Early Hepatocellular Carcinoma Treated by Radiofrequency Ablation—Mid- and Long-Term Outcomes

Amar Mukund^{*,*}, Prayas Vats^{*,*}, Ankur Jindal[†], Yashwant Patidar^{*}, Shiv K. Sarin[†]

^{*}Department of Interventional Radiology, Institute of Liver and Biliary Sciences, New Delhi, 110070, India and [†]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, 110070, India

Background: Radiofrequency ablation (RFA) is a standard treatment for small inoperable hepatocellular carcinoma (HCC). Studies on mid- and long-term outcome of RFA as first-line therapy for HCC from India are limited. **Methods:** We evaluated consecutive HCC patients who underwent RFA as primary treatment modality at our institute between July 2009 and April 2016. The median follow-up period was 26 months, range 1–84 months. We evaluated post-RFA tumor response, disease-free survival (DFS), overall survival (OS), and local tumor progression (LTP). Prognostic factors were also analyzed. **Results:** In 147 patients (male:female = 121:26; mean age, 59.2 years), 209 RFA sessions were done for 228 lesions (mean size of 21.5 ± 8.3 mm, range 10–50 mm). Primary success rate was 94.2%. The estimated cumulative proportion survival at 1, 3, and 5 years was 90.2%, 63.8%, and 60.2%, respectively. The cumulative incidence of LTP estimated at 1, 3, and 5 years was 13.1%, 19.7%, and 20.1%, respectively. The mean estimate of LTP-free survival was 53.6 months (95% confidence interval: 0.49–0.58) which is 58.2 months in <3 cm lesions and 20.4 months in >3 cm lesions ($P < 0.01$). There was no significant difference in LTP rates between lesions in perivascular versus nonperivascular location ($P = 0.71$) and surface versus parenchymal lesions ($P = 0.66$). The mean DFS was 30.3 months (95% CI: 25.6–35.0). For OS, age and Child–Turcotte–Pugh class B were significant factors while for LTP, tumor size >3 cm was significant. Higher baseline alpha-fetoprotein level and LTP were poor predictors for DFS. Complication rate per RFA session was 7/209 (3.3%). **Conclusions:** RFA is a safe and effective curative modality for first-line treatment of HCC < 3 cm. (J CLIN EXP HEPATOL 2020;10:563–573)

Hepatocellular carcinoma (HCC) represents 90% of primary liver cancers and constitutes a major global health problem.¹ Its incidence is expected to increase in the future, given the increasing prevalence of metabolic syndrome and alcohol use. The Barcelona

Clinic Liver Cancer (BCLC) staging system, which incorporates tumor size and liver disease characteristics is most commonly used staging system and has been extensively validated. Patients with very early-stage (BCLC-0) and early-stage (BCLC-A) HCC have option for resection, transplantation, or ablation depending on status of the liver, portal pressure, bilirubin, and comorbidities.² Although liver transplantation (LT) is preferred, as it not only cures HCC but also prevents other cirrhosis-related complications, but LT is often limited by shortage of suitable living donor and high cost. Many patients also have co-existing portal hypertension and associated comorbidities despite small tumor volume for which hepatic resection is also not feasible.

Tumor ablation is a widely accepted curative treatment option for patients with early-stage HCC as it is cost-effective, require short hospital stay and has no major side effects and generally more acceptable to patients. RFA is one of the most frequently used first-line ablation technique, other being microwave ablation (MWA) and cryoablation.³ A recent meta-analysis has shown RFA to be as effective to MWA and cryoablation in terms of tumor response in small HCC.⁴

Studies on mid- and long-term outcome of RFA as first-line therapy for HCC from India are limited. One such study had analyzed 41 HCCs in 31 patients ranging from 1 to 5 cm with primary success rate of 80.4% and

Keywords: hepatocellular carcinoma, radiofrequency ablation, cirrhosis, alpha-fetoprotein

Received: 22.7.2019; Accepted: 24.4.2020; Available online 4 May 2020

Address for correspondence. Ankur Jindal, MD, DM, Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), D-1, Vasant Kunj, New Delhi, 110070, India.

E-mail: ankur.jindal3@gmail.com

Amar Mukund and Prayas Vats are joint 1st authors.

