Robotic radiosurgery treatment in liver tumors: Early experience from an Indian center

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Abstract

Purpose: The purpose of this study is to report CyberKnife experience in hepatocellular carcinoma (HCC) and liver metastasis (LM). **Materials and Methods:** Fifty liver lesions in 31 consecutive patients with liver lesion [mean age 54.5 years (range 32-81 years), 77% were male patient, GTV <10cc in 5 patients, 11-90cc in 18 & >90cc in 8 patients respectively. Eighty percentage (25/31) had prior treatment (chemotherapy 18 patient & TACE in 7 patients). Dosage schedule was 21-45Gy/3# (mean PTV dose 33Gy, Prescription isodose 84%, target coverage 94%). Mean CI, nCI & HI were 1.19, 1.31 & 1.18 respectively. Mean liver dose was 5.4 Gy, 800 cc liver dose 11.1 Gy; **Results:** At mean follow-up of 12.5 months (range 1.9–44.6 months), 19 patients were expired and 12 were alive (nine patient with stable disease, two local progression, and one with metastasis). Median overall survival (OS) of all patients are 9 months (1.9–44.6 months), in HCC patients 10.5 months (2.1–44.6 months) and MT 6.5 months (1.9–24.6 months) respectively. Gr-I-II GI toxicities were in 11/50 (22%) patients. OS was influenced by PS (Karnofsky Performance Status 70–80 vs. 90–100: 9.9 vs. 16.4; $P = 0.024$), Child-Pugh (CP A/B vs. C: 23.6 vs. 6.5; $P = 0.069$), cirrhosis (only fatty liver vs. diffuse cirrhosis: 17.8 vs. 10.6; $P = 0.003$), prior treatment (no Rx vs. prior Rx: 30.1 vs. 8.2; $P = 0.08$), number of lesions (single vs. multiple: 16.4 vs. 6.9; $P = 0.001$), and target volume (<10 cc vs. >90 cc: 24.6 vs. 11.2; $P = 0.03$). **Conclusion:** Stereotactic body radiation therapy is a safe and effective treatment. Patient related factors such as performance status, Child-Pugh classification, cirrhosis status, prior treatment, number of liver lesion & target volume (GTV) influence the survival functions.

Key words: CyberKnife, Indian experience, liver tumor, robotic radiosurgery

Introduction

Infective hepatitis is a common problem in Southeast Asian population.[1,2] Unavailability and inadequate vaccination (hepatitis B and C) and lack of awareness are the common causes of high prevalence of hepatitis in this region.[2] Infective hepatitis, especially hepatitis B and C are associated with high incidences of cirrhosis and also hepatocellular carcinoma (HCC).[1,2] Surgery or liver transplant is the standard treatment option in HCCs. However, only 10%–20% of these patients are suitable for surgery. Majority of the HCC patients have background cirrhotic liver disease and are not amenable for surgical resection.[2] Other common reasons of nonresectability are large lesions at presentation, portal/periportal nodal involvement, and deep-seated lesions (subdiaphragmatic location, segment VII and VIII). Majority of these patients (80%) have poor reserve for liver function (Child-Pugh B or C) and may not tolerate aggressive surgery.[2] These patients are mostly treated with systemic therapy (Sorafenib) or with best supportive care only to have marginal benefit. HCCs mostly remain localized without metastasis even in advanced stage, and there is a potential of long-term local control with focal therapy. Resection, liver transplant, radiofrequency ablations (RFA), cryotherapy, and few other focal therapies have shown to have long-term controls in selected patients. Recent observation have shown that focal therapy along with systemic therapy have significant survival advantage *vis-a-vis* only systemic therapy in inoperable HCCs. In HCC, common focal therapies used for treatment are RFA, microwave and cryotherapies. In vast majority of cases, laparotomy is mandatory to perform such procedures in deep seated lesions. Large, deep-seated, and Child Pugh B/C HCCs are treated with transarterial chemoembolization (TACE), Y90 microspheres embolization, and transcutaneous ethanol injection.[3-7] Locoregional control with these focal therapies varies between 20% and 40%, and in majority of these patients, there is hardly any meaningful survival benefit.[1-4] Recent studies with stereotactic radiosurgery, stereotactic body radiation therapy (SBRT) in HCC is exciting noninvasive option and have shown promising results in early analysis. Majority of the results are from Western population. HCC patients from Indian subcontinent have poor nutritional status, presents with high volume disease and are suffering from infective hepatitis. The outcome of treatment may not be similar compared with the western counter-part. We need our own patient outcome data with SBRT.[5]

Inoperable, recurrent, multifocal, and metastatic HCCs are usually treated with systemic therapies.[8-10] In early days, interferon, doxorubicin, and few other chemotherapeutic and immune-modulators were used. In recent years, sorafenib mesylate (NEXAVAR®) is used more commonly in HCCs. There are three randomized studies (SHARP trial, Chang *et al*., and Abou Alfa and Lee) with sorafenib, which have shown a median overall survival (OS) benefit of 2.8 months (10.7 vs. 7.9 months; $P < 0.001$) (level I evidence), symptomatic progression free survival benefit (4.1 vs. 4.9 months; $P = 0.77$), radiological progression free survival (5.5 vs. 2.8 months; $P = 0.001$) and 1-year survival benefit increase from 20% to 40%.[6-10] Chang *et al*. ($n = 271$) evaluated the role of sorafenib in Asian population and it is shown to be lesser effective (median OS 6.5 vs. 4.2 months; $P = 0.014$ and median time to progression 2.8 vs. 1.4 months; $P = 0.0005$) and have higher side effects.[9] Sorafenib causes severe (Grade IV) diarrhea (8%), skin ulceration (10%), and nausea (5%), especially higher in Asian patient population.[8,10] A large proportion of patients do not tolerate these medicines and need either dose reduction to suboptimal dosage or withhold medication for long period.

