

## Stereotactic Radiotherapy of Hepatocellular Carcinoma: Preliminary Results

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Stereotactic radiotherapy (SRT) offers a treatment option for hepatocellular carcinoma (HCC) patients that are not eligible for surgery, embolization, chemotherapy, or radiofrequency ablation. We have evaluated the feasibility, tolerance and toxicity of SRT for 25 HCC patients who were not eligible for these other modalities. The patients (6 women and 19 men) were treated with CyberKnife stereotactic radiotherapy using respiratory motion tracking. All patients had liver cirrhosis with an Eastern Cooperative Oncology Group (ECOG) performance score of less than 2 and pre-treatment Child scores ranging from A5 to B9. A total dose of 45 Gy in three fractions of 15 Gy each was prescribed to the 80% isodose line (95% of the PTV received 45 Gy) and delivered to the target volume over 10 to 12 days. Overall the treatment was well tolerated with two Grade 3 acute toxicities and no acute Grade 4 toxicities. Late toxicity was minimal with all observed late toxicities occurring within the first six months of follow-up. Three hepatic recurrences at a distance from the target and one metastasis were observed. The actuarial 1- and 2-year local control rate was 95% (95% CI: 69–95%). At a median overall follow-up of 12.7 months (range, 1-24 months), six of the twenty-five (24%) patients have died. Overall actuarial survival at 1- and 2-years was 79% (95% CI: 52–92%) and 52% (95% CI: 19–78%), respectively. Our results suggest promising therapeutic efficacy and good clinical tolerance to CyberKnife SRT treatment for HCC patients not eligible for other treatment modalities.

Key words: Stereotactic radiation therapy; Hepatocellular carcinoma.

### Introduction

Hepatocellular carcinoma (HCC) primarily affects patients with chronic liver disease. While the underlying cause of the liver disease varies by geographic distribution, patients at highest risk are those with cirrhosis secondary to alcoholism, viral hepatitis B or C (1), and genetic factors (hemochromatosis). Indeed, 80-90% of HCC patients have cirrhosis (2). Paradoxically, improvement in treatment of cirrhosis, results in an increased life expectancy but may also allow time for HCC to develop. A decade ago the leading causes of death in cirrhotic patients were digestive haemorrhage and bacterial infections (3). Nowadays, HCC is the leading cause of death in cirrhotic patients (4). The annual incidence of HCC in cirrhotic patients is estimated to range from 2-8%, with a cumulative incidence at 5-years of 15-20% (5).

While surgical resection offers 5-year survival rates of 30-60%, only 10-30% of HCC patients are eligible for surgery (6). Other therapeutic options for HCC treatment are liver transplantation (7), percutaneous alcohol ablation (8), transarterial chemoembolization (TACE) (9), radiofrequency ablation (RFA) (10) and radiotherapy (11). Each of these modalities can be performed alone or in combination.

**C. Louis, M.D.<sup>1,2</sup>**  
**S. Dewas, M.D.<sup>2</sup>**  
**X. Mirabel, M.D.<sup>2,3</sup>**  
**T. Lacornerie, Ph.D.<sup>2</sup>**  
**A. Adenis, M.D.<sup>3</sup>**  
**F. Bonodeau, M.D.<sup>4</sup>**  
**E. Lartigau, M.D.<sup>2</sup>**

<sup>1</sup>Department of Radiation Therapy  
Liège, University Hospital  
Domaine Universitaire Sart Tilman,  
B34 4000 Liège1, Belgium

<sup>2</sup>Academic Radiation Oncology  
Department

<sup>3</sup>Gastrointestinal Oncology Department

<sup>4</sup>Medical Imaging Department Centre  
Oscar Lambret Service de Radiothérapie  
3 rue Frédéric Combemale BP 307  
59020 Lille Cedex – France

Corresponding Author:  
Xavier Mirabel, M.D.  
Email: x-mirabel@o-lambret.fr

Most of these approaches, however, are primarily local ablative therapies that are typically restricted to small lesions.