Abbreviations: AASLD: The American Association for the Study of Liver Diseases; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; CTP: Child–Turcotte–Pugh score; DFS: Disease-free survival; FNAC: Fine needle aspiration cytology; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; INR: International normalized ratio; LT: Liver transplantation; LTP: Local tumor progression; MELD: Model for end-stage liver disease; mRECIST: Modified response evaluation criteria in solid tumors; MWA: Microwave ablation; NASH: Nonalcoholic steatohepatitis; OS: Overall survival; PIVKA-II: Protein induced by vitamin K absence-II; PS: Performance status; RFA: Radio-frequency ablation; SIR: Society of Interventional Radiology; TACE: Transarterial chemoembolization; TIPS: Transjugular intrahepatic portosystemic shunt; USG: Ultrasonography

<https://doi.org/10.1016/j.jceh.2020.04.016>

overall survival (OS) rate of 63.3% at 1 year.⁵ In this study, our aim was to evaluate our experience from a single high volume center in treating HCC < 5 cm using RFA as primary modality. We evaluated post-RFA tumor response, DFS, OS, and LTP. Prognostic factors affecting survival and local recurrence were also analyzed.

MATERIALS AND METHODS

Patients and diagnosis

This retrospective study was conducted according to the standards of the declaration of Helsinki and approved by

institutional scientific review board and ethical committee (IEC/2018/65/MA11) with consent waiver for using clinical information. Informed consent was obtained from all patients for RFA procedure.

Clinical case records of all patients with a diagnosis of HCC and who underwent RFA between July 2009 and April 2016 were analyzed (Figure 1). We excluded patients who underwent RFA after April 2016, to have at least 3-year follow-up after RFA. Of total 228 patients who underwent RFA during this period, 147 were treated primarily with RFA. Main indications for RFA in HCC were 1) primary treatment for HCC <5 cm single lesion or <3 cm up to three lesions; 2) as a bridge therapy for transplant; and 3) patients ineligible/unwilling for resection. The exclusion

Figure 1 Flow chart summarizing patient selection for the study and outcome at the last follow-up.

criteria were patients with advanced stage HCC (BCLC stage C and D), prior treatment with other modality including resection, transarterial chemoembolization (TACE) or, other local ablative therapy, presence of extra hepatic metastasis, vascular invasion, gross ascites, bilirubin > 3 mg/dl, uncontrolled coagulopathy, hepatic encephalopathy, and documented sepsis. HCC was diagnosed according to the American Association for the Study of Liver Diseases (AASLD) guidelines using imaging for typical lesions and ultrasonography (USG)-guided biopsy/FNAC for atypical lesions wherever required.⁶ Of total, 125 lesions were diagnosed with noninvasive criteria while 22 were histologically proven HCC. Subcapsular lesions were defined as located or reaching at a distance of 10 mm or less from the liver capsules and other were designated as intraparenchymal. All lesions were also classified as perivascular or nonperivascular with perivascular HCC defined as tumor with any contact with first- or second-degree branches of a portal or hepatic vein that are 3 mm or greater. Management decisions were taken by consensus with hepatology and hepatopancreaticobiliary surgery teams.

The term “session” was referred to a single intervention event that consists of one or more ablations performed on one or more tumors. Single session was done in 105 patients, two in 30, three in 6, four in 4, and five in 2.

Radiofrequency ablation procedure

A detailed counseling session was conducted with an explanation of the benefits and the risks of RFA and surgical resection. A written informed consent was obtained from all patients. All RFA procedures were performed percutaneously under USG guidance (n = 110) or in combination with computed tomography (CT) (n = 37) for difficult locations and were performed by interventional radiologists (AM, YP) who had over 3 years of experience in percutaneous ablation at the beginning of inclusion period (July 2009). The procedure was performed under conscious sedation and local anesthesia along with vital monitoring. Conscious sedation consisted of IV injections of midazolam, propofol, and fentanyl was administered by an anesthesiologist. We used multitinned expandable monopolar RFA electrode (RITA StarBurst XL electrode or RITA StarBurst Talon, AngioDynamics) and the RF generator (RITA 1500X RF generator, AngioDynamics, Manchester, Georgia). The needle track from skin to the liver capsule was infiltrated with local anesthesia using 5–10 ml of 2% lidocaine. The needle was directed toward lesion using USG or CT guidance, and ablation was started with a target temperature of 105 °C and power of 150 W. In case the ablation zone was found to be inadequate by echogenic cloud formed while performing RFA, as seen on USG, the needle was repositioned to complete the ablation. Tract ablation was performed while removing the needle to

avoid peritoneal bleeding from capsular surface and tumoral seeding. After ablation, patients were monitored in the hospital for 1–2 days. Ablation was performed with the help of contrast-enhanced ultrasound (SonoVue contrast agent) in 16 patients. All CT-guided RFA (37 patients) were done in addition to USG guidance and immediate postablation contrast CT was performed in 9 patients to check for adequate ablation. Artificial perihepatic ascites was created in two cases to prevent large bowel injury and right artificial pleural effusion in one case.