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HCC has a dose-response relationship with radiation therapy; higher dose (>66 Gy) is correlated with better local control. Tolerance dose of liver is low (TD5/5 of whole liver is 35 Gy). Conventional radiation therapy delivery machines were not able to deliver high dose of radiation safely, and hence, radiation therapy was not effective in early studies.[10] Modern highly conformal "real-time" image-guided radiation therapy SBRT has the potential to deliver "tumoricidal" dose of radiation with potential benefits of long-term local control and minimal side effect.[11-18] SBRT should be evaluated in Indian HCCs with large volume disease and poor performance status. The present clinical study prospectively evaluated the role CyberKnife radiosurgery (SBRT) in liver tumors in Indian patient population.

Materials and Methods

Treatment methodology and parameters

The Institutional Multidisciplinary Tumor Board team consisting of liver transplant surgeons, hepatologists, medical oncologists, and radiosurgery specialists evaluated all the patients before accrual for CyberKnife treatment. Patients with recurrent, progressive, and inoperable tumors were accrued for radiosurgery treatment. HCC was diagnosed with atleast two imaging methods consisting of USG, triple phase computed tomography (CT) scan, magnetic resonance inaging (MRI) scan or positron emission tomography (PET) scan. Standardized gold fiducials were placed under ultrasonography (USG) guidance by radiologist (JG) within the tumor. Majority of the patients had three fiducials placed around the tumor as per specifications. Treatment plan was done with Multiplan® (version 3.5.4) treatment planning system (TPS). Plans were done with "sequential" planning algorithm. "Ray-tracing" algorithm used for dose calculation using voxels for each beam in the treatment plan. Multiplan® uses "Ray-tracing" function based on stored beam tissue phantom ratio, off-center ratio, and output factor (OF or DM). Fiducials are gold seeds with diameter of 0.7 mm to 1.2 mm and length 3 mm to 6 mm placed within the tumor (liver tissue) and tracked during treatment execution using Synchrony® system. Synchrony® tracking system use specially designed tracking vest, in which 3 tracking markers are placed to track patients respiratory motion. Location of the tumor is known from fiducial tracking (Internal movement) and respiratory tracking system on the patient body monitors external movement. The relationships between internal and external movements are found by correlation model. Fiducial with Synchrony® tracking system continuously predicts the internal movement through external movement and compensates using the Robot.

Contouring was done after fusion with triple-phase contrast CT scan and contrast MRI scan (T1 contrast and T2 flair). Gross tumour volume (GTV) contoured as seen on imaging. Margin of 3-5 mm given for planning target volume (PTV). The liver, duodenum, small intestine, and kidneys were contoured as critical organs and constraints given during planning as per the standard guideline. Treatment was started 3–5 days after placement of fiducials. Contouring and planning was done with Multiplan® TPS and treated with CyberKnife radiosurgery system. Physicists (PGG, MV, and SH) planned with MultiPlan planning system using sequential algorithm. Constraints for the critical structures, target coverage, and treatment delivery parameters (nonzero beam numbers, MU, treatment time) were approved by the radiation oncologist (DD). All patients were treated with three fractions treatment (21–45 Gy/3#) on consecutive weekdays. Before each treatment fraction, premedication with dexamethasone and ondansetron was done. In SBRT treatment with CyberKnife, real time kilovoltage X-ray based fiducial tracking with respiratory motion modeling using synchrony system is done. Patients were followed up after treatment for survival function and treatment-related adverse effects.

Data collection and statistical analysis

All the patient data were collected prospectively and analyzed with SPSS V20 [Statistical Package for Social Science (IBM Predictive Software, USA)]. Dosimetric data were collected after plan evaluation and treatment completion. All the patients were prospective followed up for survival function and toxicity parameter evaluation. Statistical analysis was done as per the standard protocol.

Results

Patient demographic profile

Individual patient details are described in Supplementary Table 1a and b. Demographic profiles of patients with HCC and liver metastasis (LM) were described in [Table 1]. Fifty liver lesions (n = 50) in 31 consecutive patients (mean age 54.5 years, range 32–81 years; 77% male) treated with fiducial-based robotic radiosurgery. Thirteen patients had HCC (n = 13) and 18 patients were LM (n = 18). Twenty patients (65%) presented with Child-Pugh A/B, eight (26%) patients had infective hepatitis (4 each with hepatitis B & C), five (16%) patients had diffuse cirrhosis, eighteen (70%) patients had single lesion in liver. GTV volume less than 10 cc were in three patients (17%), between 11-90cc in 18 patients (58%) and more than 90cc volume in 8 (25%) patients. Majority of the patients were treated with systemic therapy (58%) or TACE (22%) before accrual for SBRT treatment. Only 6 (19%) patients were treated with primary SBRT without any prior treatment. After SBRT, 23/31 (75%) of patients were on systemic therapy.

