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Robotic radiosurgery for the treatment of liver metastases

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ABSTRACT

Aim: This study evaluates the toxicity and outcome in patients treated with robotic radiosurgery for liver metastases.

Background: Modern technologies allow the delivery of high doses to the liver metastases while lowering the dose to the neighboring organs at risk. Whether this dosimetric advantage translates into clinical benefit is not well known yet.

Methods and materials: A total of 9 patients with 17 liver metastases have been treated with robotic stereotactic body radiotherapy SBRT from March 2011 to December 2014. Local response to SBRT was graded by the Response Evaluation Criteria in Solid Tumors criteria to describe change in treated tumor lesion. Adverse events after SBRT were graded on a 1–5 scale according to the National Cancer Institute common terminology criteria for adverse events v4.0.

Results: Patients received either three (78%) or five (22%) fractions. Patients were treated with a mean fraction dose of 14 Gy with a range from 9 to 20 Gy. The median total radiation dose provided to patients was 45 Gy with a range of 45–60 Gy. Four out of the 17 (23.5%) treated lesions had a complete response, 9 (53%) partial response and 3 (17.6%) stable disease. With a median follow-up of 15.2 months after SBRT treatment, local control and overall survival rated were 89% and 66%, respectively. No patient experienced grade ≥3 toxicity. The most common toxicity reported was asthenia. Only two patients had nausea and diarrhea, 10 and 14 days after SBRT, respectively.

Conclusions: Robotic radiosurgery is a safe and effective local treatment option for secondary liver tumors. Further prospective studies are ongoing to determine long-term response and survival after robotic-SBRT for liver metastases.

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1. Background

The liver is the second most common site for metastatic spread of cancer, with most liver lesions caused by colorectal cancer (CRC) followed by pancreatic, breast and lung cancers.[1] Surgical resection is currently considered the standard of care, especially for those with liver metastases from colorectal cancer.[2,3] The median survival of untreated patients ranges between 6 and 18 months.[4] Since the local control of the disease may have a positive impact on both survival and quality of life, several methods to improve resectability (i.e. neo-adjuvant chemotherapy, pre-operative portal vein embolization, radiofrequency, and cryosurgery) have been investigated. However, in selected cases, alternative therapies should be considered.

In 1954, Philipps et al.[5] published the first successful palliative radiation treatment for liver metastases. Currently, non-conformal radiation therapy (RT) has a limited role in treatment of hepatic metastases since radiation-induced liver disease (RILD) has been linked to mean liver dose.[6,7] Modern RT techniques can minimize dose to normal liver with three-dimensional conformal radiation therapy or intensity-modulated radiation therapy (IMRT).[8] However, even if these new techniques allow a very precise dose delivery to the target without exceeding dose limits in the rest of the liver volume, dose limitation in the normal liver still represents a problem for dose escalation.

Liver tumors move with the respiratory cycle. This movement requires the addition of treatment margin, which increases the dose delivered to normal tissue. While it is important to limit dose to normal liver, further studies have demonstrated the important impact of dose-escalation of RT on the control of hepatic metastases from CRC.[9,10]

Stereotactic body radiotherapy (SBRT) is a technique that allows the delivery of a high dose to a tumor while sparing adjacent normal tissues. Its use in extra cranial tumors have been limited due to the inherent movement of abdominal organs and associated tumor movement that occurs during the respiratory cycle. One device that tracks tumors during respiration and automatically adjusts during patient positioning is the CyberKnife® robotic radiosurgery system (Accuray Inc., Sunnyvale, CA, USA). This system has been explained elsewhere[11–13] and basically consists of three components: a 6 MV-photon light-weight linear accelerator (LINAC), a robotic arm able to point the LINAC anywhere in space with 6 degrees of freedom, without being constrained to a conventional isocenter and a tumor tracking system. The system tracks a patient's abdominal tumor during respiration using the Synchrony® Respiratory Tracking system[14] that consists of an in-room kV imaging system, used for fiducial tracking; infrared light emitting diodes (LEDs) placed on the patient's abdomen with a wall-mounted infrared detector that allows patient's breathing monitoring, and a software that creates a mathematical model linking the tumor movement with the abdominal wall movement, so that tumor position can be predicted at all stages of the breathing cycle. With the Cyberknife® system, SBRT is delivered in the setting of real-time tracking with implanted fiducial markers combined with respiratory motion modeling to achieve submillimeter accuracy by continually detecting and correcting for tumor motion throughout treatment.

