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Radiofrequency Ablation of Hepatocellular Carcinoma as Bridge Therapy to Liver Transplantation: A 10-Year Intention-to-Treat Analysis

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In a long-term (10-year) study of radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) as bridging therapy in patients listed for orthotopic liver transplantation (LT), we evaluated the impact of RFA on waiting list dropout rate, post-LT tumor recurrence, and long-term intention-to-treat, disease-specific survival (DSS). From March 2004 to October 2014, RFA was performed as the initial stand-alone bridge therapy to LT for 121 patients (men/women ratio, 83:38; mean age, 60.0 years) with 156 *de novo* HCCs (mean size, 2.4 cm). Follow-up period from initial RFA ranged from 1.3 to 128.0 months (median, 42.9 months). We assessed the overall and tumor-specific waiting list dropout rates, post-LT tumor recurrence, and 10-year post-LT and intention-to-treat survival rates. Dropout from the waiting list due to tumor progression occurred in 7.4% of patients. HCC recurrence after LT occurred in 5.6% of patients. The post-LT overall survival (OS) rate at 5 and 10 years was 75.8% and 42.2%, respectively, and the recurrence-free survival (RFS) rate was 71.1% and 39.6%, respectively. Intention-to-treat OS, RFS, and DSS rates for the entire study population at 5 and 10 years were 63.5% and 41.2%, 60.8% and 37.7%, and 89.5% and 89.5%, respectively. *Conclusion*: RFA as a first-line stand-alone bridge therapy to LT achieves excellent long-term overall and tumor-specific survivals, with a low dropout rate from tumor progression despite long wait list times and a sustained low tumor recurrence rate upon post-LT follow-up of up to 10 years. (HEPATOLOGY 2017;65:1979-1990)

Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, with more than 700,000 deaths per year.[1] Because most HCCs develop in patients with liver cirrhosis, liver transplantation (LT) is considered a treatment of choice for cure of both cancer and cirrhosis. However, not all patients with HCC and cirrhosis can be managed with LT due to shortage of available liver donors. Patients with HCCs on the waiting list for LT are often delisted due to tumor progression beyond the accepted criteria for LT. Therefore, locoregional therapy such as radiofrequency ablation (RFA) has been applied to HCC patients in many transplant centers before or after listing for LT, with the aim to bridge

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CR, complete response; CT, computed tomography; DSS, disease-specific survival; HCC, hepatocellular carcinoma; LT, liver transplantation; LTP, local tumor progression; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OR, odds ratio; OS, overall survival; PD, progressive disease; PR, partial response; RFA, radiofrequency ablation; RFS, recurrence-free survival.

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these patients to LT and to confer the best chance for survival.[2-5]

Achieving complete pathologic response by pretransplant locoregional therapy for HCC is known to enhance posttransplant outcomes such as HCC recurrence as well as recurrence-free survival (RFS).[6] Recent advances in RFA technology, image guidance, and assistive techniques such as hydroinfusion[7-9] are expected to improve the performance of RFA and therefore its role as a bridging therapy to liver transplantation. However, most studies reporting bridging therapy to LT contained heterogeneous mixtures of locoregional therapies,[6,10] and studies using RFA as the dominant or sole bridge therapy are rare.[5,11,12] Furthermore, most studies were published more than a decade ago, which means RFA was performed with earlier generation RFA systems. In addition, long-term (more than 5 years) outcomes of RFA specifically as a bridge therapy have not yet been reported. The purpose of this study, therefore, was to evaluate the impact of RFA on dropout rate, post-LT HCC recurrence, and 10-year long-term survival in patients with HCCs who underwent RFA as a bridge to LT.

Materials and Methods

This was a retrospective analysis of a prospective cohort from a tertiary center with large volume of LT. The study was approved by the institutional review board at the Ronald Reagan Medical Center, David Geffen School of Medicine at UCLA, and met the requirements of the Declaration of Helsinki. The need for informed consent was waived.

PATIENT POPULATION

From March 2004 to October 2014, patients who met the following criteria were included in this study: 1) cirrhosis with development of naïve HCC; 2) RFA performed as stand-alone first-line treatment at our institution, without adjunctive or combined interventions such as transarterial chemoembolization or ethanol injection; and 3) patient listed already for LT or within 6 months of the RFA. Patients who had received previous locoregional therapies were excluded.