Treatment outcome and follow-up

Follow-up was done 1 month after RFA with contrast-enhanced triple-phase CT/MRI scan of the abdomen, liver function test, and serum alpha-fetoprotein (AFP) level. The response evaluation was done using mRECIST (Modified Response Evaluation Criteria in Solid Tumors) imaging criteria.⁷ Complete ablation was defined by the absence of any enhancing area in tumor bed and incomplete if any nodular enhancing component was visualized at tumor site. Technical success (TS) and local tumor progression (LTP) were defined according to the image-guided tumor ablation: standardization of terminology and reporting criteria.⁸ TS was defined as the ablation zone completely covering the tumor with an ablative margin of at least 5 mm surrounding the lesion. LTP was defined as the appearance of enhancing tumor foci at the edge of ablation zone during follow-up after a technically successful ablation. DFS was defined as the survival without LTP or appearance of new intrahepatic or extrahepatic lesions. OS was defined as the survival until the last follow-up or demise. Those patients who had transplant or other loco regional therapy like TACE were censored at that point of time. For estimating OS, contact through telephone was done for those who were lost to follow-up to know the outcome; however, for LTP and DFS, only last hospital follow-up was taken as reference. New intrahepatic lesions <5 cm size, which were treated with RFA, are considered as another index lesion and followed from that point in time for LTP. For complications, new adverse event classification by Society of Interventional Radiology (SIR) was used.⁹

Statistical analysis

All statistical analysis was performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were denoted as mean $\pm$ standard deviation or median with range and compared using independent t-test or the Mann–Whitney U-test. Categorical variables were expressed as proportions and compared using the Pearson's chi-squared test or Fisher's exact probability test; a *P* value of <0.05 was considered statistically significant. The overall, DFS rate, and LTP rate were calculated using the Kaplan–Meier method and compared with log-rank test

Table 1 Baseline Characteristics of Patients.

Characteristics	N = 147
Age (mean $\pm$ SD)	59.2 $\pm$ 9.9
Sex (male:female)	121:26
No. of lesions—n (%)	
Single	98 (66.7%)
Multiple (>1)	49 (33.3%)
Etiology—n (%)	
HBV	48 (32.7%)
HBV, HCV coinfection	2 (1.4%)
HCV	33 (22.4%)
Ethanol	19 (12.9%)
NASH	26 (17.7%)
Cryptogenic	17 (11.6%)
Primary biliary cirrhosis	1 (0.7%)
Budd–Chiari syndrome	1 (0.7%)
Performance status at the first session—n (%)	
0	141 (95.9%)
1	6 (4.1%)
Tumor Size (mean $\pm$ SD)	21.5 $\pm$ 8.3
$\leq$ 30 mm	198 (86.9%)
>30 mm	30 (13.1%)
Lesion location—n (%)	
Subcapsular	143 (62.7%)
Parenchymal	85 (37.3%)
Relation to vessels (n = 228)—n (%)	
Perivascular	43 (18.9%)
Nonperivascular	185 (81.1%)
PIVKA-II (n = 56) (mAU/ml) (mean $\pm$ SD)	25.5 $\pm$ 5.0
AFP—median (range)	16.3 (1–9801)
<10 ng/ml	62 (42.17%)
>10 ng/ml	85 (57.82%)
Child–Pugh score—n (%)	
A	56 (38.0%)
B	80 (54.4%)
C	11 (7.4%)
MELD (mean $\pm$ SD)	12.3 $\pm$ 3.4
Bilirubin (mg/dL)—median (range)	1.5 (1.1–2.2)
Albumin (g/dL) (mean $\pm$ SD)	3.05 $\pm$ 0.59
INR (mean $\pm$ SD)	1.35 $\pm$ 0.29
Creatinine (mg/dl) (mean $\pm$ SD)	0.80 $\pm$ 0.29
ALT (IU/L)—median (range)	42 (27–65)
AST (IU/L)—median (range)	64 (42–99)
Platelet ($\times 10^9$ /L)—median (range)	90 (60–127)
ICG (n = 31) (Indocyanine Green test) (mean $\pm$ SD)	32.22 $\pm$ 12.23

HBV= Hepatitis B virus, HCV= Hepatitis C virus, NASH= Nonalcoholic steatohepatitis, PIVKA-II=Protein induced by vitamin K absence-II, AFP = Alpha-fetoprotein, MELD = Model for End-Stage Liver Disease, INR= International normalized ratio, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase.

wherever needed. Univariate and multivariate analysis were done to find out any significant association of clinical, baseline, or tumor-related variables with OS, DFS, or LTP.

