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## **Curative irradiation treatment of hepatocellular carcinoma: a multicenter phase II trial**

### **Running title : Ablative irradiation of hepatocellular carcinoma**

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## **Authors contributions**

Study concepts: X Mirabel

Study design: X Mirabel, T Lacornerie

Data acquisition: All

Quality control of data and algorithms: V Steen

Statistical analysis: E Bogart, MC Le Deley

Manuscript preparation: J Durand-Labrunie, E Bogart, MC Le Deley, D Peiffert

Manuscript review: All

## **Ablative irradiation of hepatocellular carcinoma**

Keywords : Hepatocellular carcinoma, stereotactic body radiotherapy, stereotactic ablative body radiotherapy, ablative treatment, primary liver tumour, inoperable HCC

### **Abstract**

#### *Purpose/Objective*

Liver transplantation is the standard definitive treatment for non-metastatic hepatocellular carcinoma (HCC). However, less than 5% of patients are ultimately candidates due to frequent comorbidities and graft shortage. The aim of this study was to evaluate stereotactic body radiotherapy (SBRT) as an ablative treatment for inoperable HCC.

#### *Material/methods*

A prospective phase II trial included newly-diagnosed single HCC lesion; without extra-hepatic extension; deemed unsuitable for standard loco-regional therapies; with a tumor size from 1 to 6 cm. The SBRT dose was 45 Gy in 3 fractions. Primary endpoint was the local control of irradiated HCC at 18 months, defined by RECIST (Response Evaluation Criteria in Solid Tumors).

#### *Results*

Forty three patients were treated and evaluable. Median follow-up was 4.0 years (range, 1.2 to 4.6 years). All 43 patients had cirrhosis, 37 (88%) were Child-Pugh (CP) grade A, and 5 (12%) grade B (1 missing data). No patients had received prior local treatment. Thirteen patients (31%) presented grade  $\geq 3$  acute adverse events, including 8 patients with an abnormality of the liver function tests (19%). Three patients (10%) experienced a decline in CP at 3 months post-SBRT. The 18-month local control rate was 98% (95% confidence interval, 85%-99%). The 18-month overall survival (OS) rate was 72% (56%-83%). Median OS was 3.5 years.

#### *Conclusion*

Local control and overall survival after SBRT for untreated solitary HCC were excellent despite candidates being unfit for transplantation, resection, ablation or embolization

treatments. SBRT should be considered, as bridging to transplant or as definitive therapy for those ineligible for transplant.

**Condensed Abstract**

Local control and overall survival after SBRT for untreated solitary HCC are excellent despite candidates being unfit for transplantation, resection, ablation or embolization treatments. SBRT should be considered, as bridging to transplant or as definitive therapy for patient ineligible for transplant.

## **Introduction**

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the second most common cause of death from cancer worldwide(1). Surgical resection and liver transplant (LT) are curative treatments, with a 5-year survival rate of 60–75%(2,3), but only 10–30 % of patients are eligible for those treatments due to the shortage of transplant organs, comorbidities and poor general condition(4). For patients unsuitable for surgery, ablative therapies such as radiofrequency ablation (RFA) may result in a 5-year survival rate from 40 to 50% for tumors <3 cm, while microwave ablation (MWA) may achieve similar results in larger HCC(5). Among patients inappropriate for surgery or ablative treatment, some may be candidates for hepatic trans-arterial chemoembolization (TACE) with a reported 2-year survival varying from 24% to 63%(6). Sorafenib and Lenvatinib are indicated as first line systemic agents in the treatment of HCC, and are associated with a 12 months median survival(7,8).

Stereotactic Body Radiation Therapy (SBRT) is a modern radiotherapy technique that permits to deliver ablative doses in a small number of high-dose fractions with a high conformation degree. Highly conformal planning, image guidance, and methods to minimize respiratory motion are required for optimal delivery. Several studies explored results of SBRT in the treatment of HCC with an excellent long-term control and an acceptable tolerance(9). Despite these results, SBRT is currently not considered as a standard treatment in most HCC management guidelines because most of the studies are retrospective, with heterogeneous techniques and populations. The aim of this prospective study was to estimate the local control (LC) rate according to the RECIST criteria 18 months after SBRT in patients with a single HCC lesion deemed unsuitable for standard loco-regional therapies.

## **Materials and method**

### *Trial design*

The trial was a multicenter open single arm phase II study, assessing SBRT treatment for patients diagnosed with non-metastatic unique HCC, using a one-stage Fleming design. Three XXX institutions participated to this trial. It has been funded by XXX Ministry for Health (PHRC grant n°19-08).

### *Patient's selection*

Selection criteria for the study were unique intrahepatic non metastatic inoperable HCC lesions with diameter between 1 and 6 cm, histologically proven or which fulfilled the Barcelona Clinic Liver Cancer (BCLC) criteria(10). All patients were evaluated in a multidisciplinary board and declared not eligible for the standard therapeutic options. Inclusion criteria were an ECOG performance status 0-1 and a Child–Pugh (CP) A score. Portal hypertension (PH) and portal vein thrombosis (PVT) were also accepted. All patients signed an informed consent to be treated. This study was approved by our institutional research ethics committee and by XXX Data Protection Authority (CNIL).