Dosimetric parameters

Dosimetric parameters are described in Table 2. All patients were treated with 3 fractions (21–45 Gy/3#; mean dose 33 Gy, prescription isodose 84%, target coverage 94%). Majority (22/31, 70%) of the patients were treated with >30 Gy in three fractions in 3 consecutive day schedules. Mean PTV volume was 141 cc and prescription dose was 33.3 Gy. All patients had fiducial placement at the tumor site under USG guidance and treated with fiducial tracking-based CyberKnife. Mean CI, nCI, and HI were 1.19, 1.31, and 1.18, respectively. Mean liver dose was 5.4Gy, mean 800 cc liver is 11.1 Gy and 2% small intestine dose 12.5Gy. Mean nodes, beamlets, monitor units, and treatment time were 79, 183, 44498, and 59.1 min, respectively [Table 2].

Survival functions and factors influencing survival

At mean follow-up of 12.5 months (range 1.9–44.6 months), 19/31 (61%) patients were expired and 12/31 (39%) were alive at last follow-up evaluation. At last follow up evaluation, 9 patients were alive with controlled disease (stable disease), 2 patients had local progression, and one patient was alive with metastatic disease [Table 3]. Fifteen (48%) patients had local (liver) progression with new lesions in the liver and 6 patients (18%) had multiple metastatic (multiple lesions in the lungs and bones) disease. Median OS in HCC

Table 1: Demographic profile (*n*=31)

	All patient (*n*=31)	HCC (*n*=13)	Metastasis (*n*=18)
Age (years), mean (range)	54.5 (32-81)	57 (45-71)	52.6 (32-81)
Age, *n* (%)			
<60	18 (58)	8 (61)	10 (55)
>60	13 (42)	5 (39)	8 (45)
Gender, *n* (%)			
Male	24 (77)	13 (100)	11 (61)
Female	7 (23)	0	7 (39)
ABCL stage, *n* (%)			
O	1 (3)	1 (3)	-
B	7 (21)	7 (22)	-
C	3 (9)	3 (10)	-
A	2 (6)	2 (6)	-
Child-Pugh, *n* (%)			
A	6 (20)	0	6 (33)
B	14 (45)	7 (54)	7 (39)
C	11 (35)	6 (46)	5 (29)
KPS, *n* (%)			
<70	1 (3)	0	1 (5)
70-80	19 (61)	10 (77)	9 (50)
90-100	11 (36)	3 (23)	8 (44)
Hepatitis, *n* (%)			
No	23 (74)	5 (38)	18 (100)
Yes	8 (26)	8 (61)	0
Hepatitis, *n* (%)			
B	4 (13)	4 (31)	-
C	4 (13)	4 (31)	
Liver status, *n* (%)			
Normal	9 (29)	1 (8)	8 (44)
Fatty liver	17 (54)	7 (54)	10 (56)
Diffuse cirrhosis	5 (16)	5 (38)	0
Number of lesions, *n* (%)			
1	18 (60)	10 (77)	8 (44)
2	7 (23)	2 (15)	5 (26)
3	6 (17)	1 (8)	5 (28)
Prior treatment, *n* (%)			
Yes	25 (80)	9 (69)	16 (89)
No	6 (20)	4 (31)	2 (11)
Prior treatment, *n* (%)			
No treatment	6 (19)	4 (31)	2 (11)
TACE	7 (22)	5 (38)	2 (11)
Chemotherapy	18 (58)	4 (31)	14 (78)
Post-CK treatment, *n* (%)			
No treatment	8 (25)	4 (31)	4 (22)
Chemotherapy	23 (75)	9 (69)	14 (78)
Pretreatment status, *n* (%)			
As primary treatment	5 (16)	3 (23)	2 (11)
CK for progression	24 (77)	10 (77)	14 (79)
Nonresponsive to chemotherapy	2 (6)	0	2 (11)
Site of involvement, *n* (%)			
Segment VIII	12 (39)	4 (31)	8 (44)
Segment VII	7 (23)	3 (23)	4 (22)
Porta region	5 (16)	2 (15)	3 (17)
Right lobe I/II	4 (13)	3 (23)	6 (6)
Segment VI	2 (6)	0	2 (11)
Segment III	1 (3)	1 (8)	0
Primary, *n* (%)			
Colon	13 (42)	13 (72)	-
Breast	1 (3)	1 (5)	-
Gall bladder	5 (16)	5 (16)	-
HCC, *n* (%)	13 (42)	-	13 (100)

HCC=Hepatocellular carcinoma, CK=Creatine kinase, TACE=Transarterial chemoembolization, KPS=Karnofsky Performance Status

patients was 10.5 months (2.1–44.6 months) and metastatic disease were 6.5 months (1.9–24.6 months), respectively. Nausea (Grade I) and appetite loss were the most common symptoms immediately after radiation therapy. Thirty-five percentage (20/31) of patients had Grade I–II GI toxicities, which subsided with symptomatic care. There were no Grade III–IV toxicities observed in any patient except only one patient (7%) with HCC had anicteric ascites with high serum alkaline phosphatase 2 months after CK and recovered with supportive care. Although majority of the patients complained of mild-to-moderate pain requiring medication for 1 day after fiducial placement, there were no fiducial-related severe toxicities or gross fiducial migration during treatment.

