Image-guided Robotic Stereotactic Radiosurgery for Unresectable Liver Metastases: Preliminary Results*

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Abstract. *The aim of this study was to evaluate the usefulness of image-guided robotic stereotactic radiosurgery for the local control of unresectable liver metastases from colorectal and non-colorectal cancer. Twenty-seven consecutive patients (median age 62 years, range 47-80 years) with liver metastases considered unsuitable for surgery were enrolled in the study. The diagnosis was colorectal cancer liver metastasis in 11 (41%) and other secondary malignancies in 16 (59%) patients. The patients were treated with 25 to 60 Gy (median 36 Gy) delivered in 3 consecutive fractions, and the isodose value covering the planning target volume was 80% of the prescribed dose. Overall, the mean tumour volume was 81.6±35.9 ml. Inhibition of growth or a reduction in size was obtained in 20 (74.1%) patients: 7 with complete response and 13 with partial response. There was a local complete response with other single lesions appearing in 3 (11.1%) patients and progressive disease in 4 (14.8%). The median post-treatment volume of the tumour was 24 ml (range 0-54 ml) among the responders. Mild or moderate transient hepatic dysfunction was evident in 9 patients and minor complications in five. Two patients with progressive disease died of liver failure. In conclusion, in patients with liver metastases unsuitable for surgery, stereotactic radiosurgery achieves high rates of local disease control, representing an acceptable alternative therapy, but should be further studied in larger series.*

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Most patients with liver metastases from solid tumours respond poorly to all forms of treatment, and surgical resection is currently considered the standard of care, especially for those with liver metastases from colorectal cancer (1, 2). The median survival of untreated patients ranges between 6 and 18 months (3, 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 embolisation, radiofrequency, cryosurgery) have been investigated. However, in selected cases, alternative therapies should be considered. In several reports, sterotactic body radiotherapy for the treatment of patients with cancer and metastatic disease has shown high control rates, with a two-year actuarial survival rate of about 30% and minimum toxicity (5, 6). The aim of this preliminary study was to evaluate the usefulness of CyberKnife® (Accuray Inc., Sunnyvale, CA, USA) image-guided robotic stereotactic radiosurgery for the local control of unresectable liver metastases from colorectal and non-colorectal cancer.

Patients and Methods

Twenty-seven consecutive patients with liver metastases confirmed by ultrasound (US)- or computed tomography (CT)-guided biopsy, or US-guided fine-needle aspiration cytology, discussed in a tumour board and considered unsuitable for surgery, were prospectively enrolled in the study. All the patients underwent fluorine-18 2-deoxy-2-fluoro-D-glucose (18-FDG) positron-emission tomography-

Table I. *Inclusion criteria*.

Patients	Laboratory data	CT scan findings
Age between 40 and 80 years	Total bilirubin <50 μmol/l	No extrahepatic disease
Life expectancy >3 months	Albumin >2.5 g/dl	Tumour diameter <6 cm
KPF=1-2	PT >70%	Number of lesions ≤4
No chemotherapy during the last 30 days	ALT <150 U/l	Estimated residual liver volume ≥700 ml
	AST <150 U/l	

CT scan=contrast-enhanced computed tomography scanning, KPF=Karnofsky performance score, ALT=alanine-aminotransferase, AST=aspartate-aminotransferase, PT=prothrombin time.

CT scan (PET-CT) to rule out extrahepatic metastasis. There were 14 men and 13 women, with an overall median age of 62 years (range 47-80 years). The diagnosis was colorectal cancer liver metastasis in 11 (41%, Group A), and other secondary malignancies in 16 (59%, Group B) patients. In Group B, the primary site of cancer was the pancreas in ten, breast in two, and gallbladder, lung, ovaries and stomach in one patient each. No patient had any background of chronic liver disease, active liver infection or prior radiotherapy to the liver. All gave written informed consent in accordance with institutional review board approval. As suggested by Schefter *et al*. (7), eligible patients had one to three liver metastases, a greatest tumour diameter less than 6 cm, and adequate liver function. The inclusion criteria are reported in Table I. As a measure of performance status, the Karnofsky performance score (KPF) was used: 1=ambulatory with no deficit, 2=ambulatory with a limp, 3=use of a cane or walker, 4=wheelchair requirement.