RESULTS

Clinical characteristics

The baseline characteristics of the study population is summarized in Table 1. Of 147 patients with HCC selected for RFA, 209 RFA sessions were done for 228 lesions. TS was achieved in all patients with incomplete ablation at 1-month follow-up in 13 patients (8.9%). The mean tumor size was 21.5 $\pm$ 8.3 mm (range 10 mm–50 mm). Thirty patients (20.4%) had lesion size greater than 3 cm. Upto four lesions were treated in a single session.

Survival and local tumor progression

At first follow-up imaging after 1 month, 215 of 228 targeted lesions (94.2%) showed complete response (primary success rate). Thirteen patients (13 lesions) showed residual nodular contrast enhancement at edges of ablated zone which were assessed as incompletely ablated/partial response. Of these 13 patients, 4 underwent repeat RFA with complete ablation at next follow-up, 3 underwent TACE, 1 underwent TACE plus RFA, 2 had LT after 4 and 8 months, and 3 were followed on conservative measures. The median follow-up period was 26 months and ranged from 1 to 84 months. Reason for this wide range with intended follow-up of at least 3 years is that we have calculated follow-up by last visit in hospital or by telephonic follow-up or death. So, some were lost to follow-up, and some had died before 3 years. In the last follow-up, 51 patients were alive, 38 were lost to the follow-up, 12 had LT, and 46 were dead. Of 46 patients who died, 10 were directly related to tumor progression while others had unrelated causes including sepsis with refractory shock (n = 13), large intracranial bleed (n = 2), difficult to treat subacute bacterial peritonitis (n = 4), hematemesis (n = 2), pneumonia with lung abscess (n = 1), sudden cardiac arrest (n = 1), and 13 patients died at another hospital or home. Of 147 patients (8.1%), 12 had LT after a median follow-up of 7.5 months (IQR 4.2–11.5 months). The estimated cumulative proportion surviving at 1, 3, and 5 years were 90.2%, 63.8%, and 60.2%, respectively (Figure 2). In the last follow-up, 34% had complete response, and 15.6% had progressive disease.

Of 228 nodules, LTP was found in 46 nodules at follow-up imaging after 1–38 months with a median period of 12 months. The cumulative incidence of LTP estimated at 1, 3,

and 5 years was 13.1%, 19.7%, and 20.1%, respectively. The mean estimate of LTP-free survival was 53.6 months (95% confidence interval: 49.0–58.3). However, mean estimate LTP-free survival in lesions with size <3 cm was 58.2 months (95% CI: 53.8–62.5) and in lesion with size >3 cm, 20.4 months (95% CI: 14.2–26.6, $P < 0.01$) (Figure 2).

The mean DFS was 30.3 months (95% CI: 25.6–35.0). The estimated cumulative recurrence-free survival at 1, 3, and 5 years were 61.7%, 37.8%, and 26.5%, respectively. The development of LTP significantly shortened median DFS (50 months without LTP versus 9 months with LTP) (Figure 3).

Univariate and multivariate analysis

Univariate analysis of various variables was done to determine any significant factor that can be used to predict OS, DFS, and LTP as presented in Tables 1–3. Various variables evaluated were age, male sex, number of tumors (>1), size of the tumor (>3 cm), CTP class B, Model for End Stage Liver Disease (MELD), performance status, serum albumin level, serum bilirubin level, INR, serum AFP level, platelet count, and location of the lesion. For OS in univariate analysis, serum bilirubin, serum albumin, INR, CTP class B, MELD were significantly associated, whereas age ($P = 0.054$) and PS-1 ($P = 0.056$) were tending

Figure 2 A) Kaplan-Meier OS graph of 147 patients. B) Kaplan-Meier estimation for LTP free survival for 198 patients whose size was upto 3 cm as compared with 30 patients having tumor >3cm.

toward significance. Initially for multivariate analysis using cox proportional hazards model, serum bilirubin, serum albumin, and INR were excluded when comparing CTP class and MELD as they contain these parameters (Model 1). In this analysis, age and CTP class B were the only significant factors. When excluding CTP class B and MELD for analysis, age, serum bilirubin, and serum albumin were found to be the significant predictors of OS

(model 2) (Table 2). Similarly, for LTP, only tumor size >3 cm ($P < 0.01$) was the significant factor (Table 3). In univariate analysis, serum albumin ($P = 0.05$), bilirubin ($P = 0.04$), and LTP ($P < 0.01$) were significantly associated with DFS, while in multivariate cox proportional hazard model done for variables with $P < 0.20$, serum AFP ($P = 0.05$), and LTP ($P < 0.01$) were significant predictors for DFS (Table 4).

