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ORIGINAL ARTICLE

Multicentre results of stereotactic body radiotherapy for secondary liver tumours

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Abstract

Background: Surgical resection is the standard treatment for liver metastases, although for the majority of patients this is not possible. Stereotactic body radiotherapy (SBRT) is an alternative local-regional therapy. The purpose of this study was to evaluate the results of SBRT for secondary liver tumours from a combined multicentre database.

Methods: Variables from patients treated with SBRT from four Academic Medical Centres were entered into a common database. Local tumour control and 1-year survival rates were calculated.

Results: In total, 153 patients (91 women) 59 ± 8.4 years old with 363 metastatic liver lesions were treated with SBRT. The underlying primary tumour arose from gastrointestinal (GI), retroperitoneal and from extra-abdominal primaries in 56%, 8% and 36% of patients, respectively. Metastases, with a gross tumour volume (GTV) of 138.5 ± 126.8 cm^3, were treated with a total radiation dose of 37.5 ± 8.2 Gy in 5 ± 3 fractions. The 1-year overall survival was 51% with an overall local control rate of 62% at a mean follow-up of 25.2 ± 5.9 months. A complete tumour response was observed in 32% of patients. Grade 3–5 adverse events were noted in 3% of patients.

Conclusion: Secondary liver tumours treated with SBRT had a high rate of local control with a low incidence of adverse events.

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Introduction

Liver metastases are the most common hepatic tumour. More than 40 000 patients with liver metastases from colorectal cancer are diagnosed per year in the USA.[1] Surgical resection is the standard of treatment for selected secondary liver tumours, but less than 20% of patients are amenable to an operation due to advanced local disease or a medical condition.[2] Alternative local/regional therapies have commonly been used for palliation or in an attempt to cure.[3] Radiofrequency ablation (RFA), trans-arterial chemo-embolization (TACE) and Y^{90} embolization have encountered limitations mainly as a result of the tumour location, size, number or underlying liver dysfunction.[4–7]

Stereotactic radiosurgery (SRS) was initially developed for brain tumours with response rates above 60%.[8] It allows for a precise delivery of large doses of radiation to the tumour while sparing the surrounding normal tissues.[8,9] Further advances in stereotactic body radiotherapy (SBRT) have overcome the difficulties presented by the inherent movement of abdominal organs that occurs during the respiratory cycle. Four broad categories of respiratory control have been developed in order to deliver high doses of radiation to liver tumours: tumour motion dampening,

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respiratory gating, active breathing coordination and tumour tracking. The tracking of the tumour during the patients normal respiratory cycle is performed by: (a) an internal fluoroscopic monitoring of fiducial markers placed in or around the tumours; (b) a computer software that creates an algorithm linking the tumour movement with the chest wall movement; and (c) infra-red Light Emitting Diodes (LED) placed on the patient's chest and a wall-mounted infra-red detector which allows for the construction of a patient's breathing model. The accuracy of radiation delivery during a standard treatment was 0.3 ± 0.1 mm as measured at three different SBRT facilities.[6] An initial experience with 17 patients whom underwent SBRT for liver tumours showed high response rates with low adverse events.[4] The aim of the present study was to analyse the results of SBRT for secondary liver tumours from four academic centres with the use of two different methods to deliver SBRT under the perspective of the current literature.

Materials and methods

Patient population

Information from patients who underwent SBRT as treatment for secondary liver tumours from four Academic Medical Centres were merged into Institutional Review Board (IBR)-approved databases for analysis. Patients treated from April 2000 to September 2010 were entered. They were assessed by a multidisciplinary team formed with hepatobiliary surgeons, radiation oncologists, medical oncologists and nurse practitioners. Inclusion criteria included: (i) biopsy-proven metastatic liver malignancy, (ii) non-resectable disease and (iii) a life expectancy of at least 3 months. Limited information was available for patients with ovarian, lung and genito-urinary (GU) liver metastases due to a combination of a limited number of patients and low compliance with follow-up.