Pre-treatment study. Liver volumetry was evaluated on computer models derived from CT angioportograms of reference patients with normal liver function, and relative residual liver volume (RLV) calculation was obtained relating residual to total functional liver volume (8). Pre-treatment diagnostic CT images and PET-CT images were fused to allow accurate identification of the location of the gross tumour volume (GTV) during treatment (7). As previously reported, planning target volume (PTV) was defined as the envelope of two clinical target volumes delineated in two CT data sets acquired at the end of inspiration and expiration, plus a uniform 5-mm margin (9). To create the PTV for patients who were treated using respiratory control, the GTV was expanded by a minimum 5-mm radial margin and 10-mm craniocaudal margin and considered identical to the clinical target volume (7). Treatment planning and the liver volume exposed to CyberKnife® was calculated by a volumetric CT scan and expressed as a fraction of the whole organ volume. Regional control was evaluated by volume mass changes as detected by CT scan.

The CyberKnife® radiosurgery system. The treatments were performed using the Cyber-Knife®, a robotic image-guided whole-body radiosurgical system, equipped with the Synchrony® system (Accuray Inc.), that allowed the respiratory motion tracking during irradiation (10, 11). Synchrony requires the positioning of fiducial markers (gold seeds 3×0.8 mm) inside or near the treatment target. Motion tracking is performed by means of correlation with external optical markers that can be tracked in real time. This capability allowed reduction of the PTV, with significant sparing of healthy tissues around the lesion. The fiducial markers were implanted percutaneously using a US-guided procedure, 15-20 days before the acquisition of the CT scan used for planning. This time interval was required to avoid early fiducial displacement or migration that may occur after the procedure and interfere with the following treatment. The PTV and organs at risk were delineated on the CT scan, and the system automatically performed an optimization of beam directions and beam weight in order to maximize the dose delivered to the target, minimizing the dose delivered to the organs at risk. The patients wore a treatment jacket on which the optical markers were fixed. Any displacement of the patient during treatment was detected by either internal or external fiducial markers. In the case of small movements (within ± 20 mm), the robot adjusted its system of coordinates in order to track patient movement. In the case of larger displacement, a stop signal was generated and the treatment was interrupted. All the patients were treated with 25 to 60 Gy (median 36 Gy) in 3 consecutive fractions on day 1, 2 and 3, and the isodose value covering the PTV was 80% of the prescribed dose. Every treatment took no more than 15 minutes (9).

Definitions and statistical analysis. Local complete response was defined as complete remission and stable disease, measured by repeated CT scans after 6 weeks and at 3 month intervals, while toxicity was evaluated according to the suggestions of Wulf *et al*. (5). The definition of post-treatment hepatic dysfunction was based on total bilirubin, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), and lactate serum levels, prothrombin time and signs of encephalopathy (8). The reported data are in part expressed as mean±standard deviation (SD). Comparisons between groups were performed using Student's *t*-test, when required. The differences were considered significant at a p-value <0.05.

Results

Overall, the tumour volume ranged from 20 to 165 ml (median 69 ml), and between 20-165 and 24-130 ml in Groups A and B, respectively. The age of the patients, number of lesions, tumour volume, and total dose received did not differed significantly (p=NS) between the groups (Table II). The post-treatment median follow-up was 13 months (range 6-16 months). During this period no patients underwent chemotherapy or any other tumour-related treatments. Inhibition of growth or a reduction in size were obtained in 20 (74.1%) patients (Group A=7, Group B=13): 7 with

Table II. *Differences between groups. Mean ± standard deviation (TV=tumour volume).*

