 cases and the rectum in 4 cases. All patients had a localised primary tumour at the time of diagnosis, all of them suffered from new dissemination after adjuvant therapy. Chemotherapy regimen combined with targeted therapy if indicated has been administered for all of patients. Ethical permission was granted after review at the Masaryk Memorial Cancer Institute and all patients gave written consent.

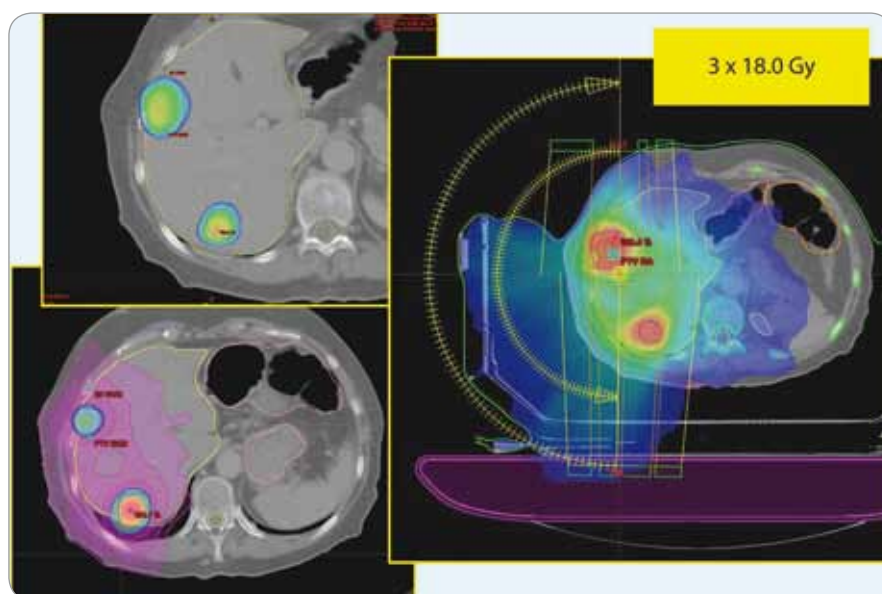


Fig. 1. 62-year old female with 2 liver metastases; dose distribution by Rapid Arc technology. Fractionation and dose – given in Grays.

SBRT

Safe daily SBRT treatment was achieved by ensuring reliable and reproducible immobilisation, accurate planning and treatment correlation, pre-treatment quality assurance using daily imaging and management of tumour and organ intrafraction motion in each treatment session. To minimise rotational shifts, the stereotactic body frame was used for patient fixation (Elekta stereotactic body frame). Abdominal compression served to reduce diaphragmatic expansion during breathing cycle [18]. Treatment plans were created using Eclipse planning system (Varian, v.8.6) with AAA algorithm and delivered by Rapid Arc technology (see Fig. 1). Daily pre-treatment imaging by cone-beam computed tomography (CBCT) on-board imaging system of our linear accelerator [19]. To ensure patient safety each plan was verified using gamma analysis.

To capture tumour movements during breathing cycle a four-dimensional CT (4DCT) scanning was used. This technology has been recently introduced to correlate CT image acquisition with the breathing cycle, allowing better analysis of variables that affect respiratory motion [20,21].

CT scans of 2–3 mm slices including target respiratory movements were performed and sent to the planning system. The data from MRI and FDG PET helped

us to identify target volume. No gold fiducials were used.

We used an internal target volume (ITV) concept for target volume definition. Gross tumour volume (GTV) was outlined as a tumour visible in CT or CT/MRI fusion without any margins. We contoured an inspiration GTV¹⁰⁰, expiration GTV⁰ and mid GTV⁵⁰ of normal breathing cycle. Then we created an ITV encompassing all these GTVs. Clinical target volume (CTV) was created volumetrically by 2 mm expansion from ITV to take a subclinical tumour spread into account. Planning target volume (PTV), which includes set-up and internal margin errors was outlined automatically with another 5 mm margin in all dimensions [8]. Where a PTV and OAR are close or even overlap, a responsible clinical decision about relative risks of tumour relapse or normal tissue damage had to be made.

For dose calculation we used a “risk adaptive concept” – dose was reduced during treatment planning when normal tissue constraints consideration contraindicated the use of primarily prescribed dose. According to this concept, total SBRT doses ranged from 40 to 56 Gy (median 54 Gy) and were delivered in 3 to 8 fractions. Six patients from our group had “ablative dose” of radiation, i.e. biological equivalent dose (BED) > 105 Gy and in 5 patients the

dose had to be reduced, i.e. a BED dose was < 105 Gy [22].