Figure 3 A) Graph showing Kaplan–Meier survival probability for disease-free survival. B) Kaplan–Meier estimation disease-free survival in patients with local tumor progression (LTP) and without LTP, which is statistically significant ($P < 0.01$).

Table 2 Univariate and Multivariate Analysis for Predictors of Overall Survival.

Characteristics	Univariate analysis			Multivariate analysis* (Model 1)			Multivariate analysis** (Model 2)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.03	1.00,1.06	0.05	1.04	1.00,1.09	0.01	1.04	1.00,1.08	0.02
Male sex	1.48	0.66,3.32	0.34						
No. of tumors (>1)	0.85	0.46,1.56	0.61						
CTP class B	3.44	1.63,7.27	<0.01	3.52	1.59,7.79	<0.01			
MELD	1.15	1.06,1.25	<0.01	1.06	0.96,1.17	0.20			
PS-1 ^{\$}	2.75	0.97,7.76	0.05	1.86	0.63,5.46	0.25	1.92	0.62,5.88	0.25
S. albumin (g/dL)	0.39	0.23,0.66	<0.01				0.56	0.31,0.99	0.04
S. bilirubin (mg/dL)	1.50	1.13,1.99	<0.01				1.40	1.00,1.95	0.04
INR	3.14	1.44,6.84	<0.01				2.10	0.76,5.81	0.15
IAFP levels (ng/ml) based on IAFP [#]	1.07	0.93,1.22	0.33						
Platelet count (x10 ⁹ /L)	0.99	0.99,1.00	0.24						
LTP	0.81	0.41,1.61	0.56						

*Excluding CTP class B and MELD. **Excluding S. bilirubin, S. albumin, and INR. \$ performance status. #IAFP = log AFP.

Table 3 Univariate and Multivariate Analysis for Predictors of Local Tumor Progression (LTP).

Characteristics	Univariate analysis			Multivariate analysis ^a		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	0.99	0.95,1.02	0.56			
Male sex	1.19	0.60,2.36	0.60			
Size (>3 cm)	4.69	2.52,8.72	<0.01	4.69	2.52,8.72	
Subcapsular location	1.14	0.62,2.09	0.66			
Perivascular location	0.85	0.38,1.92	0.71			
CTP class B	0.97	0.52,1.77	0.92			
MELD	1.01	0.91,1.11	0.78			
PS1	1.44	0.44,4.68	0.53			
Serum albumin (g/dL)	0.92	0.55,1.52	0.75			
Serum bilirubin (mg/dL)	0.93	0.66,1.32	0.70			
INR	1.53	0.59,3.98	0.38			
Serum AFP levels (ng/ml) on IAFP	1.00	1.00,1.00	0.67			
Platelet count (x10 ⁹ /L)	1.00	0.99,1.00	0.79			

^aSince only one variable was significant in univariate analysis, HR and CI of multivariate analysis are same as univariate analysis.

Complications

In total, 12 patients had minor and major complications. Excluding fever, complication rate per RFA session was 7/209 (3.3%). In majority of patients, there was transient serum transaminitis increasing 2–5 times, which usually returned to baseline in 3–4 days. Five patients (3.4%) had fever, which resolved after a course of broad spectrum antibiotic. Three patients and one patient, respectively, had mild perihepatic hemorrhagic collection (maximum upto 1.5 cm over the liver puncture site) and pneumothorax,

which were managed conservatively. Delayed major complication occurred in one case with anterior sectoral mild biliary dilatation which gradually increased for which percutaneous drainage was done at 1 year after RFA. One patient had abdominal wall needle tract seeding which became obvious after 2 years for which RFA was done and had complete response. Same patient had undergone transjugular intrahepatic portosystemic shunt (TIPS) for refractory ascites and now on follow-up. One patient had active arterial bleed from the tract after RFA which was

Table 4 Univariate and Multivariate Analysis for Predictors of Disease-Free Survival (DFS).

Characteristics	Univariate analysis			Multivariate analysis ^a		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.00	0.97,1.02	0.96			
Male sex	0.70	0.38,1.29	0.25			
No. of tumors (>1)	1.59	0.95,2.66	0.07	0.66	0.39,1.10	0.11
CTP class B	0.72	0.25,2.08	0.54			
MELD	1.04	0.98,1.10	0.13	0.99	0.93,1.06	0.88
PS1	1.32	0.53,3.28	0.55			
Serum albumin (g/dL)	0.70	0.49,1.00	0.05	0.77	0.52,1.13	0.18
Serum bilirubin (mg/dL)	1.23	1.05,1.51	0.04	1.20	0.98,1.47	0.07
INR	1.30	0.63,2.71	0.46			
Serum AFP levels (ng/ml) on IAFP	1.09	0.98,1.20	0.09	1.10	1.00,1.23	0.05
Platelet count (x10 ⁹ /L)	1.00	0.99,1.00	0.98			
LTP	4.25	1.54,11.68	<0.01	4.34	1.53,12.5	<0.01

^aMultivariate analysis of variable with $P < 0.20$ was done.

managed by endovascular coil embolization. There was no procedure-related death or liver abscess formation or liver failure after RFA.