RFA PROCEDURE

Percutaneous RFA was performed by one of five board-certified abdominal interventional radiologists (the majority by D.S.K.L., S.S.R., and J.M. with 20, 16, and 5 years of experience with RFA, respectively). All cases were selected based on multidisciplinary assessment of patient suitability and the radiologist's assessment of technical feasibility. Tumors were selected for stand-alone RFA treatment only if a minimum of 5 mm ablation margin can be confidently achieved with safety. In general, larger tumors, peri-hilar tumors, infiltrative tumors, and those where not all margins are visible or accessible due to imaging or mechanical limitations were not considered good candidates. Procedures were performed under monitored or general anesthesia. For guidance and monitoring, our standard protocol was simultaneous use of ultrasonography (HDI 5000, Advanced Technology Laboratories, Bothell, WA; iU22, Philips Healthcare, Bothell, WA) and computed tomography (CT) (Definition, Siemens Medical Solutions, Erlangen, German). Various RFA electrodes (Cool-tip RF System, Covidien, Mansfield, MA; Starburst RFA System, AngioDynamics, Latham, NY; LeVeen Needle Electrode, Boston Scientific, Natick, MA) were used according to the operator's preference and availability.

The technical goal of treatment was to achieve at least 0.5- to 1.0-cm of ablative margin where feasible,

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and overlapping ablations were performed when needed based on tumor size, geometry, and feedback from ultrasonography and CT monitoring. After RFA, tract ablation was performed to avoid bleeding and tract seeding. When tumors were close to the diaphragm or bowel, hydrodisplacement was performed as an option to avoid thermal injury, a technique that has been described previously.[7]

TREATMENT FOLLOW-UP

Patients were followed using contrast-enhanced CT or magnetic resonance imaging (MRI) after discharge at 1, 3, 6, 9, and 12 months after RFA and every 3-6 months thereafter. A treatment course was defined as all RFA sessions performed per HCC nodule based on follow-up imaging up to 3 months after initial RFA. Therefore, RFA was repeated to eradicate any number of residual tumors within the treatment course when feasible. Local tumor progression (LTP) was defined when viable tumor was found on follow-up imaging along the margin of a previous ablation zone where the RFA had been considered technically effective.[13] Distant recurrence was defined as a lesion with typical imaging features of HCC apart from a previous ablation zone. Patients with tumor recurrence were managed based on consensus of the multidisciplinary team. After transplantation, patients were monitored for tumor recurrence with serum alpha-fetoprotein (AFP) and CT or MRI every 3-6 months.

ASSESSMENT OF THERAPEUTIC EFFICACY

Treatment response was assessed individually for all 156 HCC tumor nodules initially treated with RFA based on the Society of Interventional Radiology Standardization of Terminology and Reporting.[13] Technical success was defined as a tumor treated according to protocol and covered completely by the ablation zone on post ablation CT/MRI within 1 month. Primary technique efficacy was achieved when target tumors were successfully eradicated following the treatment course by the last available CT/MRI within 3 months. Secondary technique efficacy was assessed by taking into account all repeat ablations following identification of LTP. For patients who underwent LT, radiologic/pathologic correlation of HCC nodules initially treated by RFA was performed and classified as complete response (CR) or non-CR.

Therapeutic efficacy was also assessed on a per-patient basis using the last follow-up CT/MRI before LT/delisting/death using modified RECIST criteria: CR, partial response (PR), stable disease, and progressive disease (PD).[14,15]

Complications were assessed by clinical symptoms, imaging findings, and blood tests after RFA according to Society of Interventional Radiology classification.[16] A major complication was defined as an event that led to substantial morbidity and disability that increased the level of care, resulted in hospital admission, or substantially lengthened a hospital stay. All other complications were considered minor.