Patient- and treatment-related factors influencing the local control were evaluated [Table 4]. Median OS (month) were significantly influenced by performance status (Karnofsky Performance Status [KPS] 70–80 vs. 90–100: 9.9 vs. 16.4; $P = 0.024$), Child-Pugh (CP A/B vs. C: 14.9 vs. 8.8; $P = 0.046$), cirrhosis (only fatty liver vs. diffuse cirrhosis: 23.6 vs. 6.5; $P = 0.069$), prior treatment (no Rx vs. prior Rx: 30.1 vs. 8.2; $P = 0.008$), single versus multiple lesions (16.4 vs. 6.9 months; $P = 0.001$), and target volume (<10 cc vs. >90 cc: 24.6 vs. 11.2; $P = 0.03$), respectively [Figures 1 and 2]. Patients with good performance status, better Child Pugh score, high radiation dosage in small volume disease have significantly better survival function than their counter-part.

Discussion

Radiosurgery (Gamma Knife) is in use for brain tumors for more than 50 years. The outcome (local control) in brain metastasis, acoustic schwannoma, meningiomas, and arteriovenous malformations are quite satisfactory.[17-19] Radiosurgery is the standard of care in many intracranial indications and is widely used throughout the world. SBRT for extracranial sites are in the process of evolution. There are mostly small phase II single institutional studies with small patient number and short follow-ups. Although SBRT is considered "promising" in many of the extracranial sites

Table 2: Dosimetric parameter

	All patient (*n*=31)	HCC (*n*=13)	Metastasis (*n*=18)
Dose, *n* (%)			
<39 Gy	13 (42)	8 (61)	5 (28)
>39 Gy	18 (58)	5 (39)	13 (72)
Dosage schedule, *n* (%)			
21 Gy/3#	3 (9)	-	3 (17)
24 Gy/3#	1 (3)	1 (8)	0
27 Gy/3#	5 (16)	4 (31)	1 (6)
30 Gy/3#	3 (9)	2 (15)	1 (6)
33 Gy/3#	1 (3)	1 (8)	-
45 Gy/3#	18 (58)	5 (39)	13 (72)
Prescription isodose, *n* (%)			
80%	7 (23)	5 (40)	2 (11)
85%	19 (61)	5 (40)	14 (78)
88%	1 (3)	1 (8)	-
90%	4 (12)	2 (16)	2 (11)
Target volume (cc), *n* (%)			
<10	5 (16)	3 (23)	2 (11)
11-90	18 (58)	4 (31)	14 (78)
>90	8 (25)	6 (46)	2 (11)
PTV (target)			
Mean volume (cc)	141.22	37.1	42.5
Range (cc)	10-919	27-49	21-49
Maximum dose (Gy)	42.5	40	44
Range (cc)	23-51.11	30-51	23-51
Mean dose (Gy)	37.2	34.5	39
Range (Gy)	21-45	24-45	21-45
Mean CI	1.1.9	1.12	1.24
Range	1.01-1.41	1.1-1.4	1.02-1.38
Mean nCI	1.31	1.29	1.32
Range	1.07-1.45	1.07-1.45	1.16-1.42
Mean HI	1.18	1.18	1.18
Range	1.10-1.25	1.10-1.25	1.10-1.25
Liver			
Mean volume (cc)	1103	1112	1098
Mean dose (Gy)	5.4 (2-12.6)	5 (2-9.8)	5.6 (2-12.6)
800 cc mean dose (Gy)	5.3	5	5.6
20 Gy mean volume (cc)	185.6 (10-338)	133 (4.8-338)	223.5 (10-338)
10 Gy mean volume (cc)	440.8 (20-981)	386.3 (30-770)	480 (20-981)
Intestine			
Mean dose (Gy)	3.4 (0.2-6.8)	3.5 (0.2-6.8)	3.3 (2.7-5)
2% volume dose (Gy)	12.5 (1.2-21.6)	11.4 (1.5-21.6)	12.7 (7-15.4)
Dose delivery parameters			
Nodes			
Mean number	79	73	84
Range	49-89	49-89	55-88
Beamlets			
Mean number	183	180	183
Range	128-236	128-222	140-236
Monitor unit			
Mean	44,498	49,816	40,658
Range	26,795-96,016	26,795-96,016	8599-27,560
Treat time (min)			
Mean	59.13	60.9	57.8
Range	42-96	47-96	42-63
Ave radial error			
Mean	1.14 (0.2-3.5)	1 (0.2-3.5)	1.25 (0.5-1.5)

CI=Conformity index, nCI=Normalized CI, HI=Homogeneity index, PTV=Planning target volume, HCC=Hepatocellular carcinoma

including liver primary and metastatic disease, there is no long-term hard evidence regarding the effectiveness of these modern technologies.

Liver is a "sub-diaphragmatic" organ and its movement is deeply influenced by respiratory motion. Liver moves in the range of 2–5 cm in superior-inferior direction along with respiration and

Table 3: Survival function and events

	All patient (*n*=31)	HCC (*n*=13)	Metastasis (*n*=18)
Median OS (months)	9	10.5	6.5
Mean OS±SD (months)	12.4±11.3	18.4±14.5	8.15±5.3
Range	1.9-44.6	2.1-44.6	1.9-24.6
1-year actuarial survival (%)	43.1	40	38
2-year actuarial survival (%)	30	36	5
30-month actuarial survival (%)	9.7	13	-
Status at LFU, *n* (%)			
Stable	9 (29)	2 (15)	7 (39)
Progression	15 (48)	7 (53)	8 (44.8)
Metastasis	6 (19)	3 (23)*	3 (17)**
Complete remission	1 (3)	1 (8)	0
Events, *n* (%)			
Alive	12 (39)	3 (23)	9 (50)
Death	19 (61)	10 (77)	9 (50)
Toxicity profile, *n* (%)			
GI toxicity Grade I-II	11 (35)	5 (38)	6 (33)
Grade III-IV	0	-	-
Other**			
Fiducial related toxicity, *n* (%)			
Pain requiring painkiller	10 (32)	3 (23)	7 (39)