A search of current published literature was performed by the use of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) where the keywords *metastatic liver, SBRT* and *cancer treatment* were entered into the webpage engine. From 1997 to 2011, 31 articles were published. Articles were reviewed and the ones where data were presented and reported in similar format as the present report were considered in the final pooled analysis. Fourteen studies were finally included for a total of 541 patients with a similar distribution of liver metastatic malignancies when compared with the current study population.[3–5,10–20]

Stereotactic body radiation therapy (SBRT)

Although protocols differed from one Institution to another, the radiation plan for each patient at all Centers was developed, reviewed and approved by a surgeon, a radiation oncologist, a medical oncologist and a physicist. All patients were staged with contrast-enhanced computerized tomography (CT scan), magnetic resonance imaging (MRI) and/or positron emission tomography scan (PET). Regional lymph nodes were not included in the treatment plan. Subsequent imaging for treatment plan development and contouring was obtained as needed and according to institution guidelines and payer approval. Three to six fiducial markers were placed (3 to 5 mm in size) under different techniques: percutaneously under CT guidance, using laparoscopic techniques or at open surgery. Markers were inserted within or around the tumour tissue and at a minimum distance of 2 cm between adjacent markers.[7,8,10] One week was provided between markers placement and imaging studies for SBRT treatment planning.

The treatment delivery technique varied by institution mainly because of the type of equipment available: (i) two centres had treatment delivered with the CyberKnife® system, providing therapy in several fractions on consecutive weekdays. In brief, subject's imaging was imported into the Multiplan™ treatment planning system version 2.05 (Accuray Inc., Sunnyvale, CA, USA) and digitally fused in order to contour the gross tumour volume (GTV). An additional margin of about 3–5 mm was added in order to obtain the planning target volume (PTV). Patients were immobilized for imaging using a custom Alpha Cradle (Smithers Medical Products, Akron, OH, USA) and fitted with a synchrony vest. 100 to 300 6 MV X-ray beams were used for each plan. SBRT was performed under real-time kilovoltage camera fiducial tracking and real-time respiratory motion modelling using a separate Synchrony® Respiratory Tracking System (Accuray Inc.). This system is equipped with a robotic arm which can point the linear accelerator from up to 1600 non-coplanar targeting angles. (ii) The other two centres performed treatment on their patients using the Novalis ExacTrac® patient positioning system (BrainLAB AG, Heimstetten, Germany). This consists of a vacuum cushion bag for positioning and external body fiducial markers monitor from two ceiling-mounted infrared cameras. Respiratory gating was obtained using a relaxed, end-expiratory breath-hold technique. Treatment planning was performed using the BrainScan® treatment planning system (BrainLAB). The GTV was contoured on CT scans fused with MRI and/or PET scans, when available. The PTV was generated with an expansion of the GTV of 10 mm in the craniocaudal direction and 7 mm in other directions. SBRT was delivered with the Novalis™ linear accelerator system using conformal arcs or multiple fixed coplanar beams. The average treatment time was 2 h per fraction.

Assessment of treatment response and tumour recurrence

Follow-up of patients included a full physical examination, blood work and imaging studies (CT, MRI and/or PET scans). They were scheduled every 3 months for 2 years after SBRT. Patients who survived >2 years were assessed every 3 to 6 months depending upon clinical needs. The maximum tumour diameter and the GTV were measured exporting the images to the SBRT planning system (Multiplan or BrainLAB). Local control was defined as an absence of radiological progression of the treated lesion. A tumour response to SBRT was graded using RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors version 1.1).[21,22] This system has four tumour response grades: a complete

response (CR) or disappearance of all target lesions; a partial response (PR) when at least a 30% decrease in the sum of the longest diameter (LD) of target lesions was observed, taking as reference the baseline sum of the LD; progressive disease (PD) was granted when at least a 20% increase in the sum of the LD of target lesions was noted, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD): neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD, taking as reference the smallest sum LD at the time treatment started.[20] In order to further evaluate partial tumour responses, a previously published grading system was used based on tumour volume.[4] Partial response grade I: at least a 10% decrease in tumour volume but less than 30% from the original tumour volume; Partial response grade II: a decrease in volume ≥30% but <50% from the original tumour volume; and Partial response grade III: a decrease in tumour volume ≥50%. When there was no change in tumour volume but vanishing of the enhancement or PET activity resolved, it was scored as a grade III partial response.