STATISTICAL ANALYSIS

Causes of dropout were assessed and cumulative rates of dropout from the waiting list were evaluated using the Kaplan-Meier method. Univariate associations between individual variables for tumor-specific dropout were tested using the Student *t* test or Mann-Whitney U test for continuous variables (age, serum AFP level upon first RFA, Model for End-Stage Liver Disease [MELD] score, number of HCC upon first RFA, and waiting time for LT) or chi-square test or Fisher's exact test for categorical variables (sex, Child-Pugh classification, etiology of liver disease, within Milan criteria, Barcelona Clinic Liver Cancer stage, and treatment failure at 1 and 3 months) as appropriate, and multiple logistic regression analysis was used to test the significance of predictors adjusted for one another and summarized as odds ratio (OR) and 95% confidence interval (CI). Variables with *P* values of < 0.1 on univariate analysis were chosen as variables for multivariate logistic regression analysis. For multivariate analysis, a forward stepwise selection mode was used, with iterative entry of variables based on test score *P* values of < 0.05 and the removal of variables with a likelihood ratio probability of 0.10.

For HCC nodules initially treated by RFA, the difference between radiologic and pathologic assessment was evaluated using the McNemar test. Based on explant histology, the rate of complete tumor necrosis was compared according to tumor size (tumors < 3 cm versus tumors ≥ 3 cm) using chi-square test. In addition, the rate of complete necrosis was also compared between groups with and without post-LT recurrence using the Fisher exact test.

Cumulative rates for LTP, dropout from waiting list, post-LT recurrence, and survival were estimated using the Kaplan-Meier method. For dropout time

course, the date listed for LT—or for those who developed HCC after listing, the date of HCC diagnosis—was taken as time zero.[11] Patients were censored at the time of LT, last follow-up on the waiting list, or death. For post-LT survival analysis, patients were followed from the date of LT to death or last follow-up visit before April 2016. For intention-to-treat survival analysis, the date of initial RFA was taken as time zero and the entire study population initially treated with RFA was included. Intention-to-treat overall survival (OS), RFS, and disease-specific survival (DSS) events were defined as all-cause mortality, HCC recurrence or all-cause mortality, and mortality due to HCC progression, respectively. For DSS, cases with unknown cause of death were regarded as HCC progression if patients were delisted from the waiting list due to HCC progression or had recurrent HCC after LT. *P* values < 0.05 were considered statistically significant. All statistical tests were performed using PASW statistical software (version 18.0; SPSS, Chicago, IL)

Results

STUDY POPULATION

Out of a total of 1016 patients with diagnosis of HCC prior to or after listing for LT during this time period, 121 consecutive patients (men/women ratio, 83:38; mean age, 60.0 years [range, 41-74 years]) received RFA at our institution as stand-alone first-line therapy. One hundred patients were listed for LT within 6 months of RFA, and another 21 patients had RFA more than 6 months after listing due to new development of HCC while on the waiting list. Eighty-five tumors (85/156, 54.5%) were confirmed as HCC by core needle biopsy; the remaining 71 tumors (71/156, 45.5%) were diagnosed as HCC based on American Association for the Study of Liver Diseases imaging criteria.[17,18] Patients' baseline demographics and tumor characteristics at the time of first RFA are summarized in Table 1.

DROPOUT RATE FROM WAITING LIST

Patients were categorized as CR (n = 89 [73.6%]), PR (n = 8 [6.6%]), stable disease (n = 2 [1.7%]), or PD (n = 22 [18.2%]) according to the modified RECIST criteria. Among the 121 patients, mean time on the waiting list was 10.2 months (median, 8.2 months [range, 0.3-38.0 months]). Of these patients, 89 (73.6%) underwent orthotopic LT, 16 (13.2%) were delisted from the waiting list, 14 (11.6%) died before LT or delisting, and two (1.7%) remained on the waitlist at study conclusion. No patients died from HCC. Causes of death before LT included infection (n = 4 [28.6%]), stroke (n = 2 [14.3%]), variceal bleeding (n = 2 [14.3%]), multiorgan failure (n = 2 [14.3%]), hepatic failure (n = 2 [14.3%]) and unknown cause (n = 2 [14.3%]). Causes of delisting included tumor progression (n = 9 [56.3%]), patient decision (n = 3 [18.8%]), comorbidity (n = 3 [18.8%]) and treatment in another hospital (n = 1 [6.3%]). Actual dropout rate from any tumor progression was therefore 7.4% (9/121). Cumulative dropout rates from all causes were estimated as 13.5%, 37.2%, and 58.1% at 1, 2, and 3 years, respectively (Fig. 1A). Cumulative tumor-specific dropout rates were estimated as 7.8%, 27.5%, and 27.5% at 1, 2, and 3 years, respectively (Fig. 1B).