*One patient with HCC had brain metastasis, 2 years after CK. Two HCC patients had extensive (lung and bones) metastasis after 6-month post-CK, **Liver metastasis patients had progression and new metastatic sites in liver and other organs. HCC=Hepatocellular carcinoma, CK=Creatine kinase, SD=Standard deviation, OS=Overall survival, GI=Gastrointestinal, LFU=Last follow up status

hence need a margin internal target volume (ITV) of about 5 cm with conventional radiation treatment.[20,21] On the other hand, movements of liver not only depends on the respiratory motion but also on many other factors such as filling of stomach, peristaltic movement of intestine, and abdominal muscle cramps. Apart from these factors, liver is a spongy structure and there may be collapse and expansion with change in intra-abdominal pressure. "Erratic" and unpredictable movement of the liver with respiration makes radiation delivery nearly impossible with conventional techniques. External fiducial-based tracking or "volume image"-based tracking may not be effective in tracking the actual or "real-time" movement of the liver. Internal fiducial-based "real-time" tracking with Robotic Radiosurgery Technology is an optimal solution for liver stereotaxy delivery. Tolerance of liver is low (approximately 35 Gy for whole liver) and HCC need higher dose (>60 Gy equivalent) for any effective response. In HCC, early studies with radiation therapy failed mostly because of poor delivery techniques and low radiation dosage. CyberKnife robotic radiosurgery is a fiducial based 'real-time' tracking system and it minimizes margins to GTV and hence reduce dose to normal liver parenchyma. Short course and high dose per faction schedule increases biological equivalent dose and potential to improve response (local control) to treatment. At present, SBRT in HCC are mostly recommended in recurrent, residual disease after failure of conventional focal therapy options (TACE, surgery) or patient not responding or tolerating systemic therapy. In recent years, there are few published reports of SBRT in mostly recurrent/progressive HCCs showing promising outcome.[11-18]

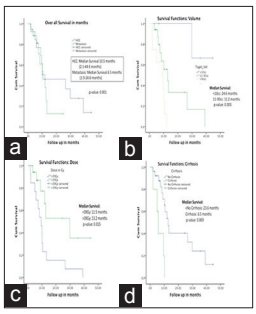

Figure 1: Survival functions and factors influencing survival. a) KPS; b) No of lesions; c) prior treatment d) Child Pugh criteria

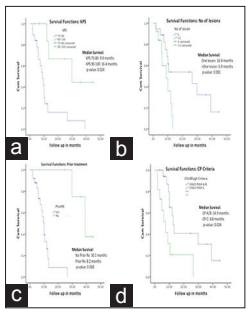

Figure 2: Factors influencing survival function. a) Overall survival; b) Volume c) Dose; d) Cirrhosis

In recent years, there are few published series on liver tumors (HCCs) treated with modern SBRT techniques. Price *et al*. reported 26 patients with small volume disease planned for liver transplant.[22] At 13-month follow-up, response rate is 73% with no severe toxicity. Ibarra *et al*. reported 21 inoperable HCC patient series with time to progression of 6.3 months.[12,13] One- and 2-year actuarial OS was 87% and 55%, respectively. Facciuto *et al*. reported 39 post-TACE residual disease patients treated with SBRT and 87% patients had stable disease.[14] Goyal *et al*. (*n* = 17) reported volume reduction of 44% with 35 Gy in recurrent HCCs.[15] In recurrent HCCs, higher dose of radiation (>45Gy) was found to be independent prognostic factor.[16] In Kwow JH (*n* = 42) study, in post-TACE progressive HCCs (dose 39 Gy/3#), 1- and 3-year OS was 92.9% and 58.6%, respectively.[17] Huang *et al*. reported retrospective series of 174 recurrent/progressive patients treated with and without SBRT.[18] At median follow-up of 20 months, 42 patients were treated with SBRT (Median dose 37 Gy) and were compared with 138 patients without SBRT. One- and 2-year local control was 87.6 and 75.1%, respectively. Two-year OS was 64% and median survival was 8 months. Patients treated with SBRT or without SBRT, 2 year overall survival were 72.6% and 42.1% respectively (p-value = 0.013). Treatment with SBRT, small volume disease (T<4cm), early stage disease (Stage I) and with good Child Pugh score (CP A) were found to be independent prognostic factor. Also evaluated role of SBRT with TACE in HCCs (*n* = 365).[23] Complete response in the cohort of patients treated with TACE alone and TACE with SBRT were 96% (29/30) and 3% (1/88), respectively (*P* = 0.001). Disease-free survival was 15.7 months in SBRT + TACE arm and only 4.2 months in TACE alone arm (*P* = 0.029). Tumor volume <5 cm, total dose >45 Gy, and dose/fraction >15 Gy had influenced the survival function (Dewas *et al*. [*n* = 48]).[24,25] It seems, in patients with good performance status having small residual disease (<5 cm) and treated with higher total dose (>45 Gy) SBRT and higher dose per fraction (>15 Gy) have significant survival advantage.[26-29]