Stereotactic radiotherapy (SRT), also known as radiosurgery, was initiated in the 1950s by neurosurgeons and radiation oncologists for intracranial targets. In recent years, important progress in the fields of image guided radiotherapy, computer science and robotics allowed indications to extracranial targets. The advantage of SRT is delivery of a high dose of radiation, in a single session (radiosurgery) or a limited number of sessions (hypofractionation), to a limited volume of tissue while sparing surrounding critical structures and healthy tissue (12, 14). This is made possible by very precise methods of target localization and positioning and by dose distribution based on convergence of multiple small beams.

Stereotactic radiotherapy offers a treatment option for HCC patients who are not eligible for surgery, embolization, chemotherapy, or radiofrequency ablation. Blomgren *et al.*, were the first to perform extracranial radiotherapy in 1995 when they treated hepatocarcinoma (20 tumors, 11 patients) and hepatic metastases (21 tumors, 17 patients) with treatment doses ranging from 15 Gy to 45 Gy in 1 to 5 fractions (15, 16). The majority of patients responded to the treatment. Shortly thereafter, in a phase I/II study, Herfarth *et al.*, treated 37 patients with 56 metastases and 4 primary tumors with a single dose ranging from 14 Gy to 26 Gy (17). The treatment was well tolerated in all patients with no major side effects. Tumor control at six weeks follow-up was 98%.

Although these first published reports using SRT only included a small number of HCC patients, they demonstrated that SRT treatment was feasible and well tolerated by patients. Following these promising initial results, additional reports on the use of SRT for HCC have been published (18-24). Taking into account the treatment approaches and results obtained in these studies, we have further evaluated the feasibility, tolerance and toxicity of SRT for 25 HCC patients that were not eligible for surgery, embolization, chemotherapy, or radiofrequency ablation.

## Materials and Methods

### Patient Characteristics

Twenty-five HCC patients (6 women and 19 men) were treated with stereotactic radiotherapy using respiratory motion tracking. Patients were informed of the nature and objectives of the study; an informed consent form was signed by all patients before treatment. All patients had cirrhosis with an Eastern Cooperative Oncology Group (ECOG) performance score of less than 2 and pre-treatment Child scores ranging from A5 to B9. HCC diagnosis was made by a multidisciplinary team

experienced in the treatment of these tumors. Diagnosis was based on biopsy or a group of clinical, biological and imaging criteria according to the Barcelona criteria (5). All patients had single lesions; 9 patients received previous treatment consisting of chemoembolization (3/25), Sorafenib (1/25), surgery (3/25) or radiofrequency ablation (2/25). Detailed patient characteristics are summarized in Table I.

The indication for SRT was made by a multi-disciplinary tumor board consisting of a hepatologist, a hepatic surgeon, a radiation oncologist, a medical oncologist and a radiologist. SRT was considered after standard therapeutic options such as resection, transplantation, chemoembolization or radiofrequency ablation were ruled out. All patients had a poor prognosis as they presented with non-operable and non-resectable hepatocarcinomas including four patients with portal vein thrombosis.

### Treatment Planning and Delivery

All patients were treated with the CyberKnife® as out patients. Multiplan® treatment planning software and Synchrony® respiratory tracking (Accuray Inc, Sunnyvale, CA) were used for real-time tracking of tumor movements.