2. Aim

To assess the feasibility, safety and clinical outcome of patients with liver metastases who underwent robotic radiosurgery.

3. Methods

We evaluated all patients treated with SBRT for liver metastasis in our institution. All included patients were discussed at a multi-disciplinary tumor board which consisted of a hepatic surgeon, medical oncologist, radiation oncologist, and radiologist. Patients were staged by imaging that consisted of contrast-enhanced computerized tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography scan (PET). Patients selected for treatment with SBRT were not considered candidates for surgical resection secondary to tumor location, comorbidities, clinical presentation, or extent of disease. Patients were included irrespective of prior primary treatment, including prior treatment with chemotherapy, surgery, or radiation therapy. No patient had any background of chronic liver disease, active liver infection or prior radiotherapy to the liver. Metastatic lesions were included from any location within the liver. Patients generally were expected to have a life expectancy greater than 3 months and adequate hepatic function (bilirubin level < 2 mg/dl; albumin level > 2.5 g/dl; and serum liver enzyme concentration less than twice the upper limit of the normal range). All patients gave their written informed consents.

3.1. *Treatment description*

All patients had two to four gold fiducials markers (1 mm diameter × 5 mm longitudinal) in each lesion, placed percutaneously under CT guidance by a radiation oncologist. All fiducials were placed within or around the tumor tissue at a minimum distance between adjacent fiducials of 2 cm. An example of CT-guided placement of fiducial markers is shown in Fig. 1. No patient presented complications during the procedure. A treatment planning CT scan (exhalation) without contrast (primary study) and another one with IV contrast (secondary study), both with slice thickness of 1.25 mm, were obtained 5–7 days after fiducial placement.

Patients were simulated in the supine position, with the arms along their bodies. When needed patients were immobilized with a customized alpha-cradle. A gross tumor volume (GTV) was delineated on the CT scan (Fig. 2). Additionally, one patient underwent MRI and another PET scan for their treatment planning. Typically, a margin of at least 3–5 mm was added to the GTV to generate the clinical target volume

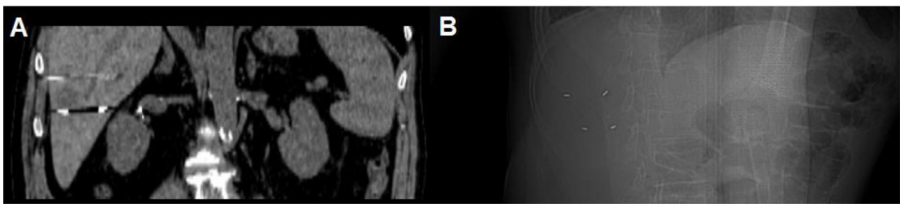

Fig. 1 – Fiducial markers placed in the liver lesion when using (A) computerized tomography scan or (B) 2-dimensional in-room X-rays.

(CTV). No additional margin was added for the planning target volume (PTV) due to the accuracy of CyberKnife® system combined with Synchrony® Respiratory Tracking system,[15] so in all cases PTV equals CTV. Adjacent critical structures were delineated.