### *Treatment*

Seven to ten days prior planning CT scan, 3 to 4 fiducial markers were implanted next to the lesion under CT guidance. Patients were immobilized in supine position. A planning computed tomography (CT) scan included an acquisition of 1 mm-thick slices, after contrast agent injection and a four dimensional CT (4D-CT) imaging. Gross Tumor Volume (GTV) was defined on the planning CT scan, facilitated by image fusion approach, using pre-treatment MRI. The Clinical Target Volume (CTV) was obtained adding 10 mm isotropic margins to the GTV, inside the liver tissue. The Planning Target Volume (PTV) was generated from the PTV by adding an overall isotropic margin of 1.5 mm. A total dose of 45 Gy in 3 fractions was prescribed to the 80% isodose, encompassing PTV. The protocol dose constraints criteria for Organs at risk (OAR) were as follows: volume receiving 21 Gy (V21) <5 cm<sup>3</sup> to the proximal duodenum and stomach, volume receiving 15 Gy (V15) < 33% to the right kidney, maximum dose received by spinal cord < 15 Gy, and volume receiving 21 Gy < 33% and V15 < 50% to healthy liver (liver minus GTV). SBRT was Cyberknife® (Accuray Inc, Sunnyvale, USA),



delivered 6 MV photons, in 3 fractions, for a total duration of 6–10 days. Synchrony system was used, allowing real time target tracking.

### *Assessment*

Patients were assessed at 3 months and every 3 months during the first year after SBRT, and every 6 months thereafter during 4 years. During the first 3 months, all patients underwent liver function blood tests (alanine and aspartate aminotransferase, alkaline phosphatase, gamma-GT, and total bilirubin) as well as other biological tests (albuminemia, creatinine level...) every 15 days in order to monitor liver and renal functions. Follow-up included clinical examination, contrast-enhanced MRI (or CT scan when MRI was not feasible), and blood work including alpha foetoprotein measure. CP score was assessed every 3 months. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and RTOG. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST)(11). All radiological exams were reviewed by an independent expert radiologist committee (two radiologists from independent institutions).

### *Quality of life*

We prospectively measured Quality of Life (QoL) at baseline, at 3 months, and every 3 months during the first year after SBRT, and every 6 months thereafter. We used two questionnaires recommended by European Organization for Research and Treatment of Cancer (EORTC) in this population: Quality of Life Questionnaire Core-30 (QLQ-C30) and Quality of Life (QLQ-HCC18)(12). The QLQ-C30 comprises 30 questions assessing global health/QoL, 5 functional domains (physical, role, cognitive, emotional, social), 3 symptom-specific scales (fatigue, pain, nausea and vomiting), and single-item assessments of dyspnea, insomnia, appetite, constipation, diarrhea, and financial difficulties. Scoring was based on the EORTC scoring manual, standardizing raw scores onto a 0-100-point scale. Higher scores indicate better QoL on functional scales but worse QoL on the symptom scales. QLQ-HCC18 includes 18 multi-item scales. These items are grouped into 6 domains namely fatigue, body image, jaundice, nutrition, pain and fever. Two remaining single items address abdominal swelling and sex life. All scales were grouped and converted to score 0 to 100 according to the scoring manual; a higher score represents a more severe symptom or problem.

### *Endpoints*

To estimate the local control rate at 18 months and the whole curve describing local control rate over time, we computed the time interval from the date of study entry until the first progression of the treated lesion (in-field). Death with no prior relapse was considered for censoring. The occurrence of distant metastases was not considered for censoring as local control was still evaluated after the occurrence of distant metastases. Patients alive without local progression were censored at the date of last follow-up. We performed a post-hoc sensitivity analysis considering death with no prior relapse as a competing event to local progression, and not as a censoring. Secondary end points were acute and late toxicity, progression free survival (PFS), and overall survival (OS). PFS was defined as the time interval from the date of study entry until the first progression at any site (in-field, out-of-field, or extra-hepatic), or death from any cause. Patients alive without progression at their last follow-up were censored at this date. OS was defined as the time interval from the date of study entry until death from any cause. Patients alive at their last follow-up were censored at this date. Safety of the study procedure was monitored considering acute adverse events defined as any adverse event occurring less than 90 days after radiotherapy, classified or not as related to the procedure, and late toxicity, defined as any adverse event classified as related to the procedure (SBRT or fiducials), occurring more than 90 days after radiotherapy treatment.

### *Statistical considerations*

Considering an 18-month LC rate of 68% as the minimal acceptable rate, based on the results of a Phase I/II evaluating SBRT published by Herfarth et al. (13) 39 evaluable patients were needed to conclude positively at one-sided alpha of 5% with an 80%-power for an expected 18-month LC rate of 85% (one-stage Fleming design), leading to a total of 44 patients including non-evaluable patients. Statistical analyses were performed including all study patients providing they had started study treatment (modified intention-to-treat approach). Anticipating possible censored data over time as previously defined, local control rates and survival estimates were calculated using the Kaplan-Meier method. For the sensitivity analysis, we used the Kalbfleisch and Prentice method to estimate the local control rate considering death as competing event to local progression. Adverse events (AE) were

analyzed considering the maximum grade per patient and per type of AE. Statistical analysis was performed using the Stata statistical software version 13.

## Results

### *Patients and treatment*

Forty four patients were included between September 2009 and September 2014 in 3 XXX university specialized oncologic centers. Eight patients had minor deviations to the protocol and 1 patient was not treated because of a second HCC lesion discovered after inclusion and was excluded from analysis, leading to 43 patients treated and evaluated (modified intention-to-treat analysis, Figure 1). Baseline patient and tumor characteristics are displayed in Table 1. Most of patients were men (81%). Median age at the time of inclusion was 72 year, and most of patients had a performance status (PS) 0-1 (95%). The median tumor size was 28 mm. Seven patients had a T2 disease (16%) and 1 patient a T3 disease (2%). All patients were N0M0. No patient received antitumor treatment prior to SBRT. All HCC were developed on cirrhosis, mostly related to alcohol use (57%), and viral hepatitis (25%). CP was A for 37 patients (88%) and B for 5 patients (12%). The median pretreatment CP score was 5 (range, 5-9). Five patients (12%) had a PVT, and 17 patients (40%) PH. Five patients (11%) had grade  $\geq 3$  laboratory abnormalities at baseline. Median alphafoetoprotein (AFP) at baseline was 5.9 UI/mL (range, 1.2-23 672).