Adequate target coverage was achieved when 98–100% of planning target volume was covered by 95% of prescribed dose while the mean dose was 100% of prescribed dose. Dose gradient was also controlled and the treatment plans should meet a number of organs at risk dose constraints. Tab. 3 summarises ITV and SBRT dosage details.

Responses and Toxicity Assessment

Patients were followed up and tumour response assessment performed by computed tomography at 2, 4, 6, 9, 12, 15, 18 and 24 months after SBRT (when possible, we performed PET/CT scan at 6, 12, 18 and 24 months after SBRT; see Fig. 2). Local progression was defined as a new tumour lesion in the irradiated area or an increase in tumour size of more than 20%. Disease progression free survival was defined as a time from SBRT treatment termination to date of local progression, regional progression (new lesion in the liver outside the irradiated area) or distant metastasis (progression outside the liver tissue). Acute and late toxicities were sorted by the time of 3 months after treatment completion. RTOG Toxicity Criteria was used to evaluate acute and late side effects of the treatment.

Results

Response to SBRT was evaluated using CT scans performed between 2 and 4 months after SBRT completion. The number of patients with complete regression was 4 (36%), there were 5 patients (45%) with partial response and 2 patients (18%) showed stable disease. During follow-up, 6 patients (55%) experienced local recurrence, distant metastases, or both. Both local and distant failure occurred in 3 patients (27%), distant failure alone in 2 patients (18%) and local failure alone occurred in 1 patient (9%). Distant metastasis was the first form of recurrence. Patients underwent additional salvage or palliative treatments according to the failure pattern after recurrence.

Local control rates at 2, 4, 6, 9 and 12 months after completion of SBRT

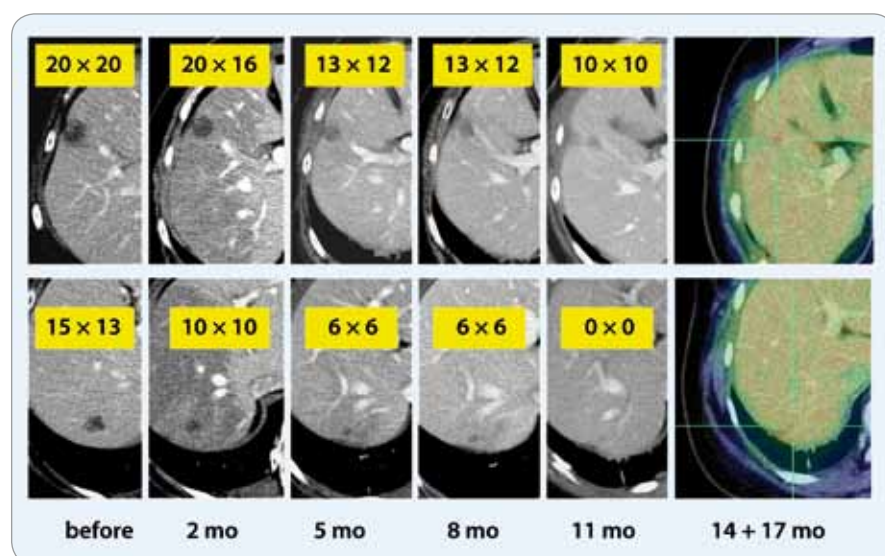


Fig. 2. 62-year old female with 2 liver metastases; both metastases shrinkage and no PET/CT activity after 12 months. mo – months, size of metastases – given in mm

were 100%, 91%, 91%, 6% and 50%, respectively. Disease progression-free survival rates at 2, 4, 6, 9 and 12 months were 82%, 82%, 64%, 50% and 50%, respectively and median follow-up was 15 months. Three patients of the total number of six who were followed up more than 12 months, were alive with no evidence of disease. There were 2 deaths according to the distant progression after 15 and 16 months after SBRT completion.

Acute grade 1 toxicity occurred in 4 of the 11 patients (mainly nausea, fatigue, fever), and there were no grade 3 or 4 acute side effects. No radiation-induced liver disease (RILD) was observed, 2 patients suffered from temporary intercostals nerve irritation, 1 from asymptomatic ascites. No other late toxicities were observed.

Conclusion

High precision focused ablative hypofractionated radiation therapy is a very effective and safe palliative treatment modality suitable for patients presenting one to three liver metastases of CRC. Due to its good common tolerability and minimal toxicity, SBRT is a suitable option for patients who cannot undergo surgery for any reason. This method showed excellent local control and also occasional long-term survivors without any serious side effects of therapy. Indeed, the optimal doses, fractionation schemes and the indications have to be established in the future by numerous prospective trials.

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