Predictors of tumor-specific dropout are summarized in Tables 2 and 3. On univariate analyses, the only significant predictors were serum AFP level ($P = 0.041$) and treatment failure of the initial RFA treatment course of 3 months ($P = 0.001$). On multivariate analysis, both serum AFP level and treatment failure of the initial RFA treatment course of 3 months were predictive factors for tumor-specific dropout (OR, 1.002; 95% CI, 1.000-1.004; $P = 0.046$ and OR, 8.541; 95% CI, 1.312–55.608; $P = 0.025$, respectively).

LONG-TERM OUTCOMES AND SURVIVAL

Long-term outcomes after RFA compared with other relevant LT bridging therapy studies are summarized in Table 4. Of the 89 patients who underwent LT, HCC recurred in five (5.6%) patients 19.6-49.2 months after LT during post-LT follow-up (mean ± SD, 50.2 ± 35.2; median, 45.1 months [range, 0.0-125.7 months overall follow-up time]) One patient had intrahepatic recurrence, whereas others had metastatic disease. Cumulative rates of HCC recurrence after LT were estimated as 2.5%, 5.3%, 7.2%, 7.2%, and 7.2% at 1, 3, 5, 8, and 10 years, respectively (Fig. 2).

A total of 22 (24.7%) patients died during the follow-up period. Causes of death included sepsis (n = 4 [18.2%]), perioperative complication (n = 2 [9.1%]), cancers other than HCC (n = 2 [9.1%]), posttransplantation lymphoproliferative disease (n = 1 [4.5%]), HCC tumor progression (n = 1 [4.5%]),

TABLE 1. Baseline Characteristics of the Study Population

Characteristics	Value
Patients, n	121
Sex, n	
Men	83
Women	38
Age, years, mean (range)	60.0 (41-74)
Etiology of liver disease, n (%)	
Hepatitis C	75 (62.0)
Hepatitis B	21 (17.4)
Alcohol	10 (8.3)
Nonalcoholic steatohepatitis	6 (5.0)
Cryptogenic cirrhosis	4 (3.3)
Others*	5 (4.1)
Child-Pugh classification upon first RFA, n (%)	
Class A	68 (56.2)
Class B	51 (42.1)
Class C	2 (1.7)
Serum AFP level upon first RFA, ng/mL, mean ± SD (range)	137.2 ± 465.7 (1.3-4450.0)
Serum AFP level upon first RFA, n (%)	
<20 ng/mL	64 (52.9)
≥20- < 200 ng/mL	42 (34.7)
≥200 ng/mL	15 (12.4)
MELD score upon first RFA, mean ± SD (range)	11.4 ± 5.8 (6-31)
MELD score upon first RFA, n (%)	
<10	69 (57.0)
≥10-<20	30 (24.8)
≥20	22 (18.2)
No. of HCCs upon first RFA, n (%)	
1	88 (72.7)
2	25 (20.7)
3	5 (4.1)
≥4	3 (2.5)
Tumor burden, n (%)	
Within Milan criteria	109 (90.1)
Beyond Milan criteria	12 (9.9)
Barcelona Clinic Liver Cancer stage, n (%)	
0	13 (10.7)
A	98 (80.9)
B	10 (8.3)
Tumors, n (%)	156 (100)
<3 cm	117 (75)
≥3 cm	39 (25)
Tumor size, cm, mean ± SD (range)	2.4 ± 1.0 (0.8–5.7)

*Includes hepatitis C virus and hepatitis B virus, hepatitis C virus and alcohol, hemochromatosis, glycogen storage disease, and primary biliary cirrhosis.

respiratory failure (n = 1 [4.5%]), multiorgan failure (n = 1 [4.5%]), brain hemorrhage (n = 1 [4.5%]), and unknown cause (n = 9 [40.9%]). Cumulative rates of post-LT RFS (Fig. 3A) and OS (Fig. 3B) were estimated as 93.1%, 78.3%, 71.1%, 66.9%, 39.6% and 93.1%, 79.7%, 75.8%, 71.3%, and 42.2% at 1, 3, 5, 8, and 10 years, respectively.

During follow-up after initial RFA, intention-to-treat RFS (Fig. 4A), OS (Fig. 4B), and DSS (Fig. 4C) for the entire study population at 1, 3, 5, 8, and 10 years were estimated as 87.6%, 65.4%, 60.8%, 54.8%, and 37.7%; 87.6%, 67.2%, 63.5%, 60.0%, 41.2% and 98.3%; and 89.5%, 89.5%, 89.5%, and 89.5%, respectively.