All the patients received the full planned 45 Gy doses. However, for one patient, SBRT was not delivered on the target HCC lesion, but on a benign angioma. This patient was kept in the analysis as he received SBRT. Three patients (7 %) received 4 fractions instead of 3 due to intra fraction interruptions.

### *Adverse events*

All 43 patients have been treated and were evaluable for safety. Figure 2 and table 2 give a description of all acute AEs encountered. Considering all AEs, of any grade, the most frequent acute AEs were abnormalities of liver function tests (93%), hypoalbuminemia (42%), gastrointestinal disorders (19%), and fatigue (7%). Among gastrointestinal disorders, ascites (7%), nausea (7%), diarrhea (5%), dysphagia (2%), gastrointestinal reflux (2%), gastrointestinal hemorrhage (2%), abdominal pain (2%), and vomiting (2%) were reported. Most of grade  $\geq 3$  AE were abnormalities of liver function tests (21%), and gastrointestinal disorders (5%). Grade 3 elevation in aspartate aminotransferase ( $>5N$ ), alkaline phosphatase ( $>5N$ ), gamma-GT ( $>5N$ ), and total bilirubin levels ( $>3N$ ) occurred in 1 (2%), 1 (2%), 5 (12%),

and 4 (9%) patient within 90 days of SBRT, respectively Grade 3 ascites and gastrointestinal hemorrhage occurred in 1 (2%) and 1 (2%) patient within 90 days of SBRT, respectively. . An increase of 2 points or more of the CP score compared to baseline score was observed in 4 out of informative 29 patients (13%) at 3 months, 3 out of 24 informative patients (12%) at 6 months and 5/22 patients (23%) at 18 months. We observed a significant increase of CP between baseline and measure at 3 months (mean difference= 0.6; non-parametric test for paired measures,  $p=0.0021$ ) with no significant further variation at the following time points. One patient died in the setting of hepatic encephalopathy following lung infection 3 months after SBRT; causal relationship of this adverse event to the study treatment is questionable. No other grade  $\geq 3$  late toxicity has been reported (figure 2).

#### *Local response*

Considering death as a censoring event (primary analysis), the local control rate was 98% (95% CI, 85% to 99%; Figure 3), and 94% (79% to 99%) at 18 and 24 months, respectively. Results were very similar when considering death as a competing event (98%, 95%CI, 89 to 99 at 18 months and 96%, 95%CI, 86% to 99% at 24 months). Two patients had a local progression, at 3.8 months and 19 months, respectively. The patient who had not received SBRT on the target HCC had an early progression of the HCC. The HCC lesion was secondarily and successfully treated with SBRT. Another local progression was reported 19 months after initial treatment for an 18 mm tumor with a good PTV coverage that was in CR at 6 months. Among the 40 patients evaluable, best response was as follows: complete response (CR) in 10 patients (25%), partial response (PR) in 22 patients (55%), stable disease in 7 patients (18%), and progressive disease for 1 patient (3%); 3 patients were not evaluable for local response, due to early death or progression at a distant site. Supplementary table 1 presents results according to the lesion size (<30 versus  $\geq 30$  mm) (figure 3).

#### *Overall Survival and Progression-Free Survival*

Median follow-up of the 43 patients was 4.0 years (range: 1.2 – 4.6 years). At the time of analysis, 24 deaths were observed: 10 from HCC progression, 7 from cirrhotic

decompensation, 4 from unknown cause without reported local progression, and 3 from other causes. Median OS was 3.5 years (95% CI, 2.4 years to not reached; Figure 4). Overall survival rates were 72% (56% to 83%) and 69% (53% to 81%) at 18 months and 24 months respectively. Median PFS was 2.0 years (1.5 to 2.4 years; Figure 5). PFS rates were 65% (48% to 77%) and 48% (32% to 62%) at 18 months and 24 months, respectively. Overall, 15 patients had experienced disease progression including 2 local progressions (in-field), 11 intra-hepatic (out-of-field), and 2 metastatic progressions and 18 patients had died without prior HCC progression.

We observed a borderline significant decrease of AFP between baseline measure and measure at 3 months (non-parametric test for paired measures,  $p=0.049$ ) with no further significant variation at the following time points.

#### *Quality of life*

Of 44 treated patients, 41 were eligible for QoL analysis. Data are available for the QLQ-C30 in 41 patients and for the QLQ-HCC18 in 40 patients. Number of patients that completed QoL questionnaires decreased during follow up, to 27 and 26 patients at 18 months for QLQ-C30 and QLQ-HCC18 respectively, and to less than 5 patients at 24 months. Supplementary figures 3 and 4 summarize the changes over time in mean QoL scores for each domain of the QLQ-C30 and QLQ-HCC18 respectively. Relative to baseline, all patients reported stable QoL (Baseline QLQ-C30: 66.7%; 3 months: 58.3%; 18 months: 58.3%). There was no clinically significant worsening (Baseline QLQ-HCC18 Fatigue/Pain: 33.3/16.7%; 3 months: 22.2/16.7%; 18 months: 22.2/16.7%).