DISCUSSION

This study describes our experience with RFA at one of the tertiary care high volume centers in India. We treated 147 patients with 228 lesions meeting our inclusion criteria with 100% TS and primary success rate of 94.2%, which is comparable with a study by Lee et al.¹⁰ Various studies have described success rate ranging from 92% to 96.2% as summarized in Table 5. Study by Shiina et al. needs mention as authors had achieved 99.4% success rate for initial as well as repeat RFA for recurrence and also calculated success rate according to size with 99.6% for ≤ 2.0 cm, 99.2% for 2.1–3.0 cm, 98.6% for 3.1–5.0 cm, and 97.7% for > 5-cm lesions.¹¹ They did CT after 1–3 days and if there was residual nodular area, repeat RFA of that lesion was done, probably explaining the high treatment success rate described by authors. We did follow-up imaging after 1 month of RFA, as per our institutional protocol.

The OS rate in our study at 1, 3, and 5 years is 90.2%, 63.8%, and 60.2%, respectively, which is similar to that of other studies in literature.^{10–14} These results are also comparable with surgical series for hepatic resection.^{15,16} As INR, serum albumin, and serum bilirubin are the components of CTP, multivariate analysis was done in two parts. Age, serum albumin, and serum bilirubin are poor predictors in one analysis, and age, CTP class B were significant when INR, serum albumin, and serum bilirubin were excluded from the analysis. It can be concluded that among all components of CTP, serum albumin and serum bilirubin are the most significant. Serum albumin repre-

sents the synthetic function of the liver and serum bilirubin as overall function of the liver, naturally it has an effect on OS of patients and may also play a role in pathogenesis and local tumor recurrence of HCC. These findings also corroborate well with a study by Kim et al. who have shown age and CTP class as significant factors and serum AFP level was insignificant for predicting OS. AFP is a tumor marker for HCC; however, it is nonspecific, and elevated level can be seen in chronic liver disease and non-hepatic malignancies.¹⁷ Many other studies had demonstrated child status as a predictor factor for OS.^{10,12,18,19} As MELD is not significant in multivariate analysis, it is inferior to CTP for predicting OS post RFA. One important conclusion is that despite local recurrence of tumor, it is not an independent predictor for OS as also reported by N Kontchou et al.²⁰ Logical explanation given by authors for this conflicting results was low recurrence rate in their studies probably due to technical and technological advancement in RFA and iterative RFA controlling the local tumor recurrence. Hence, if LTP is timely tackled, it did not affect the OS of a person, and a regular follow-up is important.

LTP occurred mainly in the first year with cumulative incidence of 13.1% and also LTP significantly affected the DFS (9 months with LTP versus 50 months without LTP), similarly reported by Lee et al.¹⁰ LTP is because of proliferation of microscopic foci at margin of treated lesion, which are not identified at 1-month follow-up imaging. The cumulative LTP rates reported in various studies at 5 years ranged from 10% to 27%, while in our study, it is 20.1%.^{10,13,18,21} LTP-free survival was significantly lower in tumor size less than 3 cm at 58.2 months and 20.4 months in size >3 cm. Tumor size >3 cm is an independent predictor for LTP in multivariate analysis.

Table 5 Summary of all Major Studies on Radiofrequency Ablation compared With This Study.