THERAPEUTIC RESPONSE TO RFA

A total of 171 RFA sessions (mean ± SD, 1.4 ± 0.9; median, 1 [range, 1-8]) were performed in 121 patients. Twelve patients did not meet the Milan

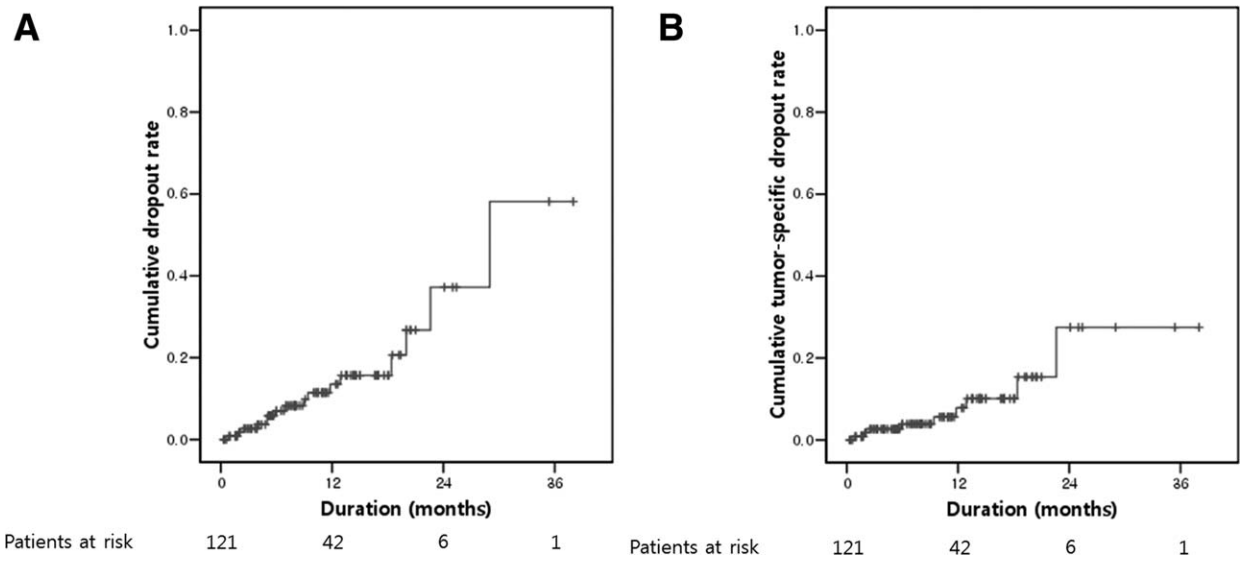

FIG. 1. (A) Cumulative overall dropout rates and (B) cumulative tumor-specific dropout rates were estimated using the Kaplan-Meier method. Cross-marks (+) indicate censored data.

criteria before initial RFA. Of these, successful downstaging was achieved in 11 (91.7%) patients with RFA sessions (mean ± SD, 2.1 ± 2.0; median, 1 [range, 1-3]). The remaining patient underwent two RFA sessions but had residual tumor on follow-up CT images and died from variceal bleeding 5 months after initial RFA.

Among 156 HCC nodules treated by RFA, 143 showed no residual tumor on CT/MRI obtained within 1 month after RFA, corresponding to a technical

TABLE 2. Univariate Analysis for Predictors of Tumor-Specific Dropout

Variable	Patients with Tumor-Specific Dropout (n = 9)	Patients Without Tumor-Specific Dropout (n = 112)	*P*
Age, years, mean ± SD	60.7 ± 8.5	60.0 ± 7.1	0.783
Serum AFP level upon first RFA, ng/mL, median (range)	80.8 (4.6-4450.0)	11.5 (1.3-1147.0)	0.041
MELD score upon first RFA, median (range)	8 (7-17)	9 (6-31)	0.190
Number of HCC upon first RFA, median (range)	1 (1-2)	1 (1-5)	0.243
Waiting time for LT, months, median (range)	9.4 (0.9-22.6)	8.2 (0.3-38.0)	0.774
Sex, n			0.718
Men	7	76	
Women	2	36	
Child-Pugh classification (class A:B:C)	7:2:0	61:49:2	0.390
Etiology of liver disease, n			0.917
Hepatitis C virus	6	69	
Hepatitis B virus	2	19	
Alcohol	1	9	
Nonalcoholic steatohepatitis	0	6	
Cryptogenic cirrhosis	0	4	
Others*	0	5	
Within Milan criteria (yes:no)	9:0	100:12	0.596
Barcelona Clinic Liver Cancer stage (0:A:B)	2:7:0	11:91:10	0.366
Treatment failure at 1 month (yes:no)†	1:8	12:100	1.000
Treatment failure at 3 months (yes:no)†	3:6	5:107	0.001