## Discussion

### *Stereotactic body radiotherapy*

This is the first multicentric prospective series in which no patient has received prior treatment and all tumors received the same SBRT regimen. Several prospective series, using various SBRT techniques and dose fractionation regimens, have been published for heterogeneous patients with early to advanced HCC and are summarized in table 4 (14–18). Comparison with previously published trials is delicate because of heterogeneity especially in terms of population, biological effective doses (BED) and target sizes. However Kang *et al.* and Takeda *et al.* had a similar population regarding tumor sizes, CP scores and TNM staging, and obtained identical outcomes with 94-96% LC and a 68-69% OS at 2 or 3-year. Nevertheless, in these trials a large proportion of patients had received previous TACE treatments, which represents a bias that outcomes of SBRT may be due to the association of different treatments. In our series, the fact that patient received SBRT as first line treatment demonstrates that SBRT is an effective ablative treatment with a high local control at 18 months (94%). In terms of grade  $\geq 3$  adverse events, most of trials found less than 12% GI toxicity and less than 15% worsening in liver function tests. We found almost 20% of grade  $\geq 3$  liver function test aggravation which is higher than all others published series. These biological alterations were in most patients without any clinical complication (5% GI grade  $\geq 3$ ) and reversible after 6 months. In our trial, we observed a CP decrease of 10% at 3 months, comparable to the findings of other published trials with a similar population (9-13%). In a recently published series, Chapman *et al.* found that increase of CP score  $\geq 2$  strongly predicts OS(19). In our trial, 13%, 12% and 23% of patients had  $\geq 2$  points increase of the CP score at 3, 6 and 18 months respectively. Distinction between CP increase due to SBRT toxicity, or cirrhotic evolution, or out-field HCC progression is difficult. In a randomized controlled trial comparing sorafenib to placebo including 97% patients CP A at baseline, 24% patients in the placebo arm developed ascites and 8% liver dysfunction (7). Among our population, 34% of patients presented an HCC progression at 18 months with only 2 local in field progression (4%). These findings are consistent with other trials in which most of progression are intrahepatic outfield or extra hepatic progressions. We found no reported alteration in QoL after SBRT. These findings are consistent with other published studies using an identical questionnaire (QLQ-C30). Klein *et al.* published the largest prospective cohort with 205 patients (among which 98 HCC) treated with a median dose of 36 Gy in 6 fractions.

They found similar outcomes with no significant worsening vs baseline beyond 3 months. A higher baseline score on QLQ-C30 Global Health was associated with improved survival(20). A smaller prospective series of 28 patients (among which 9 HCC) treated with 25 to 37.5 Gy in 3 to 5 fractions concluded that SBRT did not significantly influence QoL(21).

### *Early stage HCC treatments*

Current guidelines on the management of HCC by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) for the treatment of early HCC recommend curative treatments: LT, tumor resection, and RFA(1,22). LT is the HCC standard treatment for patients diagnosed with HCC meeting the Milan criteria(23). It cures both tumor disease and underlying cirrhosis, and is associated with excellent long-term survival rates from 50 to 60% after 5 years, reaching over 70% in high-volume established centers. Despite the expansion of tumor size limits beyond Milan criteria, a large amount of patients cannot benefit from transplant due to graft shortage and frequent comorbidities. Surgical HCC resection is an alternative proposed to early stage candidates with single nodules, absence of PH and vascular invasion, and well preserved liver function, with 5-year survival rates of 60%, and a peri-operative mortality of 2–3%(24). Five year survival rates drops according to tumor size (52% for tumors 2–5 cm and 37% for tumors >5 cm) and vascular invasion(25). RFA is also a validated alternative treatment for early HCC with a complete ablation of lesions smaller than 2 cm in more than 90% of cases, and a 3 year overall survival from 60 to 80% for lesion up to 5 cm(10). Radiofrequency ablation is less effective, with complete necrosis in only 30% to 40%, for HCCs greater than 3 cm(26). MWA seems to have similar outcomes than RFA with possible superiority of MWA in larger HCCs(1). There is no randomized trial comparing SBRT to surgical resection or RFA. A retrospective series compared outcomes of 224 HCC patients receiving RFA or SBRT, and reported similar 2-year LC (80.2% for RFA vs. 83.8% for SBRT) and no significant difference in OS and acute AE grade  $\geq 3$ (27). For tumors larger than 2 cm, local control rate was significantly higher in the SBRT group. Another retrospective series comparing outcomes of 26 HCC patients undergoing surgical R0 resection with 22 similar patients treated with SBRT. The 2-year LC rate was 90% for SBRT group. There was no difference for OS, complications, performance statuses, causes of death, and the disease-specific survival(28).



### *Indications of SBRT*

SBRT remains absent from most of international HCC management guidelines, explained by the lack of randomized phase III trials, and the heterogeneity of patients treated in terms of tumor stage and treatment modalities. Nevertheless, SBRT has been added to NCCN guidelines as an alternative to ablation and embolization techniques when these therapies have failed or are contraindicated(29). Level of evidence remains poor and indications of SBRT as a treatment of HCC unclear. In addition to our trial, two prospective phase II studies with comparable population (solitary HCC, inferior to 6 cm, without extra hepatic disease, for patients with CP A cirrhosis, non-eligible for standard curative treatments) reported 94% of 2-year local control after SBRT with low toxicity(14,18). Thus SBRT should be considered, in future guidelines at least as an alternative treatment for early stages HCC, such as surgical resection and RFA. The restrictive Milan criteria's and the delays in waiting for a LT lead to curable patients becoming delisted for the best curative treatment(30). A retrospective comparison of SBRT, RFA and TACE as bridging therapies found similar drop-out rates between groups (16.7% SBRT group vs. 20.2% TACE group and 16.8% RFA group,  $p=0.7$ ). Five year OS and postoperative complications were similar between groups(31). Guarneri *et al* investigated SBRT as a bridge option in HCC patients subsequently submitted to LT. Of the 13 pathologically evaluated lesions, 8 (61.5 %) lesions had a CR. Intra-operative surgical complications were observed in 3 out of 13 patients (23 %), but modification of the surgical strategy was needed only in 1 case (8 %)(32). In our series, radiological CR rates after SBRT were 25% at 18 months according to RECIST criteria's, which underestimates radiological response(33). The modified RECIST criteria's established in order to improve reproducibility of post treatment HCC evaluation(34) were used by the expert committee, resulting in 63% of CR at 18 months in our study. These results suggest that SBRT may be a viable alternative for bridging strategies.

### *Systemic treatments*

Despite the excellent LC results, PFS after SBRT remains low(35). In our series PFS was 47% at 2 year, due to recurrences occurring outside the radiation treatment fields. This raises the question of improving SBRT with systemic treatments. Several immune checkpoint inhibitors demonstrated significant clinical activity in the treatment of different cancer types.