Recurrences were also graded according to a previously published scale.[4] Grade 1: local recurrence (tumour progression within or at the periphery of the radiation field manifested as increased size or enhancement) with two subgroups, Grade 1a: 1 local recurrence and Grade 1b: > 1 local recurrences; Grade 2: distant intra-abdominal recurrence (new tumour >3 cm away from the radiation field or in another organ); Grade 3: distant extra-abdominal recurrence; and Grade 4: a combination of local and distant recurrences.

Adverse events

Adverse events after SBRT were graded on a 1–5 scale according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0, http://www.cancer.gov). Causes were attributed to surgery, the placement of fiducial markers, chemotherapy or radiation therapy or related to medical comorbidities.

Statistical analysis

A common database of clinical, imaging and SBRT variables for each patient was created from four medical centres. Subjects and tumour characteristics were expressed in mean ± standard deviation. Parametric variables were compared by ANOVA and when differences were detected multiple comparisons between two groups were performed using Student's *t*-test. Non-parametric variables, i.e. the occurrence of adverse events were compared between groups using chi-square methods. A probability < 0.05 was defined as statistically significant using JMP Statistical Discovery Software version 9.0 (SAS Institute, Cary, NC, USA). Radiological evaluation of the tumour response was calculated at 3 months post-treatment follow-up and the 1-year overall survival (OS) rate was calculated from the date of SBRT to the day of last follow-up or death.

Results

The cohort of patients consisted of 153 patients (91 = 59% female) with at a mean age of 59 ± 8.4 years. A total of 363 tumours were treated. Patient demographics, characteristics of their malignant condition and SBRT treatment parameters are summarized in Table 1. The number of treated lesions per patient was 2.5 ± 1.1 with a gross tumour volume (GTV) of 138.5 ± 126.8 cm^3 and a mean follow-up of 25.2 ± 5.9 months. The 1-year overall survival was 51% whereas the overall local control rate was 62%. Using RECIST criteria, 46 subjects had a complete response (32%), 38 individuals had a partial response (27%), 36 remained stable (26%) and 19 subjects (13%) showed progression during follow-up (patients with ovarian malignancy were not included). Ninety-two patients (60%) underwent chemotherapy prior to SBRT treatment, 58 resections (38%), 34 RFA (22%) and 15 patients TACE (10%). The total radiation dose delivered was 37.5 ± 8.2 Gy in 5 ± 3 consecutive fractions at an isodose line of 70%. Grade 1 and Grade 2 adverse events from SBRT were noted in 58 patients (38%) whereas Grade 3 & 4 toxicity was observed in five subjects (3%). No deaths were recorded from SBRT treatment.

Eighty-five patients (56%) had metastases from the GI source. The most common was from colorectal primary ($n = 53$ or 70%) followed by pancreatic adenocarcinoma ($n = 16$ or 21%) and few from other GI sources (GIST, $n = 6$ or 8%). There were no statistical significant differences in the age or number of treated lesions per patient when colorectal was compared with pancreatic primary ($P > 0.05$, *t*-test, Table 1). Treated liver metastases from colorectal cancer were significantly larger when compared with liver metastases from pancreatic tumours [182 versus 60 cm^3, (means provided), respectively, $P < 0.05$, *t*-test]. In addition, the method used to deliver a prescribed radiation dose to the tumour (respiratory gating versus tumour tracking) had no effect on the tumour response ($P > 0.05$, chi-square, Table 2). Recurrence patterns of liver metastases were different. Patients with liver metastases from a colorectal and pancreatic origin tend to have recurrences both in field as well as distant from the treatment site. The main pattern of recurrence for patients with liver metastases from GIST was in the field. Local failures to SBRT (recurrence Grade 1A) were noted mainly for liver metastases from adenocarcinoma of the pancreas (Table 1). Secondary liver tumours from an abdominal primary other than the GI tract suffered small numbers (Table 1). A complete or partial tumour response was observed in 43 patients (65%) with other than GI-treated tumours.