	Age (years)	No. of lesions	Pre-treatment TV (ml)	Dose received (cGy)	Post-treatment TV (ml)
Overall	62.0±7.2	1.8±0.9	81.6±35.9	3629.6±773.0	36.2±44.1
Group A	63.4±7.0	1.7±1.0	81.4±44.6	3554.5±672.8	42.6±62.1
Group B	61.1±7.4	1.8±0.8	82.3±29.6	3750.0±834.3	31.7±27.4
p-Value	0.425	0.775	0.950	0.523	0.539

complete response and 13 with partial response. There was a local complete response with other single lesions appearing in 3 (11.1%) patients and progressive disease in 4 (14.8%). Recurrent disease was observed from 6 to 8 months later and all the new lesions were successfully retreated with 45-50 Gy. Overall, the median post-treatment volume of the tumour was 24 ml, ranging from zero to 54 ml among the responders (N=20). In this subgroup, the pre- and post-treatment tumour volumes were 80.1±35.5 and 20.6±18.0 ml, respectively ($p<0.001$), with an overall reduction rate of 75.3%. Crude local control was 74%. No relationship (p=NS) was found between age, tumour volume, irradiated volume, or dose received and post-treatment tumour volume. No major toxic events were observed. Mild or moderate transient hepatic dysfunction were evident in 4 (36.4%) and 5 (31.2%) patients of Group, A and B, respectively. Pleural effusions were found in two (7.4%), and partial portal vein thrombosis, pulmonary embolism and upper gastrointestinal tract bleeding in one (3.7%) patient each. Two patients with progressive disease died during follow-up. Both developed liver failure, in one associated with sepsis.

Discussion

The survival of untreated patients with liver metastases from solid tumours is very poor and reported overall 5-year survival ranges from 20% to 50% when surgical resection is feasible (12, 14). Unfortunately, due to poor hepatic reserve, the bad general condition of the patients, and multicentric or extrahepatic sites of tumours, only a limited number of patients are amendable for surgery (15, 16). Neo-adjuvant chemotherapy may improve both quality of life and survival and downstage liver disease, and should give the possibility of obtaining long-term survival, in selected cases (17, 18). Similar results are obtained with a preoperative portal vein embolisation, while both cryotherapy and radiofrequency ablation are limited by the size of the tumour, which should not exceed 3 cm (4, 19, 20). Moreover, the local recurrence rate is high, and randomised trials are needed, until genomic markers of the aggressiveness of tumours are better understood (14, 21). Recently, image-guided radiotherapy systems with an on-board X-ray source for cone-beam volumetric CT acquisition were introduced into clinical practice for non-small cell lung cancer and lung metastases (9). However, optimum values in the treatment of these patients are not well established, and variable doses and number of fractions have been applied, depending on different target volumes and various proximities of normal tissues (9, 22). The CyberKnife® is a frameless, image-guided robotic radiosurgical system that can deliver radiation precisely to virtually any body site with submillimetric accuracy (23, 24). Phantom dosimetric studies and experimental studies showed that the pathophysiological mechanisms of radiation-induced normal tissue damage are similar for biologically equivalent doses of radiotherapy (25, 26). Image guidance reduces residual systematic and random set-up errors, individualizing the radiotherapy strategy (27). Using stereotactic radiosurgery, the one-year local control ranged between 76% and 86%, and no Grade 3 or higher acute or late toxicity from treatment were reported (5, 16, 28). Also in the present patients, who received 25-60 Gy doses, no severe acute or late toxicity was observed. Herfarth *et al*. (29), who administered single-dose stereotactic radiation therapy to liver malignancies, safely escalated the dose from 14 to 26 Gy, while Schefter *et al*. (7) showed that it was safe to deliver 60 Gy in three fractions for patients with liver metastases, suggesting that this dose regimen is predicted to yield a high rate of tumour control. A borderline correlation between dose and local control has been reported, with a high *versus* low dose as a factor predicting local control (28). In the present study, no similar relationship was found. A mathematical measurement from a 3D graphical analysis for assessing the difficulty of liver resection has recently been proposed (30). In conclusion, this promising treatment strategy, representing an acceptable alternative in patients with liver metastases unsuitable for surgery, should be further studied in larger series.

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