Nivolumab and Pembrolizumab have already been approved in the US as a second line treatment, and are currently being tested in phase III trial in the first line setting (NCT02576509, NCT03713593)(36). Clinical reports suggest that local radiation treatment may cooperate with immune checkpoint inhibitors to systemically enhance tumor response(37). Clinical trials are already evaluating association of SBRT and immunotherapy in liver cancer (NCT03203304; NCT03316872).

## **Conclusion**

Local control and overall survival after SBRT for untreated solitary HCC were excellent for candidates being unfit for liver transplantation, resection, ablation, or embolization treatments. With a 2-year local control > 95%, SBRT should be considered in international guidelines as an ablative treatment for early stage HCC, not eligible for resection or RFA, or candidate for bridge therapy.

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**Figure legends :**

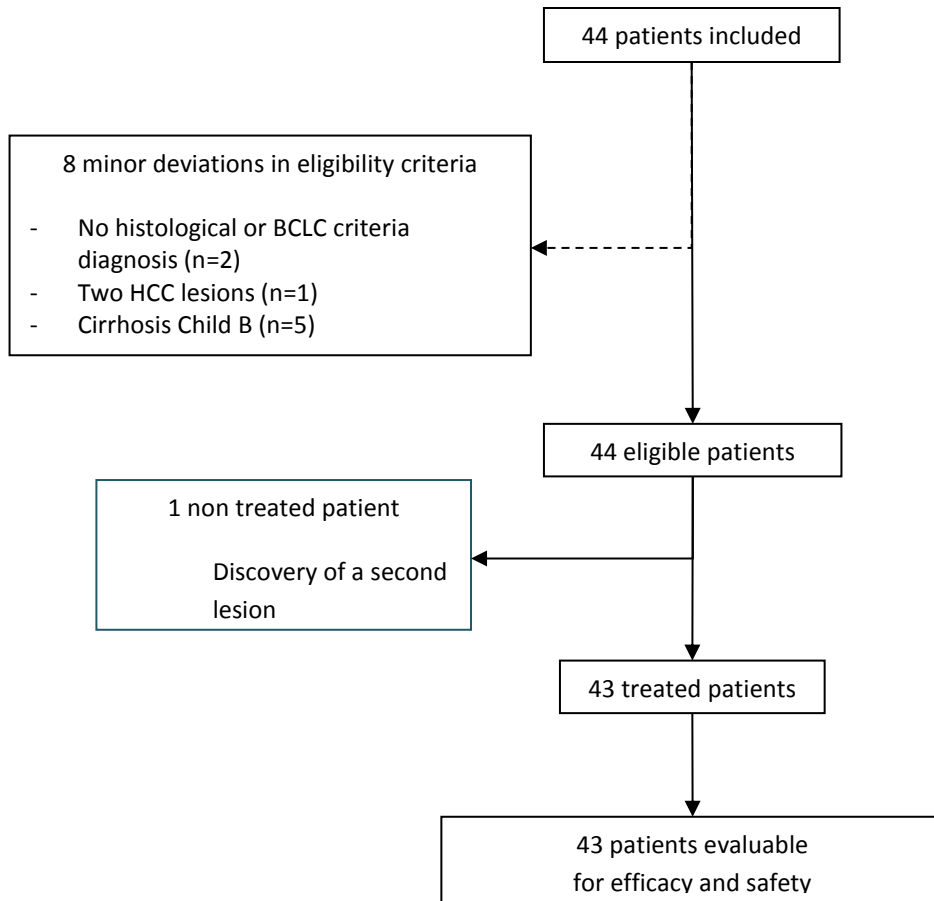
Figure 1: study flow-chart

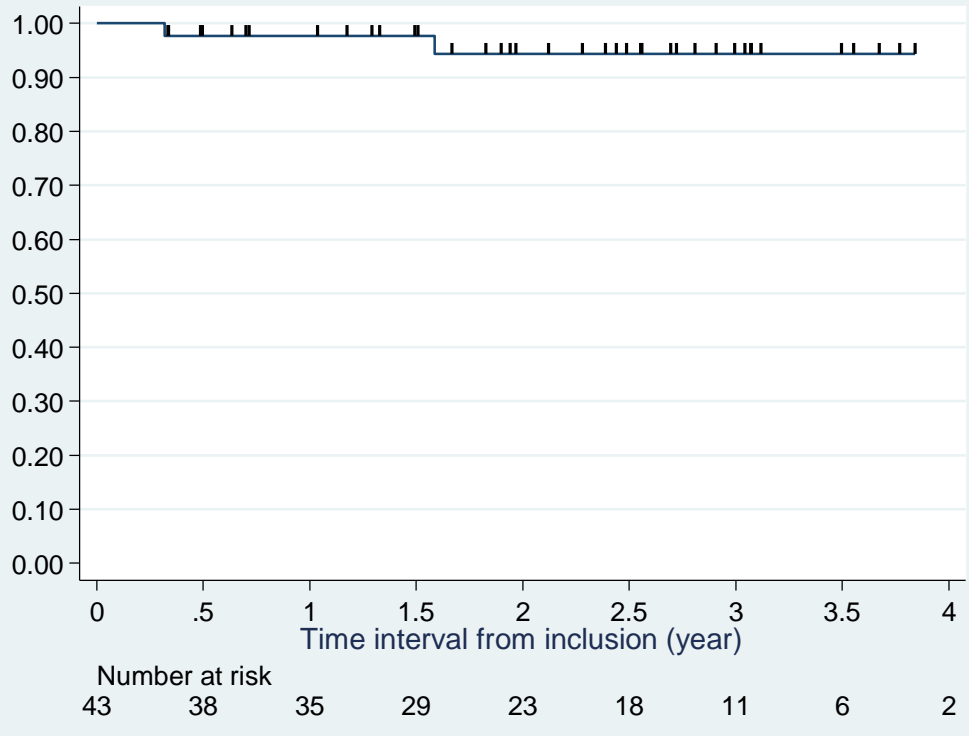
Figure 2: Frequency of maximum grade per patient and type of acute adverse events

Figure 3: Local control rate, estimated by the Kaplan-Meier method. Death with no prior relapse was considered for censoring. The occurrence of distant metastases was not considered for censoring as local control was still evaluated after the occurrence of distant metastases. Patients alive without local progression were censored at the date of last follow-up.