**Table I**  
Patient characteristics.

Characteristic	Value	
Patients (n)	25	
Sex (n, %)	male	19 (76%)
	female	6 (24%)
Age (yr)	mean	70
	median	69
	range	56–85
ECOG Performance status	range	0–2
Lesion size (mm)	mean	48
	median	45
	range	18–100
Cirrhosis origin (n, %)	medicinal	1 (4%)
	alcoholism	20 (80%)
	viral	1 (4%)
	genetic	3 (12%)
Previous treatment (n, %)	none	16 (64%)
	surgery	3 (12%)
	chemoembolization	3 (12%)
	Sorafenib®	1 (4%)
Child score	radiofrequency ablation	2 (8%)
	A5/A6	22 (88%)
	B7/B8/B9	3 (12%)
Okuda score	I	20 (80%)
	II	5 (20%)
BLCL score	A	12 (48%)
	B	1 (4%)
	C	7 (28%)
	NA	5 (20%)
Meld	1–16	

On average four (range, 2-6) gold seeds, called “fiducials”, measuring 0.88 mm in diameter by 5 mm in length (Ab Medica, Milan, Italy) were implanted around each lesion. A minimum of seven days after placement of the fiducial markers, treatment planning CTs were recorded in the treatment position (supine position) with the patient immobilized either in a vacuum mattress or a self-expanding foam mattress. For planning, a spiral CT without contrast and three phases of a spiral CT with contrast (arterial, portal and late phase) were acquired. Slice thickness was 2 mm. This exam was performed in partial exhale; 4D CT was not used. The gross tumor volume (GTV) included the contrast-enhancing disease visible on the partial exhale contrast-enhanced CT scan. Contouring was done on the most informative sequence being, in the majority of the cases, one of the injected phases. The clinical target volume (CTV) was defined as the GTV with a 10 mm margin in all directions within the liver (25, 26). The planning target volume (PTV) was equal to the CTV plus a 1.5 mm margin. Dose constraints for organs at risk (27) were applied as summarized in Table II. A total dose of 45 Gy in three fractions of 15 Gy each was prescribed to the 80% isodose line (95% of the PTV received 45 Gy) and delivered to the target volume over 10 to 12 days. Table III provides a detailed summary of the treatment planning parameters. Figure 1 presents a representative treatment planning image.

This retrospective single-institution, cross-sectional study was approved by our Institutional Committee on Human Research with a waiver for the requirement for written consent.

#### Patient Follow-Up

Each patient had a clinical and biological evaluation six weeks following completion of treatment. Subsequent clinical, biological and radiological follow-up occurred every three months during the first 15 months following treatment and every 6 months thereafter. At each follow-up visit, a CT-scan or MRI was obtained. The images were systematically reviewed by an expert who classified responses as partial, complete or progression based on vascularization according to the European Association for the Study of the Liver

**Table II**  
Dose constraints for organs at risk.

Organ/Critical Structure	Dose Constraint
Liver	V21<33%
Spinal cord	Dmax 22 Gy
Kidneys	V15<33%
Stomach	V21<5 cm <sup>3</sup>
Intestine	V16<5 cm <sup>3</sup> Dmax<27 Gy
Duodenum	D15<5 cm <sup>3</sup> Dmax<24 Gy

Vn - tumor volume that receives a dose of n Gy or less; Dn - dose received by n% of tumor.

**Table III**  
Stereotactic radiotherapy treatment parameters.

	mean	median	min	max
Collimator size (mm)	44	50	25	60
Implanted fiducial markers (n)	4	4	2	6
Tracked fiducial markers (n)	3	3.5	1	5
Treatment length (minutes)	104	107	23	190
Number of beams	138	150	29	233
GTV (cm <sup>3</sup> )	88	48	7	363
CTV (cm <sup>3</sup> )	171	120	44	555
PTV (cm <sup>3</sup> )	194	150	65	660

GTV – gross tumor volume; CTV – clinical target volume; PTV – planning target volume.

(EASL) criteria (28) and the Response Evaluation Criteria in Solid Tumours (RECIST) (29) Local control rates were calculated based on the EASL criteria. Toxicity was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (30). Acute toxicity was defined as those events occurring within the first three months following treatment.