The total dose delivered to the tumor (Table 2) and the fractionation schedules were determined by constraints regarding the adjacent normal tissues based on the recommendation published by the American Association of Physicists in medicine.[16]

All treatments were performed using the CyberKnife® system and were planned using Multiplan® treatment planning software. Radiation plans were developed using an inverse-planning methodology and were prescribed to the isodose line that provided adequate coverage of the PTV (>95%). Synchrony® Respiratory Tracking System was used to continuously track fiducial position and adjust for respiratory motion during treatment.[14]

3.2. *Follow-up*

Patients were assessed every 3 months after completion of treatment by physical exam, blood test, and imaging. CT, MRI, and/or PET scans were performed at each follow-up. Local response to SBRT was graded by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria to describe change in a treated tumor lesion.[17] This grading system has four tumor response grades: progressive disease (at least 20% increase of the lesion), stable disease, partial response (at least 30% decrease of the target lesion), and complete response (disappearance of all target lesions). Local or distal recurrent disease was also evaluated. Local recurrence to treatment was defined as tumor progression within or at the periphery of the radiation field.

Adverse events after SBRT were graded on a 1–5 scale according to the National Cancer Institute common terminology criteria for adverse events v4.0. Causes were attributed to either placement of fiducial markers or radiation induced. Overall survival and local control rates were calculated as the number of patients without having the event divided by the total number of patients, expressed as a percentage.

4. Results

A total of 9 patients with 17 liver metastases were treated from March 2011 to December 2014 in our institution with robotic stereotactic body radiotherapy SBRT. The treatment center is equipped with one Cyberknife® VSI™ system v9.6 (6 MV X-ray beam, dose rate 1000 MU/min, Multiplan® treatment planning system (TPS) v4.6). The Cyberknife® unit staff includes 2 radiation oncologists, 3 radiation therapists, 1 medical physicist and 2 administrative assistants.

Clinical characteristics of the 9 patients treated with SBRT for liver metastases prior to therapy are reported in Table 1. There were 3 males and 6 females with a median age of 65 (49–83) years at the time of SBRT. Eleven metastases were located in the right lobe and 6 in the left lobe. The median maximum diameter of the metastatic liver lesions was 23 mm (range, 7–77 mm). Five patients were treated for a solitary

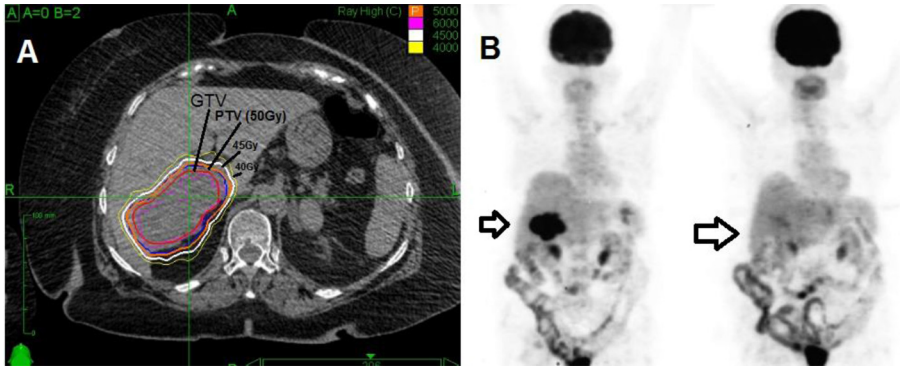

Fig. 2 – Dose distribution (A) relative to the planning target volume (PTV) for a patient treated with 50 Gy at 10 Gy/fraction and (B) the pretreatment (left) metabolic activity and the response 6 months after treatment (right).

Table 1 – Patients characteristics.