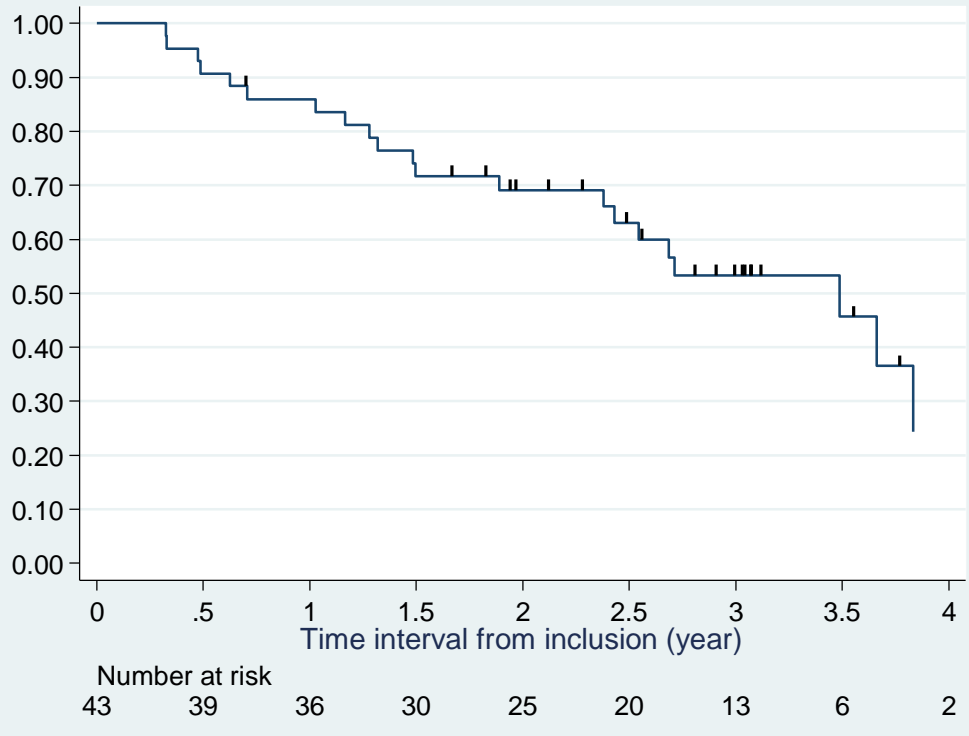
Figure 4: Kaplan-Meier estimate of the overall survival

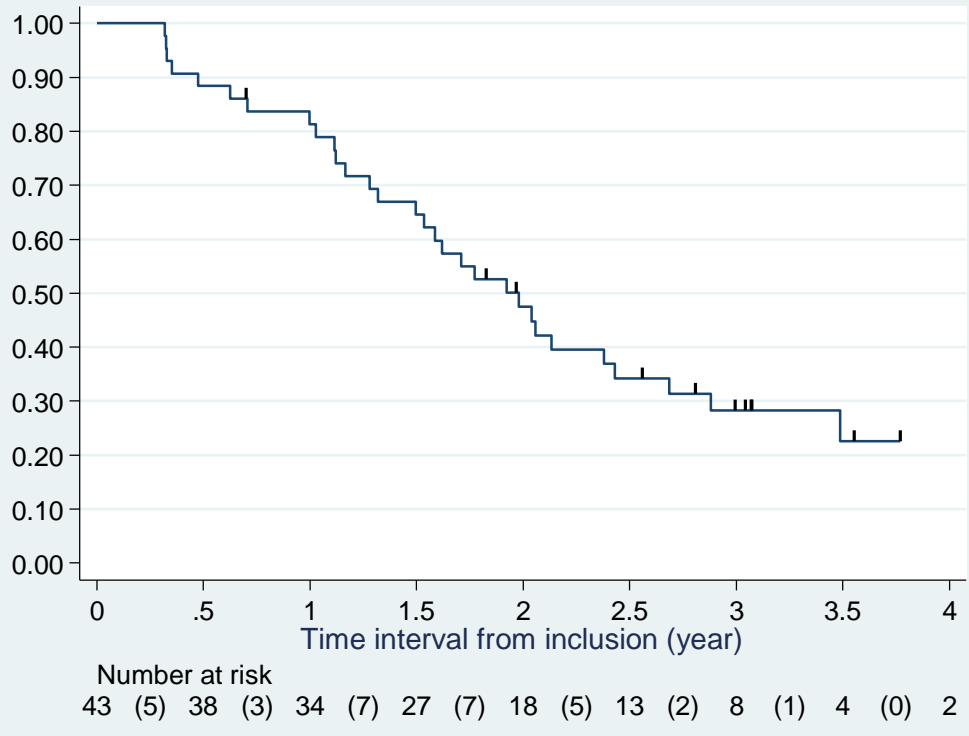
Figure 5: Kaplan-Meier estimate of progression free survival