#### Statistical Analysis

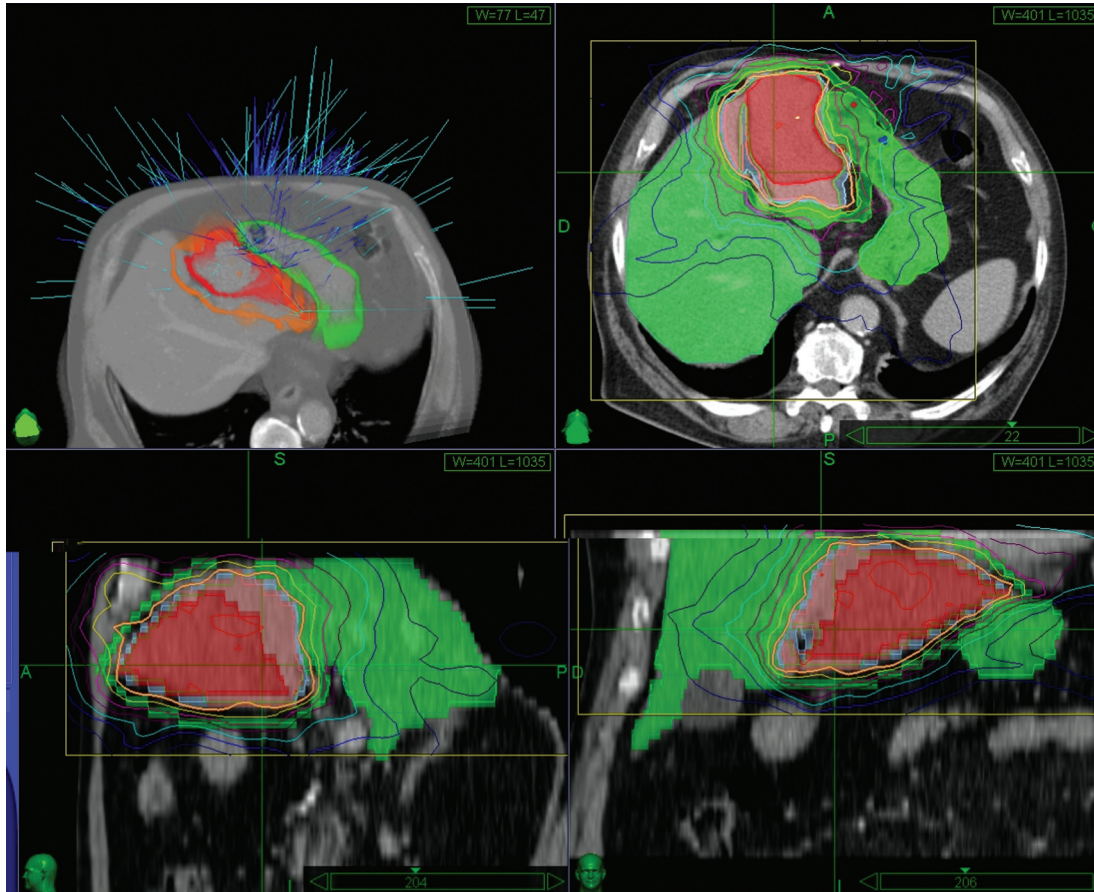
SPSS 13 (SPSS Inc., Chicago, IL) software was used for the statistical analysis. The primary endpoint was performed for overall survival. Survival rates were calculated from the start of irradiation using the Kaplan-Meier method. Differences between the survival curves were tested with the log-rank test. Fisher’s exact test and Pearson’s chi-square test (with Yates correction) were used to evaluate associations between category variables.

#### Results

##### Toxicity

Overall the treatment was well tolerated. A detailed summary of all observed NCI CTCAE toxicity events is provided in Table IV. During fiducial marker placement, one Grade 1 hematoma occurred which did not delay treatment or cause hospitalization. Two Grade 3 acute toxicities occurred; one patient experienced Grade 3 liver pain immediately following treatment and one patient experienced Grade 3 hepatic toxicity at 3 months. The remaining acute toxicity was minimal and primarily of digestive nature. No acute Grade 4 toxicity occurred.