Overall adverse events were noted in 63 of the treated patients (41%). No difference was noted in adverse events on patients treated for colorectal metastases by the method used (respiratory gating versus tumour tracking) even although the number of fractions used to deliver the prescribed radiation dose was significantly different (10 versus 3 fractions, $P < 0.05$ by *t*-test, Table 2). Grade 1 adverse events, including fatigue and nausea, were

Table 1 Demographics, baseline characteristics and response of tumours treated using stereotactic body radiation therapy (SBRT) from patients with non-resectable liver disease from four Academic Medical Centres

	From abdominal primary			From retroperitoneal primary			From extra-abdominal primary		
	Colorectal	Pancreas	Other GI	Carcinoid	Gen-urinary	Sarcoma	Breast	Ovarian	Lung
Number of patients	53	16	6	10	7	6	32	12	11
Age (years)									
*mean (range)	66 (62–73)	64 (41–70)	59 (51–63)	48 (23–64)	64 (61–67)	59 (42–70)	56 (53–61)	70 (68–71)	65 (60–68)
Gender									
Male/female	1.7:1	1:1	0.75:1	1.25:1	0.75:1	1.1:1	0.75:1	0.75:1	0.75:1
Lesions per patients	1.6 (1–6)	1.2 (1–3)	1.1 (1–3)	2.4 (1–3)	2.9 (1–3)	2.8 (2–3)	3.3 (1–5)	2.5 (1–4)	1.7 (1–4)
Median follow-up (months)	17	14	33	11	92	21	13	21	19
One-year survival (%)	56	75	50	100	75	0	67	50	77
Overall local control (%)	60	39	81	70	38	84	62	NA	58
Tumour volume									
GTV cm^3 (mean and range)	182 (60–581)	60 (22–476)	61 (38–215)	141 (8–301)	184 (41–326)	266 (42–340)	44 (10–85)	71 (32–116)	107 (63–206)
SBRT									
Total dose (Gy)	41	36	27	39.2	43	31.3	38	30	46.5
RECIST, number (%)									
CR	12 (23)	0	6 (100)	7 (70)	5 (71)	4 (66)	9 (29)	NA	4 (40)
PR	20 (38)	4 (25)	0	0	0	1 (17)	11 (35)	NA	2 (20)
SD	15 (28)	10 (62)	0	2 (20)	0	1 (17)	8 (25)	NA	0
PD	6 (11)	2 (13)	0	1 (10)	2 (29)	0	4 (11)	NA	4 (40)
Partial tumour response									
Grade 1	10 (20)	3 (19)	0	NA	NA	NA	NA	NA	NA
Grade 2	9 (16)	1 (6)	0	NA	NA	NA	NA	NA	NA
Grade 3	1 (2)	0	0	NA	NA	NA	NA	NA	NA
Tumour recurrence									
Grade 1a	0	1 (6)	0	NA	NA	NA	NA	NA	NA
Grade 1b	8 (15)	4 (25)	6 (100)	NA	NA	NA	NA	NA	NA
Grade 2	3 (6)	6 (40)	0	NA	NA	NA	NA	NA	NA
Grade 3	5 (9)	0	0	NA	NA	NA	NA	NA	NA
Grade 4	8 (15)	9 (56)	0	NA	NA	NA	NA	NA	NA

GTV, gross tumour volume; NA, not applicable.
'Other GI' refers to other gastrointestinal tumours excluding colorectal, pancreatic and carcinoid tumours.

observed in 55 subjects (36%) whereas Grade 2 and Grade 3 toxicities were recorded in 3 (1.9%) and 5 (3.2%) patients, respectively (Table 3). No Grade 4/5 adverse events were noted.

Discussion

The present series report a multicentre experience with the use of SBRT for non-resectable liver metastases from GI, non-GI and extra-abdominal primaries. One hundred and fifty-three patients with 363 metastatic liver lesions were treated with SBRT. There were no differences in the tumour response for colorectal metastases treated by SBRT using two different methods of radiation delivery (respiratory gating versus tumour tracking). The 1-year overall survival was 51% whereas the overall local control was 62% at a mean follow-up of 25.2 ± 5.9 months with an overall rate of Grade 2–3 adverse events of 5.1% and no Grade 4–5 toxicity.