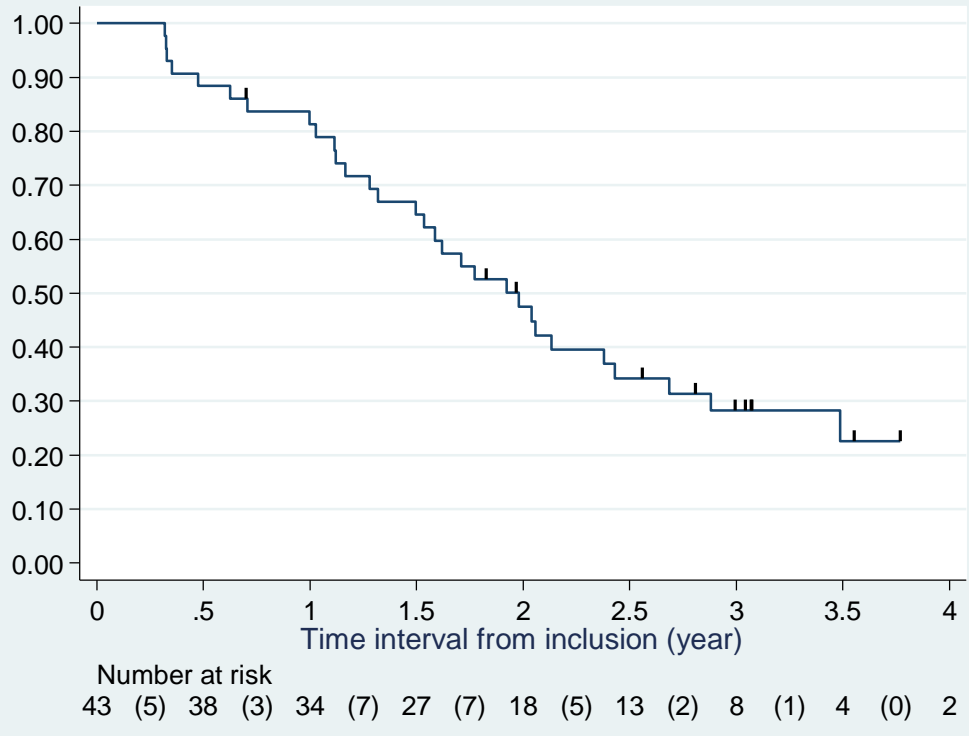


Table 1: Patient and tumor characteristics (43 treated patients)

Characteristics (N=43)	n	%
<b>Sex</b>		
Men	35	81%
Women	8	19%
<b>Age</b>		
Median - (Range)	72.0	(43-91)
<b>TNM (7<sup>th</sup> edition)</b>		
T1	35	82%
T2	7	16%
T3	1	2%
<b>Diagnosis</b>		
Histologic	2/43	5%
BCLC criteria	40/4	93%
<b>Performance status</b>		
0	17	40%
1	24	55%
2	2	5%
<b>Tumor size (mm)</b>		
Median - (Range)	28.0	(10-60)
<b>Portal vein thrombosis</b>	5/43	12%
<b>Portal hypertension</b>	17/4	40%
<b>Cirrhosis</b>		
Alcohol	23	57%
Non-alcoholic steatohepatitis	3	8%
Hepatitis B and C	10	25%
Other	4	10%
Unknown	3	
<b>Child-Pugh score</b>		
A (5-6 points)	37	88%
B (7-9 points)	5*	12%
Unknown	1	
<b>OKUDA Score</b>		
I (0 point)	39	93%
II (1 point)	3	7%
Unknown	1	
<b>MELD Score</b>		
Median - (Range)	9.0	(6-19)
Unknown	2	
<b>ALBI Score</b>		
Grade 1 (score $\leq$ -2.6)	13	32%
Grade 2 (-2.6 < score $\leq$ -1.39)	25	61%
Grade 3 (-1.39 < score)	3	7%
Unknown	2	
<b>Alpha-foetoprotein (UI/mL)</b>		
Median - (Range)	5.8	(1.2-23672)
Unknown	1	

\*Child-Pugh score B: 3, 1 and 1 patients with a score 7, 8 and 9, respectively

Table 2: Acute adverse events

Adverse events occurring in the first 90 days classified by system organ class	No AE	Grade 1	Grade 2	Grade 3	Grade4	Grade ≥1	Grade ≥3
<b>Blood and lymphatic system disorders</b>	<b>41 95%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>2 5%</b>	<b>1 2%</b>
Anemia	42 98%	0 0%	1 2%	0 0%	0 0%	1 2%	0 0%
Platelet count decreased	42 98%	0 0%	0 0%	1 2%	0 0%	1 2%	1 2%
<b>Gastrointestinal disorders</b>	<b>35 81%</b>	<b>3 7%</b>	<b>3 7%</b>	<b>2 5%</b>	<b>0 0%</b>	<b>8 19%</b>	<b>2 5%</b>
Abdominal pain	42 98%	1 2%	0 0%	0 0%	0 0%	1 2%	0 0%
Ascites	40 93%	1 2%	1 2%	1 2%	0 0%	3 7%	1 2%
Diarrhea	41 95%	1 2%	1 2%	0 0%	0 0%	2 5%	0 0%
Dysphagia	42 98%	1 2%	0 0%	0 0%	0 0%	1 2%	0 0%
Gastroesophageal reflux	42 98%	0 0%	1 2%	0 0%	0 0%	1 2%	0 0%
Gastrointestinal hemorrhage	42 98%	0 0%	0 0%	1 2%	0 0%	1 2%	1 2%
Nausea	40 93%	3 7%	0 0%	0 0%	0 0%	3 7%	0 0%
Vomiting	42 98%	1 2%	0 0%	0 0%	0 0%	1 2%	0 0%
<b>General disorders and administration site conditions</b>	<b>40 93%</b>	<b>3 7%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>3 7%</b>	<b>0 0%</b>
Fatigue	40 93%	3 7%	0 0%	0 0%	0 0%	3 7%	0 0%
<b>Injury, poisoning and procedural complications</b>	<b>42 98%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>1 2%</b>
Dermatitis	42 98%	0 0%	0 0%	1 2%	0 0%	1 2%	1 2%
<b>Liver function tests</b>	<b>3 7%</b>	<b>11 26%</b>	<b>21 49%</b>	<b>6 14%</b>	<b>2 5%</b>	<b>40 93%</b>	<b>8 19%</b>
Alanine aminotransferase increase	29 67%	12 28%	2 5%	0 0%	0 0%	14 33%	0 0%
Aspartate aminotransferase increase	15 35%	24 56%	3 7%	1 2%	0 0%	28 65%	1 2%
Blood alkaline phosphatase increase	22 51%	17 40%	3 7%	1 2%	0 0%	21 49%	1 2%
Blood bilirubin increase	14 33%	8 19%	17 40%	4 9%	0 0%	29 67%	4 9%
GGT increase	9 21%	14 33%	15 35%	3 7%	2 5%	34 79%	5 12%
<b>Hypoalbuminemia</b>	<b>25 58%</b>	<b>8 19%</b>	<b>9 21%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>18 42%</b>	<b>1 2%</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>42 98%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>0 0%</b>
Arthralgia	42 98%	1 2%	0 0%	0 0%	0 0%	1 2%	0 0%
<b>Nervous system disorders</b>	<b>42 98%</b>	<b>0 0%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>1 2%</b>
Encephalopathy	42 98%	0 0%	0 0%	1 2%	0 0%	1 2%	1 2%
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>41 95%</b>	<b>0 0%</b>	<b>1 2%</b>	<b>1 2%</b>	<b>0 0%</b>	<b>2 5%</b>	<b>1 2%</b>
Bronchial stricture	42 98%	0 0%	0 0%	1 2%	0 0%	1 2%	1 2%
Pleural hemorrhage	42 98%	0 0%	1 2%	0 0%	0 0%	1 2%	0 0%