The present study is one of the very few prospective reports in liver tumors from Indian subcontinent treated with Robotic Radiosurgery Technique and reported relative long-term results. Majority of the patients received either TACE or systemic therapy. Hence, the present cohort of patients is progressive recurrent disease with expected guarded prognosis. In these recurrent/progressive patients cohort, median OS was

Table 4: Factors influencing survival function

Factors	All patient (*n*=31)			HCC (*n*=13)			Metastasis (*n*=18)		
	n	Median OS (months)	*P*	*n*	Median OS (months)	*P*	*n*	Median OS (months)	*P*
Age (years)									
<60	18	11.9	0.547	8	17.5	0.655	10	7.5	0.133
>60	13	13.1		5	20		8	8.9	
Gender									
Male	24	13.6	0.02	13	8.4	0	11	7.8	0.384
Female	7	8.5		0	0		7	8.5	
KPS									
70-80	19	9.9	0.024	10	12.9	0.57	9	6.5	0.2
90-100	12	16.4		3	36.7		9	9.7	
Child-Pugh									
A/B	20	14.9	0.046	7	24.9	0.017	13	9.5	0.195
C	11	8.8		6	10.8		5	4.6	
Cirrhosis									
No	26	23.6	0.069	8	25.9	0.012	18	8.1	-
Yes	5	6.5		5	6.5		0	0	
Prior treatment									
Yes	25	8.2	0.008	9	10	0.919	16	7.2	0.001
No	6	30.1		4	37.3		2	15.7	
Hepatitis									
No	23	10.6	0.003	5	19.4	0.314	18	8.1	-
Yes	8	17.8		8	17.8		0	0	
Dose (Gy)									
<39	13	11.5	0.416	8	13.6	0.468	5	8.2	0.499
>39	18	13.2		5	26.2		13	8.1	
Volume (cc)									
<10	5	24.6	0.03	3	36.7	0.142	2	6.6	0.201
11-90	18	11.2		4	20.8		14	8.5	
Number of lesions									
1	18	16.4	0.001	10	21.5	0.004	8	10.1	0.001
>2	13	6.9		3	8.3		10	6.5	
Fiducial									
1-2	17	13.1	0.229	4	30.5	0.854	13	7.7	0.8
3-4	14	11.6		9	13.1		5	9.1	

HCC=Hepatocellular carcinoma, OS=Overall survival, KPS=Karnofsky performance status

12.4 months, which is comparable with the literature. Mean survival for HCC and metastasis were 18.4 and 8.15 months, respectively. Mean survival in HCC patients treated with focal therapy along with systemic therapy was higher compared with historical cohort of patients treated with systemic therapy alone. Patients with smaller volume disease had significantly better survival. Performance status and Child-Pugh criteria also influence survival. Background chronic liver disease (cirrhosis) had detrimental effect on survival functions. Patients treated with radical intent upfront SBRT have better outcome. Patients treated with higher dose of radiation therapy (>39 Gy) do have better survival compared with patients treated with lower dosage of radiation. Patients with smaller volume disease survive more than large volume disease. Patients with good performance status, better Child-Pugh score (A), small volume disease treated with higher dose (>45 Gy), and no prior treatment have the best survival function. In our data, HCC volume <10 cc, good performance status (KPS >80) patients without prior treatment when treated had median survival of 24.6 months. Patients with high volume (GTV >90cc), poor performance status (KPS<80) and with prior treatment had poorer survival (median survival 6.2 months; $P = 0.001$). There was no difference in survival function in patients treated with single or multiple fiducial placement (13.1 vs. 11.6 months; $P = 0.229$). After fiducial placement, majority of these patients had mild-to-moderate pain requiring analgesics. No gross migrations of fiducials were recorded and no patient required repeat simulation because of gross migration of fiducials. Post-SBRT response assessment was challenging, as there was diffuse enhancement and necrosis in the high-dose region. However, there was gross reduction of serum alpha-fetoprotein level after treatment. Hence, only OS function was considered for evaluation of the efficacy of treatment. The survival outcome, toxicity profile, and dosimetric parameters were comparable with literature. There was no additional toxicity in our patient population with poor nutritional status and in patients with moderate-to-severe chronic liver disease.

In the present analysis, majority of the patients had moderate-to-severe cirrhosis; mostly due to infective hepatitis. Whereas, nonalcoholic steatohepatitis (NASH), metabolic (hereditory) disorders and alcohol-induced cirrhosis are the common causes in developing countries. Majority of our patients were treated with conventional methods (TACE, systemic therapy) before CyberKnife treatment, whereas in literature, a large proportion of patients were treated with radiosurgery as the initial treatment. Response to systemic therapy (Sorafenib)

is also different in Asian patient cohort.[9] In Chang *et al*. study, median survival in Asian patients treated with Sorafenib was only 6.5 months, whereas in similar patient cohort from Western population was 7.8 months. These suggest that there may be differential susceptibility and tolerance to sorafenib in different ethnic patient cohort. In the similar background, impact of radiation therapy may also need to be evaluated in Asian patient population. Patients with compromised liver function, large volume disease, and in patients with poor nutrition status and performance status may not tolerate high-dose radiation therapy, and these factors may influence outcome functions. Apart from these factors, patient selection, contouring and planning, and appropriate delivery may also influence outcome. In the present cohort, comparisons between the first and last five patients were done. Patient selection criteria were more stringent after the initial learning period. After the initial 'learning' period, the patient selection criterias were more stringent which resulted in better outcome. The present study provides the survival outcome in patients from Indian subcontinent with different disease profile compared with published literature from the Western patient population. Majority of our accrued patients had recurrent/residual disease and were treated with systemic therapy. These patients had moderate-to-severe background cirrhosis liver with infective hepatitis. In recent years, radiosurgery is more convincingly getting accepted as upfront treatment modality even as an alternative to TACE or systemic therapy. Multimodality approach will be the future of HCC treatment with both invasive therapies such as TACE or RFA will be utilized along with radiosurgery as primary modality and in recurrent/residual disease.