Patient	Age (years)	Gender	Primary tumor	Time to MTX (month)	Time to SBRT (month)	Location (no.)	Tumor size (mm)	Prior chemotherapy	Prior local therapy
1	69	Male	Pancreas	6	12	Right (3)	26	Yes	No
2	78	Male	Lung	7	22	Right (1)	36	No	No
3	83	Female	Colorectal	9	9	Right (1)	77	Yes	No
4	50	Female	Breast	48	6	Left (3)	12	Yes	No
						Right (2)	14		
5	60	Female	Breast	108	27	Left (1)	10	Yes	No
						Right (1)	8		
6	70	Female	Lymphoma	Sync	23	Left (1)	19	Yes	No
7	55	Female	Breast	Sync	6	Right (1)	7	Yes	No
8	49	Female	Breast	84	7	Left (1)	70	Yes	No
						Right (1)	14		
9	71	Male	Lung	7	3	Right (1)	20	Yes	No

Abbreviations: MTX: metastases; SBRT: stereotactic body radiotherapy; Sync: synchronic.

liver metastatic lesion and four patients were treated for two or more liver metastatic lesions. In addition, liver metastases in 7 patients were metachronous. Five patients were cytologically or pathologically diagnosed and four patients were diagnosed on the basis of two imaging studies, including enhanced CT, PET/CT, and MRI. The median time period from diagnosis of primary cancer to SBRT was 38.4 months (range, 6–108 months). Median time interval between diagnosis of liver metastases and SBRT was 12.7 months (range, 3–27 months). The primary tumor included 4 breast cancers, 2 lung cancers, 1 CRC, 1 pancreas, and 1 lymphoma (Richter's syndrome).

The majority of patients ($N = 8$; 89%) had undergone surgical resection of their primary tumor and chemotherapy for the treatment of metastatic disease. None had received prior liver local therapy. Two patients had stable extrahepatic disease located in the bone and retroperitoneum, respectively.

The PTV ranged from 7 to 182 cc (median 41 cc). The median prescription isodose line was 82% (range 72–88%) with a mean coverage of PTV of 95%. A mean of 161 non-isocentrics and non-coplanars beams of treatment were used (range 72–264). The mean conformity and homogeneity index was 1.13 and 1.21, respectively. SBRT treatments were delivered over a median of 5 days (3–13 days). Patients were treated with a mean fraction dose of 14 Gy with a range from 9 to 20 Gy. The median total radiation dose provided to patients was 45 Gy with a range of 45–60 Gy. Patients received either three (78%) or five (22%) fractions, being the most common regimen used either 45 Gy at 15 Gy/fraction or 50 Gy at 10 Gy/fraction. The mean biological equivalent doses ($BED = nd[1 + d/(\alpha/\beta)]$, with n being the number of fractions, d the daily single fraction dose and alpha-beta for tumor tissue of 10 Gy)[18] was 118 Gy (range 86–180 Gy). The dosimetric parameters are listed in Tables 3 and 4. None of our patients showed any elevation of their liver laboratories during follow-up. This was probably due to the low doses received by the healthy liver during treatment on account of the reduced margin needed to be added to the GTV when using a breathing tracking system.

With a median follow-up of 15.2 months after SBRT treatment (October 2015), local control and overall survival rated were 89% (8/9) and 66% (6/9), respectively. Four out of the 17 (23.5%) treated lesions had complete response, 9 (53%) partial response and 3 (17.6%) stable disease. No patient experienced grade ≥3 toxicity. The most common toxicity reported was asthenia. Only two patients had nausea and diarrhea, 10 and 14 days after SBRT, respectively.

5. Discussion

Initial reports on CyberKnife® SBRT for liver tumors (Table 5) have shown promising local control with minimal toxicity for select patients with hepatocellular (HCC) carcinoma,

Table 2 – Protocol dose constraints.