Table 3: Recurrence patterns

<b>Recurrence patterns</b>	<b>N (%)</b>
Local (in-field)	2 (4%)
Intra-hepatic (out-field)	11 (25%)
Extra-hepatic	2 (4%)

Table 4: Published Phase I/II trials evaluating SBRT as a treatment of HCC

Trials Patients Median age (Range)	Median Follow up (Range)	CP score BCLC score TNM score	Prior treatment Details	Median size (Range)	Dose (Gy/fr) BED <sub>10</sub>	Toxicity G3+	LC ORR (RECIST)	OS Median OS	PFS Recurrence site
Kang <i>et al.</i> 2012 N=47 Unicentric Phase II NR	17m (6–38)	A 87%, B 13% A 17%, B 66%, C 17% T1 68%, T2 17%, T3 15%	100% TACE 100%	2.9 cm (1–8)	42-60/3 100-180 Gy	GI 11% (3 ulcers and 2 perforations) Liver function tests 4% Worsening CP 13%	95% (2y) 76.6%	69% (2y) Not Reached	34% (2y) 2 local (in-field) (4%), 19 intra-hepatic (out-field) (40%), 10 extra-hepatic (21%)
Bujold <i>et al.</i> 2013 N=102 Unicentric Phase I/II 69y (40-90)	31m (24-36)	A 100% A-B 34%, C 66% T1 13%, T2 14%, T3-4 66%	52% Surgery 9% TACE 22% RFA 34%	7.2 cm (1.4-23.1)	24-54/6 34-103 Gy	GI 11% (2 GI bleed and 7 liver failure) Liver function tests 14% Worsening CP 29%	87% (1y) 54%	NR 17m	NR 72 intrahepatic (71%) 33 extrahepatic (32%)
Lasley <i>et al.</i> 2015 N=59 Unicentric Phase I/II 61y (24-86)	CPA 33m (3-61) CPB 46m (4-70)	A 64%, B 36% NR T1 80%, T2 10%, T3 3%	15% NR	33.6 cm <sup>3</sup> (2–107)	40/5–36-48/3 72-125 Gy	GI NR Liver function tests 10% CPA, 38% CPB Worsening CP 50% CPA, 33% CPB	91% (3y) CPA, 82% (3y) CPB NR	61% (3y) CPA, 26% (3y) CP B 45m CPA, 17m CPB	48% (3y) CPA, 23% (3y) CP B NR
Kim <i>et al.</i> 2016 N=18 Unicentric Phase I 59y (42–83)	23m (11–38)	A 100% NR NR	83% TACE 33% Multimodality 50%	1.9 cm ( 1–3)	36-60/4 68-150 Gy	GI 0% Liver function tests 0% Worsening CP NR	71% (2y) NR	69% (2y) NR	49% (2y) 5 local (in-field) (28%), 7 intra-hepatic (out-field) (39%), 3 extra-hepatic (17%)
Takeda <i>et al.</i> 2016 N=90 Unicentric Phase II 73y (48–85)	42m (7-96)	A 91%, B 9% 0 34%, A 50%, C 16% T1 90%, T2 7%, T3 3%	64% TACE 50% Multimodality 14%	2.3 cm (1-4)	35-40/5 59-72 Gy	GI NR Liver function tests 2% Worsening of CP by 2 points 9%	96% (3y) NR	68% (3y) 55m	NR 3 local (in-field) (3%), 63 intra-hepatic (out-field) (70%), 9 extra-hepatic (10%)
Current trial N=44 Multicentric Phase II 72y (43-91)	48m (14-175)	A 88%, B 12% 0-A 100% T1 82%, T2 16%, T3 2%	None	2.8 cm (1-6)	45/3 112 Gy	GI 5% (1 ascites and 1 GI bleeding) Liver function tests 19% Worsening CP 10% Worsening of CP by 2 points 13%	94% (2y) 80%	69% (2y) 42 m	48% (2y) 2 local (in-field) (4%), 11 intra-hepatic (out-field) (25%), 2 extra-hepatic (4%)

NR= Not Reported ; y=years ; m=months ; CP=Child-Pugh Score