In summary, stereotactic radiosurgery is safe and effective local treatment modality in selected patients with liver malignancies with minimal adverse events. Factors such as performance status, Child-Pugh classification, cirrhosis status, prior treatment, radiation dosage schedule, and target volume significantly influence survival function. There may be differential response to treatment in Asian and Western patient population suffering from inoperable HCCs. Prospective adequately powered multicentric randomized study in different patient cohorts will confirm impact of patient-related and treatment-related factors influencing response to treatment.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1a: Individual patient parameters (*n*=31)

Diagnosis	Age (years)	Gender	Child-Pugh	Prior Treatment	KPS	Number of lesions	Hepatitis	Liver status	Site	Dose (Gy)	Follow-up		
											Status at LFU	Event	Median OS (months)
HCC	60	Male	C	Chemo	70-80	1	No	Fatty liver	Porta hepatis region	33	Local progression	Dead	10.6
Colon	81	Male	C	Chemo	70-80	1	No	Normal	Porta hepatis region	20	Local progression	Dead	7.4
Colon	44	Female	B	Chemo	70-80	1	No	Normal	Porta region	21	Local progression	Dead	8.3
Colon	45	Male	B	No prior Rx	70-80	1	No	Fatty liver	Porta hepatis region	27	Local progression	Dead	39.1
HCC	63	Male	B	TACE	70-80	2	Hepatitis C	Diffuse cirrhosis	Segment VII	30	Local progression	Dead	5.9
Colon	54	Male	C	Chemo	<70	3	No	Normal	Right lobe	21	Local progression	Dead	1.9
GB	55	Female	A	Chemo	70-80	1	No	Normal	Segment VI	27	Local progression	Dead	10.2
HCC	61	Male	B	TACE	70-80	2	Hepatitis C	Diffuse cirrhosis	Segment VIII	24	Metastasis	Dead	10.1
HCC	71	Male	B	TACE	70-80	1	Hepatitis B	Diffuse cirrhosis	Segment VII	27	Local progression	Dead	9.6
HCC	59	Male	C	Chemo	70-80	1	No	Normal	Segment VIII	30	Metastasis	Dead	26.5
GB	35	Female	B	Chemo	90-100	3	No	Normal	Segment VIII	30	Metastasis	Dead	13.3
HCC	61	Male	B	No prior Rx	90-100	1	Hepatitis B	Fatty liver	Right lobe	45	CR	Dead	29.8
HCC	53	Male	C	TACE	70-80	1	Hepatitis B	Diffuse cirrhosis	Segment VIII	27	Local progression	Dead	2.1
GB	61	Male	B	TACE	70-80	2	No	Fatty liver	Porta hepatis region	45	Local progression	Dead	12.8
HCC	59	Male	B	No prior Rx	90-100	1	Hepatitis C	Fatty liver	Right lobe	45	Stable	Alive	35.8
HCC	71	Male	B	No prior Rx	90-100	1	Hepatitis B	Fatty liver	Segment III	45	Metastasis	Alive	44.6
HCC	45	Male	C	Chemo	70-80	1	Hepatitis C	Diffuse cirrhosis	Right lobe	27	Local progression	Dead	4.9
HCC	47	Male	C	TACE	70-80	1	No	Fatty liver	Segment VII	45	Stable	Alive	12.1
HCC	48	Male	C	Chemo	70-80	3	No	Fatty liver	Segment VIII	45	Local progression	Dead	9
Colon	39	Female	B	Chemo	90-100	3	No	Fatty liver	Segment VIII	45	Local progression	Dead	12
Colon	49	Male	C	Chemo	70-80	3	No	Fatty liver	Segment VIII	45	Local progression	Dead	3.5
GB	32	Female	C	Chemo	70-80	2	No	Fatty liver	Segment VIII	45	Local progression	Dead	6.2
Colon	35	Male	B	TACE	90-100	1	No	Fatty liver	Segment VII	45	Stable	Alive	6.3

Contd...

Supplementary Table 1a: Contd...

Diagnosis	Age (years)	Gender	Child-Pugh	Prior Rx	KPS	Number of lesions	Hepatitis	Liver status	Site	Dose (Gy)	Follow-up		
											Status at LFU	Event	Median OS (months)
Colon	63	Male	C	Chemo	70-80		No	Fatty liver	Segment VII	45	Stable	Alive	4.3
Colon	66	Male	B	Chemo	90-100	2	No	Fatty liver	Segment VIII	45	Stable	Alive	3.8
Colon	34	Male	A	Chemo	90-100	1	No	Fatty liver	Segment VIII	45	Metastasis	Alive	6.9
Colon	61	Male	B	Chemo	70-80	3	No	Fatty liver	Segment VII	45	Stable	Alive	4.8
Breast	49	Female	A	No prior Rx	90-100	1	No	Normal	Segment VIII	45	Stable	Alive	6.9
GB	65	Male	A	No prior Rx	90-100	1	No	Normal	Segment VI	45	Metastasis	Alive	24.6
Colon	62	Male	A	Chemo	90-100	1	No	Normal	Segment VII	45	Stable	Alive	10.4
Colon	62	Female	A	Chemo	70-80	2	No	Fatty liver	Segment VIII	45	Stable	Alive	3.2