Organ at risk	3 fractions constraints	5 fractions constraints
Liver	V15 Gy < 700 cc; V15Gy < 50%	V21 Gy < 700 cc
Spinal cord	V18 Gy < 0.35 cc; V12 Gy < 1.2 cc Dmax 21 Gy	V23 Gy < 0.35 cc; V14.5 Gy < 1.2 cc Dmax 30 Gy
Stomach	V16.5 Gy < 10 cc; Dmax 22 Gy	V18 Gy < 10 cc; Dmax 32 Gy
Duodenum	V16.5 Gy < 5 cc; V11.5 Gy < 10 cc Dmax 22 Gy	V18 Gy < 5 cc; V12.5 Gy < 10 cc
Jejunum/ileum	V18 Gy < 5cc; Dmax25 Gy	V19.5 Gy < 5 cc; Dmax 35 Gy
Colon	V24 < 20 cc; Dmax 28 Gy	V25 < 20 cc; Dmax 38 Gy
Kidney	V16 Gy < 200 cc	V17.5 Gy < 200 cc

Table 3 – Dosimetric parameters.

Characteristic	N (%)
Planning studies	
Computerized tomography	7 (78)
Positron emission tomography	1 (11)
Magnetic resonance Imaging	1 (11)
Planning tumor volume (cc)	
Mean	62.4
Median	40.9
Range	7.2–181.7
Prescribed dose (Gy)	
Mean	48
Median	45
Range	45–60
Number of fractions	
Mean	3
Range	3–5
Median dose per fraction (Gy)	14
Treatment duration (days)	
Median	5
Range	3–13
BED_{10}, Gy	
Mean	117.9
Median	112.5
Range	85.5–180
Prescription isodose line (%)	
Mean	82
Median	84
Range	72–88
Conformality index	
Mean	1.13
Median	1.13
Range	1.03–1.24

Abbreviations: BED, biological equivalent doses.

metastases, and mixed populations of both HCC and metastases.[19–26]

Fumagalli et al.[20] reported one of the largest series of SBRT for patients with unresectable hepatic metastases. A total of 113 liver metastatic lesions were treated between July 2007 and June 2010. Median diameter of the lesions was 28 mm (range, 7–110 mm) and local control rates at 1 and 2 years were 84.5% and 66.1%, respectively. Two-year overall survival rate was 70% (95% CI: 55–81%). The 1 and 2-year disease-free survival rates were 27% (95% CI: 18–37%) and 10% (95% CI: 4–20%), respectively. Median duration of disease-free survival was 6.7 months (95% CI: 5.1–9.5 months). Observed toxicities included grade 1–2 acute toxicities. Only one grade 3 toxicity was reported. Our findings are consistent with the French study showing excellent outcome for one year survival and local control.

In terms of toxicity, the vast majority of reports[19–26] show a very low incidence of grade ≥3. For instance, Choron et al.[22] reported the outcome of patients with hepatic metastases treated with SBRT from 2008–2010. Thirty-three patients had 37 liver metastases treated with a median SBRT dose of 30 Gy. With a median follow-up being 8.1 months, five patients reported nausea and seven reported pain after SBRT. There were no grade 4–5 toxicities or cases of liver failure. There were not any patients that reported diarrhea or gastrointestinal distress. There was one patient who experienced an asymptomatic elevation of her liver laboratories. Wilcoxon rank sum test did not reveal significant changes in total bilirubin ($p = 0.687$), alkaline phosphatase ($p = 0.151$), or albumin ($p = 0.716$) before and after SBRT. We did not observe elevation of the liver laboratories in our series probably due to the low doses received by the healthy liver (>65% of healthy liver volume did not receive any doses above the maximum recommended). In addition, the use of the device that tracks tumors during respiration helps to achieve submillimeter accuracy by continually detecting and correcting for tumor motion throughout treatment.

Among the non-surgical therapies, radiofrequency ablation (RFA) has superseded during the last decade other ablative therapies in the treatment of colorectal liver metastases.[27] A German study[26] compared treatment efficacy and toxicity of the widely used percutaneous, CT-guided, RFA and robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. To compare the 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. 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 disease-free survival (DFS) of patients treated with RRS compared to RFA (34.4 months vs. 6.0 months; p 0.001) was showed. Therefore, there was a trend toward longer DFS in patients treated with RRS when compared to RFA.

Table 4 – Liver dose–volume parameters for all patients.