Late toxicity was minimal with all observed late toxicities occurring within the first six months of follow-up. No late toxicity of Grade 4 or higher was observed. The duration of late toxicity was also short, resolving within 1 to 3 months after initial appearance. No radiation induced



**Figure 1:** Representative treatment planning image. Shown is the CyberKnife treatment plan for an 84 year-old male, Child A, cirrhotic patient with hepatic pain and an alpha foetoprotein value of 281. The lesion was larger than 6 cm. Lesion contouring (red) and isodose lines are shown.

liver disease (RILD) was observed, but two patients had cirrhotic decompensation. Two late Grade 2 and one late Grade 3 duodenal ulcers were observed resulting in a digestive hemorrhage for the patient presenting with the Grade 3 ulcer. These duodenal toxicities were related to the proximity of the duodenum to the target volume. Following observation of these toxicities we reviewed the treatment plans which revealed that the dose constraints at the level of the duodenum had not been respected. Specifically, the volume of duodenum receiving a dose equal to or greater than 15 Gy exceeded 5 cm<sup>3</sup>. All subsequent treatment plans were critically examined and dose constraints on the duodenum, as well as the other organs at risk, such as healthy liver, stomach, intestine, and kidneys, were strictly respected (Table II).

#### Response

Using the EASL vascularization criteria, response was evaluated at the level of the treatment area for the 14 patients with a minimum of 12.7 months follow-up. Of these 14 patients, a complete response (CR) was obtained in 8 patients (57%),

partial response (PR) in 4 patients (29%), progression in 1 patient (7%), and 1 patient was non-evaluable (7%). The overall objective response rate was 86% (12/14). Three hepatic recurrences at a distance from the target and one metastasis were observed. The actuarial 1- and 2-year local control rate was 95% (95% CI: 69–95%).

#### Survival

At a median overall follow-up of 12.7 months (range, 1–24 months), six of the twenty-five (24%) patients have died. Figure 2 presents Kaplan-Meier plots for overall and disease free survival for all patients and overall survival according to Child score. The median disease free survival was 15.8 months. Table V presents an overview of the survival duration, disease characteristics and causes of death. Overall actuarial survival at 1- and 2-years was 79% (95% CI: 52–92%) and 52% (95% CI: 19–78%), respectively. Overall survival was significantly longer in Child A patients than Child B patients ( $p = 0.005$ ). The 1-year overall actuarial survival for Child A was 86% (95% CI: 55–96%) and 33% (95% CI: 1–77%) for Child B.

Table IV

Observed toxicity after SRT at various follow-up times based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v3.0).

Follow-up time	End of Treatment		3 Months		6 Months		9 Months		Late	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Dermatitis										
Nausea			2		1				3	
Vomiting	3		1		1				2	
Gastritis			1						1	
Gastro duodenal ulcer					2	1			2	1
Hepatic toxicity				1						1
Dysphagia			1						1	
Hepatic/epigastric pain	1	1	3		1				4	
Hematoma										
Fatigue			1		1				2	
Anorexia	1									
Diarrhea			1		1				2	
Total (n/%)	5 (20%)	1 (4%)	10 (48%)	1 (5%)	7 (39%)	1 (6%)	0	0	17 (81%)	2 (10%)
Evaluable patients (n)	25		21		18		14		21	

## Discussion

We report the results of SRT treatment for 25 HCC patients that were not eligible for surgery, embolization, chemotherapy, or radiofrequency ablation. Our treatment approach is based on previously published reports (19-22), see Table VI. Our hypofractionation scheme delivered a total dose of 45 Gy in three fractions of 15 Gy. Following the occurrence of 3 duodenal ulcers, the prescription was modified in order to fulfill the gastrointestinal (GI) constraints (duodenum and stomach). Subsequently, we did not observe any additional ulcers or any Grade 3 acute toxicity. Furthermore, hypofractionation allowed us to deliver the treatment in a much shorter time than with conventional RT treatment in this frail population of patients.