To the best of the authors' knowledge, the present study is the largest experience with SBRT for liver metastases to date. It showed SBRT as a safe technique for the precise delivery of radiation to liver tumours minimizing parenchymal toxicity. It supports further studies of SBRT as an alternative loco-regional treatment modality for liver metastasis. Prospective trials, including phase II and III studies, are in need to fully evaluate both the

Table 2 Response of liver metastases from colorectal primary to stereotactic body radiation therapy (SBRT) using a radiation delivery method to the tumour

	Radiation delivery method		*P*-value
	RG	TT	
Number of patients	37	16	
Characteristics of lesions			
Number per patient (M ± STDV)	1.7 ± 1.4	1.5 ± 0.8	NS
Tumour gross volume (cc)	217 ± 181	183 ± 172	NS
Total +partial response (%)	58	61	NS
Total radiation dose (Gy)	46 ± 9	39 ± 9	NS
Number of fractions	10 ± 2	3 ± 3	<0.05
Grade 3–5 adverse events (%)	0	0	

RG, respiratory gating; TT, tumour tracking; NS, no significant.

Table 3 Adverse events reported in 153 patients with non-resectable secondary liver tumours treated by stereotactic body radiation therapy (SBRT) (A) from four Academic Centres and (B) from the published literature

(A) Academic Centres (*n* = 153)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Primary tumour, *n* (%)					
Colorectal	32 (21)	0	0	0	0
Pancreas	8 (5.2)	0	0	0	0
Other GI	1 (0.06)	2 (1.3)	0	0	0
Carcinoid	5 (3.2)	0	5 (3.2)	0	0
Breast	9 (5.8)	1 (0.06)	0	0	0
Sarcoma	0	0	0	0	0
Total (%)	55 (36)	3 (1.9)	5 (3.2)	0	0
(B) Published literature (*n* = 541)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Primary tumour (%)					
Colorectal	21	9	6	0.2	0
Pancreas	68	27	0	0	0
Other GI	29	2	3	0	0
Carcinoid	27	9	0	0	0
Breast	26	15	6	0.9	1.3
Total as mean (%)	34	12	3	0.22	0.3

role of SBRT as part of a multimodality primary approach and its long-term efficacy.[2] Patients with colorectal liver metastases amenable to a resection have 5-year survival rates between 30% to 60%. Nevertheless, recurrences are frequent and in spite of advances in chemotherapy the 5-year survival of patients with recurrences is less than 5%.[16,23–25] The current series and the published data have shown a high local control rate for liver colorectal metastases treated with SBRT[20,26,27] even although treated lesions in the present series were significantly larger (182 versus 44 cm^3, $P < 0.05$, *t*-test). In the present study, 53 patients with colorectal liver metastases had a local control rate of 60% with a 1-year survival rate of 56%. These results are concordant with a 42% local control rate and 73% 1-year survival of 239 patients in the literature[3–6,10–12,15,16,20] (Table 4). The treatment of liver metastases from pancreatic cancer is controversial. Patients tend to have a tendency for systemic involvement and thus an overall poor prognosis. Low numbers of patients in this group preclude further meaningful analysis. While patients with liver metastases from colorectal and pancreatic primaries tend to recur both in the field and systemically, those with liver metastases from GIST had in field recurrences. Local failures to SBRT (recurrence Grade 1A) were noted mainly for adenocarcinoma of the pancreas. Recurrence patterns for specific tumours may help authors to develop protocols that optimize long-term results after SBRT treatment.