Child-Pugh (A, B, C). KPS=Karnofsky performance status, OS=Overall survival, TACE=Transarterial chemoembolization, HCC=Hepatocellular carcinoma, LFU=Last follow up status; GB=Gall bladder; CR=Complete response

Supplementary Table 1b: Individual patient parameters (*n*=31)

Diagnosis	PTV								Liver					Treatment parameters			
	PTV volume (cc)	Maximum dose	CI	nCI	HI	Mean dose	Percentage coverage	Prescription isodose (%)	Volume	20 Gy volume	10 Gy volume	800 cc dose	Mean dose	Nodes	Beamlets	Monitor unit	Time (min)
HCC	519	40.6	1.24	1.35	1.25	36.00	92	80	909	222	673	7.7	15.20	62	194	75,932	79
Colon	56.2	23.5	1.19	1.22	1.18	21.90	98	85	834	21	33	1.2	1.33	72	196	43,229	42
Colon	43.9	26.2	1.11	1.16	1.25	23.70	96	80	707.6	1.8	118	0.8	6.40	55	140	27,560	51
Colon	78.4	31.7	1.33	1.38	1.18	29.60	96	85	1278	95.6	332	4.7	8.00	73	160	26,795	51
HCC	83.5	37.5	1.2	1.3	1.21	32.80	95	80	1049	247	593	3.7	13.00	82	128	96,016	96
Colon	628	26.2	1.38	1.42	1.25	23.80	97	80	1973	272	981	12.6	11.30	66	159	30,015	63
GB	56.5	31.8	1.02	1.20	1.18	28.50	85	85	1921	47	257	4.1	5.10	57	187	30,707.	62
HCC	92	30	1.12	1.23	1.25	27.00	92	80	1019	26.2	296	4.2	8.20	52	152	34,183	52
HCC	157	31.8	1.06	1.20	1.18	28.70	89	85	1299	88	292	3.2	7.00	60	187	28,592	58
HCC	62.5	37.5	1.32	1.37	1.25	34.00	96	80	1801	18	235	5.6	5.50	49	174	67,001	60
GB	50.7	35.3	1.17	1.26	1.18	32.10	92	85	1452	73.3	249	4.6	6.80	79	236	68,521	63
HCC	10.3	47.1	1.14	1.20	1.10	46.00	95	90	1030	4.8	301	2.1	3.10	78	180	40,000	56
HCC	919	31.8	1.05	1.07	1.18	29.00	90	85	1336	256	771	9.8	13.00	89	222	32,621	71
GB	67.2	50.9	1.30	1.38	1.18	49.80	95	85	983	338	644	6.9	17.70	84	183	40,179	60
HCC	11.3	51	1.20	1.30	1.10	46.00	96	90	1050	5.1	30.	2.2	2.60	67	137	50,500	55
HCC	10.3	51.1	1.41	1.45	1.14	47.60	97	88	730	4.8	32.5	2.3	2.60	67	136	55,658	54
HCC	421	33.8	1.27	1.32	1.25	30.70	96	80	978	187	545	6.1	12.80	78	194	50,067	53
HCC	67.2	50.9	1.30	1.38	1.18	49.80	95	85	983.5	337	671	6.9	17.70	84	183	40,172	60
HCC	215	49.2	1.20	1.30	1.20	46.00	95	85	993	240	550	7	11.00	86	190	50,002	47
Colon	212	49.3	1.20	1.30	1.20	46.00	95	85	991	240	551	7.1	11.00	88	193	50,002	47
Colon	67.2	50.9	1.30	1.38	1.18	49.80	95	85	983.6	338	644	6.9	17.70	84	183	40,181	60
GB	67.1	51.1	1.30	1.39	1.2	49.9	95	86	984	348	676	7.1	17.7	84	183	40,283	61
Colon	10.1	47.3	1.15	1.20	1.12	46.1	95	90	1030	4.9	310	2.2	3.10	78	177	40,001	56
Colon	67.2	51.1	1.30	1.38	1.18	49.80	95	85	984	342	642	6.9	17.70	87	189	41,082	60
Colon	69.1	50.9	1.30	1.39	1.2	48.5	95	85	983	338	642	7.3	17.70	84	183	40,183	60
Colon	10	47.5	1.14	1.20	1.10	46.00	95	90	1030	4.80	410	2.2	3.10	78	180	40,001	56
Colon	69.2	51	1.30	1.38	1.2	51.8	95	85	983.5	339	644	6.9	17.70	84	183	40,126	58
Breast	65.7	52.8	1.31	1.42	1.17	49.7	95	85	984	332	653	6.9	17.70	84	181	40,183	60
GB	67.6	51.7	1.30	1.37	1.19	49.8	95	85	995	339	651	6.7	18.1	85	182	40,187	61
Colon	59.3	48.2	1.33	1.39	1.12	49.9	95	85	984	340	642	6.8	17.60	84	183	40,185	60
Colon	67.3	53.9	1.32	1.38	1.18	49.80	95	85	986	338	643	6.9	17.70	86	179	40,172	59

PTV=Planning target volume, CI=Conformity index; nCI=Normalized conformity index, HI=homogeneity index, HCC=Hepatocellular carcinoma, GB=Gall bladder