## Toxicity

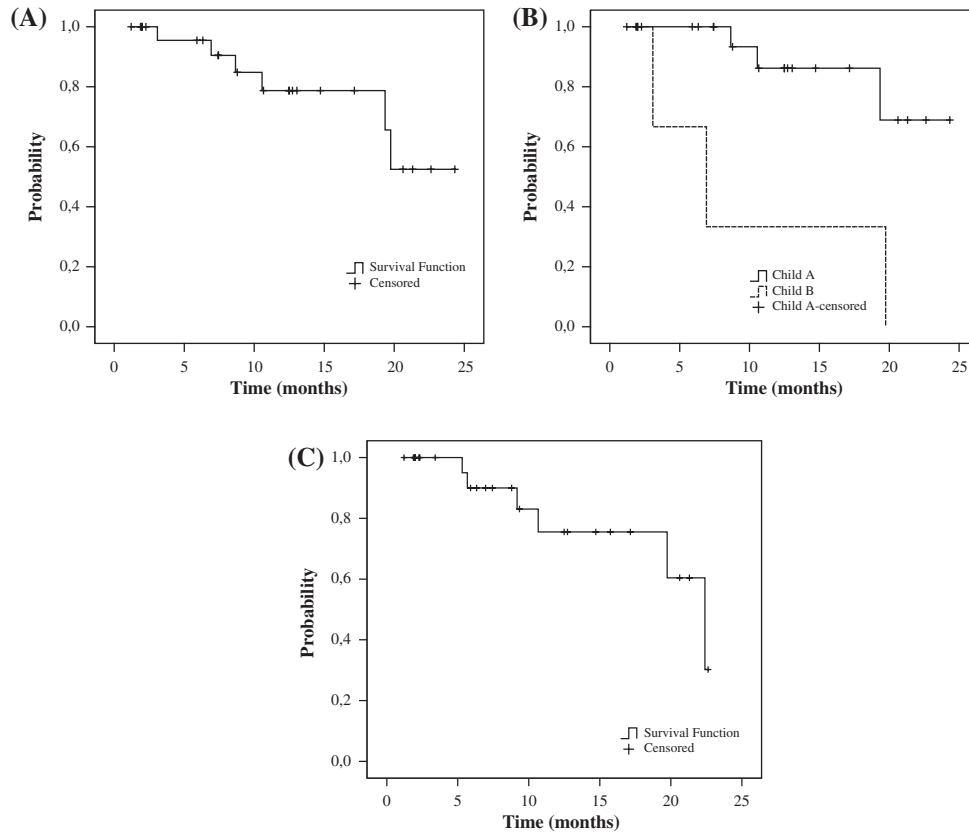
Overall, tolerance to our hypofractionated SRT treatment was good. The observed GI related toxicities were similar to the ones observed in the other studies (See Table VI). As hepatic pain was the most commonly observed toxicity (6 patients, see Table IV), we investigated whether there was a causal link between the level of pain and either the lesion size or lesion location (relative to the hepatic capsule). Our analysis showed that a tumor diameter larger than 45 mm (median tumor size) was associated with 60% of the hepatic pain cases. There was no significant correlation between post-treatment pain and sub-capsular localization. The relatively small size of our study, however, did not allow us to evaluate a possible relationship between local control and staging of the tumor (Okuda, Child, MELD, DCLC, TNM scores), or a causal link between pain and the

number of beams, the duration of the treatment and previous treatments.