Liver metastases develop in more than half of the patients with stage IV breast cancer.[29] Out of all the patients with metastases to

Table 4 Demographics, baseline characteristics and response of tumours treated by stereotactic body radiation therapy (SBRT) from patients with non-resectable liver disease from the published literature

	From abdominal primary			From retroperitoneal primary			From extra-abdominal primary		
	Colorectal	Pancreas	Other GI	Carcinoid	Gen-urinary	Sarcoma	Breast	Ovarian	Lung
Number of patients	239	21	9	20	11	130	62	13	36
Age (years)									
Mean (range)	61 (55–72)	58 (55–60)	61 (55–70)	60 (60–65)	55 (60–65)	60 (55–60)	58 (55–60)	58 (55–64)	57 (55–60)
Gender									
Male/female	1.4:1	0.9:1	1:1	0.75:1	NR	1.1:1	0.75:1	0.75:1	0.75:1
Lesions per patients	1.5	NR	NR	1.5	NR	NR	3.3	NR	NR
Median follow-up (months)	16	12	14	14	10	16	14	12	14
One-year survival (%)	73	69	61	77	74	61	64	73.3	81
Overall local control (%)	42	77	76	81	81	76	NR	NR	85
Tumour volume									
GTV in cc (mean & range)	44 (10–252)	23 (10–386)	23 (10–229)	37 (22–46)	23 (10–46)	23 (10–229)	20 (10–386)	37 (18–386)	23 (10–386)
SBRT									
Total dose (Gy)	40	32	39	34.4	32.3	39.3	36.3	35.7	37.4
RECIST (%)									
CR	50 (21)	4 (18)	3 (35)	6 (33)	4 (36)	46 (35)	NR	NR	NR
PR	100 (42)	5 (25)	4 (44)	9 (45)	4 (36)	52 (40)	NR	NR	NR
SD	45 (19)	4 (18)	1 (11)	0	3 (27)	8 (6)	NR	NR	NR
PD	41 (17)	0	1 (11)	4 (22)	0	24 (18)	NR	NR	NR

GTV, gross tumour volume; NR, not reported.
'Other GI' refers to other gastrointestinal tumours excluding colorectal, pancreatic and carcinoid tumours.

the liver, 5% will have isolated liver involvement. Even with systemic chemotherapy, the median survival for those patients with liver exclusive or limited extra-hepatic disease is 19 to 26 months.[29] Hormonal therapy is of limited use because breast tumours that metastasize to the liver typically are hormone receptor negative.[29] After a resection, if feasible, the median survival is 27 to 57 months.[30] SBRT has also been used as treatment modality for breast metastases to the liver.[31] In the present review of the literature, 62 patients were identified as having been treated with SBRT with a 1-year survival rate of 64%[3–5,10–12,15,16,26] (Table 4). Within the current series, treated patients with breast liver metastases ($n = 32$) had a 1-year survival rate of 67% and a local tumour control rate of 62%. Other secondary liver tumours such as GU tumours had a significantly lower tumour response to SBRT when compared with the published series[5,10–12] (38% versus 81%, $P < 0.05$, t-test). This discrepancy may be as a result of a longer follow-up in the current series (92 versus 9.6 months, means provided, respectively) and larger GTV's (184 versus 23 cm^3, means provided, respectively) at a similar delivered radiation dose. The 1-year survival rate of patients with liver metastases from sarcoma was null in this study and 61% in the literature[3,10–16] (Table 4). This difference in tumour response may be explained by a more advanced stage of the disease as manifested by larger GTV's in the patients from the present series (266 versus 23 cm^3, means provided, respectively).

Overall adverse events were noted in 41% ($n = 58$) of treated patients (Table 3). Most of the recorded adverse events in the present study were Grade 1 including nausea and transient fatigue, rates comparable with the rates observed by others (Table 3). Grade 4 and 5 toxicities were rare and reported in <1% in the present series and the reported literature.[3–5,10–20] One death was observed from liver failure 7 weeks after SBRT in a patient who received greater than 10 Gy to 60% of his liver.[28] Another patient was found to have liver fibrosis, portal hypertension and bleeding from oesophageal varices after treatment with SBRT of two liver metastases close to the liver hilum.[12]

The presented descriptive series should be interpreted in the light of its relative small numbers. Patients were managed in a multidisciplinary and multi-modality approach under IRB-approved protocols. The present study describes the largest series of patients with metastatic liver tumours treated with SBRT, in whom 1-year survival was 51% with low toxicity. Future studies are required to better define the role of SBRT for the treatment of liver metastases.

Conflicts of interest

None declared.

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