Studies	Patients/ lesions/ sessions	Size median or mean (cm)	Primary success rate	Follow-up (median or mean, months)	Local tumor progression	New lesions	Disease- free survival (1,3, and 5 yr), in percent	OS (1, 3, 5, and 10 yr)	OS predictors	LTP predictors	DFS predictors	Complications Major/minor Most common
Lencioni et al. 2005 ¹⁷	187/240	2.8 ± 0.7 (1.5 cm– 5cm)	92%	24 ± 21 (3–78)	1 yr—4%, 3 yr—10%, 5 yr—10%, 10 yr—5.3%	49.7% Recurrence rate 1 yr—14%, 3 yr—49%, 5 yr—81%	—	ITT analysis 97%, 67%, 41% OS 97%, 71%,48%	CTP class, Solitary HCC v/s multiple	—	—	2%/5%
Tateishi et al. 2004 ¹³	664/2140 (319 patient primary)	302 have <5 cm 17 have >5 cm	—	27.6 (2.0–61.2)	1yr-1.3%, 3 yr—2.4%,	—	—	94.7%,77.7%, 54.3%	Child status, tumor size, AFP, DCP	—	—	Major: 4% per treatment 1.9% per session Minor:1.7% per treatment, 0.8% per session Neoplastic seeding Biloma
Shiina et al. 2012 ¹⁰	1170/2982	2.5 ± 1.0	99.4%	38.2	1 yr—1.4%, 3 yr—3.2%, 5 yr—3.2%, 10 yr—3.2%	1 yr—25.6%, 3 yr—63.3%, 5 yr—74.8%, 10 yr—80.8%	—	96.8%,80.5%, 60.2%,27.3%	Age, anti-HCV, CTP class, tumor size, tumor number, DCP levels, AFP-L3	PIVKA-II levels	—	Major: 2.2% per treatment 1.5% per procedure
Kim et al. 2012 ¹²	1305/1502	2.2 ± 0.8	94.8%	33.4 (0.4–146.6)	19.4% (2.4– 113.2Months) 1 yr—9.7%, 3 yr—21.4%, 5 yr—27%, 10 yr—36.9%	54.8% 1 yr—24.4%, 3 yr—59.5%, 5 yr—73.1%, 10 yr—88.5%	—	95.5%,77.9%, 59.7%,32.3%	Old Age, CTP classB, Absence of antiviral therapy during follow up, Presence of extrahepatic recurrence	Large tumor size	—	8.3% overall 2% major
Francica 2012 ²⁵	365	≤3	92%	37 (12–132)	—	—	~50%,41.8% Median (36 Months)	~80%,64% (Median 74 Months)	Age>62yrs, Ascites, CTP score B 8 or higher	—	—	2.2%/6.3%
Our study	147/228/ 209	2.1 ± 0.8^{1–5}	94.2%	22 months (1 to 72 months)	20.1% Mean 12.5 months 1 yr—13.1%, 3 yr—19.7%, 5 yr—20.1%,	34.7%	61.7%, 37.8%, 26.5%	90.2%, 63.8%, 60.2%	Age, CTP class B OR Age, S. Albumin, S. Bilirubin	Size >3 cm	S. AFP LTP	Overall 3.3% Major 2.0%

Thus, tumor size significantly lowered the tumor-free period. Naturally with larger tumor probability of residual tumor component was high, thus affecting the LTP. Similar results were also shown in various studies with size greater than 2–3 cm as the only significant factor for LTP.^{10,13,20,22} Other than size, studies have shown ablative margin less than 5 mm, serum DCP levels as other predictors of LTP.^{14,22} We had not included DCP levels in analysis as data of only 56 patients were available. The advantage of RFA is that, by repeat session, recurrent tumor at margin can be targeted with good secondary success rate, which is why LTP had no effect on OS. Study by Nakazawa et al. showed that the presence of vessels contiguous with the tumor significantly correlated with LTP; however, in our study, we found no significant difference in local progression between lesions in perivascular versus nonperivascular location.²³ These results can be attributed to smaller caliber of vessels adjacent to tumor. This study found no significant difference in LTP of surface versus parenchymal lesion, which was similar to one study which concluded that efficacy and complication rate were comparable for surface and exophytic HCC.²⁴ Therefore, surface lesions can be safely targeted by RFA without increasing complication rates.

Very few studies had evaluated the predictors of DFS till now.^{10,12,20} Serum AFP was a common predictor in these studies with multinodular form of lesions, LTP, and child class B being other factors. In this series, serum AFP level and LTP were found to be independent predictors of DFS, with patients having high baseline AFP or LTP on follow-up had shorter DFS or in other words more likelihood of local or distant intrahepatic tumor recurrence. Thus, AFP did not affect OS; however, high AFP level had role in either local or intrahepatic distant recurrence of HCC. Table 5 summarizes all the major studies on RFA long-term outcomes. Per session complication rate in our study was 3.4% which is comparable with 3.1% major complication reported by Lee et al.¹⁰ The complication rate reported ranges from 0.9% to 2.7% per session in various studies.^{11,14,20,25}

Our study has certain limitations like selection bias since it is a single-center retrospective study. Another limitation is that almost one-fourth patients were lost to follow-up after a certain time; many of them could have developed HCC, which were not reported. Additionally, complete information about oral antivirals and other anticancer treatment is not available, which could have altered the final outcome. In spite of these limitations, to our knowledge, this is largest study from the Indian subcontinent highlighting the independent predictors of disease-free survival which only few studies had previously evaluated.