## Tumor Response

The evaluation of hepatocarcinoma response to non-surgical treatments remains a challenge. We evaluated response according to EASL criteria and compared that to RECIST criteria (Table VII). Overall response varies substantially between the two methods. RECIST criteria are based on a measure in one-dimension. Although it is used in some clinical studies, it may not be appropriate to assess response in HCC because the size of the tumor does not vary much. In fact, RECIST criteria are not appropriate to accurately evaluate a response mainly consisting of a hypodense zone surrounded by a hypervascularized ring related to vascularization disorders occurring after irradiation (28). For this reason, a panel of European experts has recommended the use of EASL criteria (5) and hence measure the viable tumor volume (vascularization) assessed by spiral CT and report it according to WHO criteria (31). Although the EASL criteria still need to be validated, the development of an alternative response assessment criterion for HCC is encouraging. A possible improvement in the assessment may be obtained by using of contrast-enhanced ultrasound.

These controversies in HCC response assessment may be one of the factors explaining variability in response rates among published HCC SRT studies. In one of the publications reporting HCC response rates, Choi *et al.*, treated 22 HCC patients with small, non-resectable hepatocarcinoma lesions (23 lesions, group A) and advanced hepatocarcinomas with portal vein thrombosis (PVT) (9 lesions, group B) using the



**Figure 2:** Kaplan-Meier plots depicting (A) overall survival for all patients, (B) overall survival according to Child score, and (C) disease free survival for all patients.

CyberKnife (19). The total dose ranged from 30 to 39 Gy (median, 36 Gy) prescribed to the 70-85% isodose line and was delivered in three fractions. Response was assessed using a modification of the WHO response evaluation criteria. At a median follow-up of 10.5 months, 7 (21.9%) lesions had CR, 16 (50.0%) lesions had PR, and 9 (28.1%) lesions had SD. Their overall response rate (CR + PR) was 71.9% (group A: 82.6%, group B: 44.4%). In comparison to their data, the overall response rate of 85% in this series was higher for a similar follow-up duration. Given the differences in response

evaluation it is difficult to draw any conclusion from this comparison.

*Survival*

Overall actuarial survival in this study at one year is 79% and 52% at two years which is comparable to most other published HCC SRT results with one-year overall survival rates ranging from 70-81% (18-20, 23). The outlier in this range is a phase I study by Tse *et al.*, who treated 41 HCC

**Table V**  
Summary of survival length, disease characteristics and cause of death.

Survival length following treatment (months)	Initial Child Score	Meld Score	Okuda Class	Cause of Death
1	B9	16	II	Cirrhosis decompensation
5	B8	14	II	Digestive hemorrhage due to cirrhosis with pneumopathy
7	A5	2	I	Tumor progression
9	A5	8	I	Digestive hemorrhage due to cirrhosis
16	B7	10	II	Plurifocal evolution of hepatic tumor with digestive hemorrhage due to cirrhosis
18	A6	4	I	Natural causes not related to hepatocarcinoma

Table VI

Comparison of published results on the treatment of hepatocarcinoma (HCC) using stereotactic radiotherapy. Publications that treated 10 or less HCC patients and/or did not provide outcomes based upon tumor type were excluded. Unless noted otherwise results are for HCC treated lesions only.

Study	Treated Lesions (n)	Total Dose (Gy)	Number of Fractions	Lesion Volume (median, range, cc)	Number of Patients	Follow-up (median, range) months	Grade 3+ toxicities (n)	Overall Response	Local Control (1-year)	Overall Survival (1-year)
Mendez <i>et al.</i> , 2006	HCC (n = 11) M (n = 34)	25 – 37.5	3 × 12.5 5 × 5 3 × 10	22.2† (1.1 – 322)	25 (8 HCC)	12.9 (1.1 – 322)	1 Acute No late	NR	94% WG 75% HCC 100% M	82% WG 75% HCC 85% M
Choi <i>et al.</i> , 2006	HCC (n = 20)	50	5 or 10	3.8 mean (2 – 6.5)	20	23 (3 – 55)	None	80%	NR	70%
Tse <i>et al.</i> , 2008	HCC (n = 31) IHC (n = 10)	24 – 54	6	173 (9.1 – 913)	31	17.6 (10.8 – 39.2)	8 Acute 1 Late	49%‡	65%‡	48% HCC 58% IHC
Choi <i>et al.</i> , 2008	HCC (n = 32; 9 w/PVTT)	30 – 36 *	3	25.2 (3.6 – 57.3)	31	10.5 (2 – 18.5)	1	71.9% (HCC 82.6%, PVTT 44.4%)	71.9% at median 10.5 months	81.4% (HCC 88.1%; PVTT 43.2%)
Yang <i>et al.</i> , 2009	HCC (n = 20)	50 Gy ¶	10	3.2 mean (2 – 5.2)	40	35 (11–44)	None	70%	65%	73%
Current Study	HCC (n = 25)	45	3	45 (18–100)	25	12.7 (1–24)	2	85% of 14 patients.	95%	79%