Patient	Liver volume without GTV (cc)	V15 (%)	V21 (%)	Volume (cc) of liver receiving ≤15 or ≤21 Gy (%)
1	1596	23		1224 (77)
2	1659	33		1104 (67)
3	1478		30	1039 (70)
4	1222	17		1011 (83)
5	1241	7		1155 (93)
6	1343	10		1202 (90)
7	1169	6		1097 (94)
8	1594		18	1311 (82)
9	1390	13		1204 (87)

Abbreviations: V15, liver volume receiving 15 Gy in three fractions; V21, liver volume receiving 21 Gy in five fractions.

Table 5 – Studies including Cyberknife treatment for liver metastases.

Report	Study	N	Size (range)/volume (range)	Histology	Dose (Gy)/fraction	Follow up (month)	Toxicity	Outcome
Kress et al.[16]	Retrospective	11	–/99.7 cc (21–225)	Colorectal	16–42/3–5	21	1 patient G3; no GIV-V	OS 2y: 26% LC: 80%
Fumagalli et al.[17]	Retrospective	75	2,8 cm (0.7–10)/–	70% gastrointestinal tumors	27–54/3–6	17 (14–21)	0% >GIII	LC 1y: 84% LC 2y: 66% OS 2y: 70%
Yuan et al.[18]	Retrospective	57	–/27.62 cc (2.5–126)	Colorrectal (31.5%), pancreas (14%), breast (12.2%), lung (12.2%), HCC (8,7%), stomach (7.2%), renal (3.5%)	39–54/3–7	20,5 (1–64)	0% ≥GIII	LC 1y: 94% LC 2y: 90% OS 1y: 69% OS 2y: 56%
Choron RL et al.[19]	Retrospective	33	4 cm (1.6–13.9)/–	Colorectal (*N* = 13), ovarian (*N* = 4), breast (N = 4), melanoma (*N* = 3), liver (*N* = 2), lung (*N* = 2), others (*N* = 5)	22.5–42/3–5	8.1 (1.2–23.5)	Nausea (*N* = 5) pain (*N* = 7) 0% ≥GIII	OS: 11 m LC: 87%
Frączek M et al.[20]	Retrospective	13	–/40.9 cc (1.3–430)	Colorectal (*N* = 7), hepatocarcinoma (*N* = 2), stomach (*N* = 2), others (*N* = 2)	30–45/3–6	10.8 (7–16)	0% ≥GIII	LC: 72%
Lanciano et al.[21]	Retrospective	23	–/25.33 cc (0.5–316)	60% gastrointestinal tumors	36–60/3	22 (10–40)	0% ≥GIII	LC 2y: 75% (if BED >100 Gy)
Ambrosino et al.[22]	Prospective	27	–/69 cc (20–165)	Colorrectal (*N* = 11), pancreas (*N* = 10), breast (*N* = 2), other (*N* = 4)	25–60/3	13 (6–16)	3.7% GIII, 0% >GIV	LC:74%
Garcia et al.	Retrospective	9	2.3 cm (0.7–7.7)/40.9 cc (7.2–181.7)	Breast (*N* = 4), lung (*N* = 2), colorectal (*N* = 1), pancreas (*N* = 1), other (*N* = 1)	45–60/3–5	15,2 (6–28)	0% ≥GIII	LC 1y: 89% OS 1y: 66%

Abbreviations: G, grade; OS, overall survival; LC, local control; BED, biological equivalent dose.

6. Conclusions

Robotic radiosurgery is a safe and effective local treatment option for secondary liver tumors.[28] In the multidisciplinary management of malignant lesions of the liver, SBRT adds to our armamentarium of local treatment modalities as complementary or salvage therapy. The role of SBRT as primary form of therapy remains to be determined. Further prospective studies with larger number of patients are ongoing to determine long-term response and survival after SBRT for liver metastases.

Conflict of interest

None declared.

Financial disclosure

None declared.

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