In conclusion, RFA is a primary, safe, and effective curative modality for HCC <3 cm with comparable OS with hepatic resection. Its use as first-line treatment modality for

lesion <3 cm is justified as LTP is significantly lower compared with larger lesions. Also, very low overall complication rate and easy to repeat sessions after local tumor recurrence are its major advantages.

CONFLICTS OF INTEREST

All authors have none to declare.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Amar Mukund: Conceptualization, Methodology. **Prayas Vats:** Data curation, Writing - original draft. **Ankur Jindal:** Conceptualization, Methodology. **Yashwant Patidar:** Data curation, Writing - original draft. **Shiv K. Sarin:** Writing - review & editing, Project administration.

REFERENCES

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European association for the study of the liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182–236.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet Lond Engl*. 2018 31;391:1301–1314.
3. Breen DJ, Lencioni R. Image-guided ablation of primary liver and renal tumors. *Nat Rev Clin Oncol*. 2015 Mar;12:175–186.
4. Luo W, Zhang Y, He G, et al. Effects of radiofrequency ablation versus other ablating techniques on hepatocellular carcinomas: a systematic review and meta-analysis. *World J Surg Oncol*. 2017 Jul 10;15, 126–126.
5. Kalra N, Kang M, Bhatia A, et al. Role of radiofrequency ablation in unresectable hepatocellular carcinoma: an Indian experience. *Indian J Radiol Imag*. 2013;23:139–144.
6. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatol Baltim Md*. 2018;67:358–380.
7. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010 Feb;30:52–60.
8. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update. *Radiology*. 2014 Jun 13;273:241–260.
9. Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a new adverse event classification by the society of interventional Radiology standards of practice committee. *J Vasc Intervent Radiol*. 2017 Oct 1;28:1432–1437.e3.
10. Lee DH, Lee JM, Lee JY, et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology*. 2013 Oct 30;270:900–909.
11. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol*. 2012 Apr;107:569–578.
12. Yang W, Yan K, Goldberg SN, et al. Ten-year survival of hepatocellular carcinoma patients undergoing radiofrequency ablation as a first-line treatment. *World J Gastroenterol*. 2016 Mar 14;22:2993–3005.
13. Kim Y, Lim HK, Rhim H, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular

- carcinoma: analysis of prognostic factors. *J Hepatol*. 2013 Jan;58:89–97.
14. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. *Cancer*. 2005 Mar 15;103:1201–1209.
 15. Yamamoto J, Kosuge T, Saiura A, et al. Effectiveness of hepatic resection for early-stage hepatocellular carcinoma in cirrhotic patients: subgroup Analysis according to milan criteria. *Jpn J Clin Oncol*. 2007 Apr 1;37:287–295.
 16. Park Y-K, Kim B-W, Wang H-J, Kim M-W. Hepatic resection for hepatocellular carcinoma meeting Milan criteria in Child-Turcotte-Pugh class a patients with cirrhosis. *Transplant Proc*. 2009 Jun;41:1691–1697.
 17. Liu Y, Lin B, Zeng D, et al. Alpha-fetoprotein level as a biomarker of liver fibrosis status: a cross-sectional study of 619 consecutive patients with chronic hepatitis B. *BMC Gastroenterol*. 2014 Aug 16;14, 145–145.
 18. Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology*. 2005 Mar;234:961–967.
 19. Yan K, Chen MH, Yang W, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. *Eur J Radiol*. 2008 Aug;67:336–347.
 20. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatol Baltim Md*. 2009 Nov;50:1475–1483.
 21. Hao Y, Numata K, Ishii T, et al. Rate of local tumor progression following radiofrequency ablation of pathologically early hepatocellular carcinoma. *World J Gastroenterol*. 2017 May 7;23:3111–3121.
 22. Lam VW-T, Ng KK-C, Chok KS-H, et al. Risk factors and prognostic factors of local recurrence after radiofrequency ablation of hepatocellular carcinoma. *J Am Coll Surg*. 2008 Jul;207:20–29.
 23. Nakazawa T, Kokubu S, Shibuya A, et al. Radiofrequency ablation of hepatocellular carcinoma: correlation between local tumor progression after ablation and ablative margin. *AJR Am J Roentgenol*. 2007 Feb;188:480–488.
 24. Patidar Y, Singhal P, Gupta S, Mukund A, Sarin SK. Radiofrequency ablation of surface v/s intraparenchymal hepatocellular carcinoma in cirrhotic patients. *Indian J Radiol Imag*. 2017;27:496–502.
 25. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatol Baltim Md*. 2008 Jan;47:82–89.