IHC – intrahepatic cholangiocarcinoma; HCC – hepatocarcinoma; M – metastases; PVTT – portal vein tumor thrombosis; TACE – transarterial chemoembolization; WG – Whole group, NR – not reported.

†includes liver metastases; ‡ includes IHC; \* PVTT patients received TACE; ¶ Additional 20 patients received recombinant adenovirus, SRT only results listed.

patients with six fractions of SRT over two weeks (21). The dose per fraction was based on the volume of the irradiated liver and estimated considering the risk of developing radiation-induced hepatitis. The delivered dose ranged from 24 to 54 Gy (median 36 Gy). Their observed one-year overall survival was 48%. This much lower one-year-survival rate could potentially be related to the associated liver disease: 26 out of 31 patients had liver disease of viral origin which is known to be of poor prognosis. However, other studies have mixed populations of patients with large variation in the origin of the underlying liver disease. Another factor that could account for differences is the tumor size. In the Tse *et al.*, study, the median volume of the lesion was 173 cc (range, 9.1 – 913) which is substantially larger than in any other published SRT study.

Child B score is also an important factor in survival. In the current study, the three Child B patients all died. In contrast only 3 of the 21 Child A patients died to date. The patients with a Child B score were very frail and did not respond well to the treatment suggesting that the treatment of Child B patients remains a challenge.

Our survival results also show that some patients progress at a distance from the treated area. In recent years, there has been a growing interest in the development of some of these new targeted therapies with clinical phase I, II or III studies currently evaluating targeted therapies such as sorafenib (32), erlotinib (33), bevacizumab (34), and cetuximab (35). To date, there are only limited published reports (36, 37) on the combination of these targeted treatments with radiotherapy HCC. Their combinations have been widely studied in other cancers, such as colon, pulmonary or head and neck cancers (38, 39–42). It seems logical to expect that these combinations are potentially active against tumors characterized by a typical vascularization pattern, as is the case in HCC. However, carefully designed clinical trials are necessary to confirm the effectiveness of such combined treatments.

## Conclusion

Our results suggest promising therapeutic efficacy and good clinical tolerance to CyberKnife SRT treatment for HCC patients not eligible for other treatment modalities. Longer follow-up is necessary to evaluate long term response, local control, survival and toxicity. In particular, further clinical studies are required to determine the exact role of SRT among other treatment options such as chemoembolization, antiangiogenic treatment, proton therapy and others. To that end, Oscar Lambret Cancer Center, in collaboration with two other hospitals, has been granted a multicenter phase II clinical study by the French National Cancer Institute. The aim is to treat 44 patients with Child A hepatocarcinomas smaller

Table VII

Assessment of tumor response at a median 12,7-months follow-up.

	Response within PTV according to RECIST n (%)	Response within PTV based on vascularization information (EASL) n (%)
Complete response	4 (28%)	8 (57%)
Partial response	4 (28%)	4 (29%)
Stable disease	2 (14%)	0 (0%)
Progression	1 (7%)	1 (7%)
Non-evaluable	3 (22%)	1 (7%)

PTV - planning target volume, RECIST - response evaluation criteria in solid tumors.

than 6 cm using the CyberKnife in order to determine the clinical efficacy of SRT.

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