*Includes hepatitis C virus and hepatitis B virus, hepatitis C virus and alcohol, hemochromatosis, glycogen storage disease, and primary biliary cirrhosis.
†If a patient has multiple HCCs, treatment failure was defined when any enhancing tumor was depicted on post-RFA CT or MRI.

TABLE 3. Multivariate Analysis for Significant Predictors of Tumor-Specific Dropout

Variable	OR	95% CI	*P*
Treatment failure at 3 months	8.541	1.31-55.608	0.025
Serum AFP level upon listing	1.002	1.000-1.004	0.046

success rate of 91.7%. Of the 13 nodules with residual tumor, 12 were completely ablated by a second (n = 11) or third (n = 1) RFA session. The remaining nodule showed tumor progression with portal vein invasion after a second RFA session and thus was considered an unsuccessfully treated tumor.

Of 156 nodules, 148 showed no residual tumor after a 3-month treatment course, a primary technique efficacy rate of 94.9% (148/156). Residual tumors were identified in three nodules where the initial RFA had been considered technically successful in the treatment course. Among them, two tumors with portal vein invasion were considered unsuccessfully treated tumors. One patient with residual tumor died before a second RFA session because of variceal bleeding. There were four cases where the presence of residual tumor was uncertain; all eventually developed residual tumor on later follow-up CT or MRI. These tumors were followed over the treatment course and were completely treated by second RFA sessions 4, 5, and 10 months after initial RFA, respectively.

LTP was identified in 11 (7.4%) of 148 HCC nodules with initial primary technique efficacy. Cumulative rates of LTP were estimated as 10.7%, 19.2%, and 19.2% at 1, 2, and 4 years, respectively. Among 11 nodules with LTP, seven were completely treated by additional RFAs. However, one nodule showed tumor progression after two additional RFA sessions. In one case, radioembolization was performed because RFA was considered infeasible. For the remaining two nodules, LT was performed without additional RFA. Taking into account all RFA sessions including initial course and repeated treatments for LTP, secondary technique efficacy, or overall tumor control rate, was 93.6% (146/156).

Radiologic/pathologic correlation of 113 HCC nodules was performed based on explant histology and it revealed residual tumor in 28.3% (32/113) of cases on histopathologic examination. Sensitivity, specificity, positive predictive value, and negative predictive value for diagnosis of residual disease on radiologic evaluation were 3.1% (1/32), 98.8% (80/81), 50.0% (1/2), and 72.1% (80/111), respectively. The rate of complete necrosis was significantly higher for tumors <3 cm than tumors ≥ 3 cm (78.9% [60/76] versus 56.8% [21/37]; $P = 0.014$). The rate of complete necrosis of HCC was lower in patients with post-LT HCC recurrence than in those without recurrence (20.0% [1/5] versus 67.9% [57/84]; $P = 0.048$).

TABLE 4. Relevant Studies Reporting Neoadjuvant Treatment Before LT and Their Outcomes

Study	Neoadjuvant Treatment	No. of Patients	Waiting Time, Months	Disease-Specific Dropout Rate, %	Post-LT HCC Recurrence, %	Post-LT Survival, %	Intention-to-Treat Survival, %
Fontana et al.[12]	RFA	23	Mean, 7.9	NA	13	OS, 85 (3 years)	NA
Mazzaferro et al.[5]	RFA	50	Median, 9.5	0	3.3	OS, 83 (3 years)	NA
Lu et al.[11]	RFA	52	Mean, 12.7	5.8	0	OS, 76 (3 years)	OS, 74 (3 years)
Millonig et al.[22]	TACE	116	Median, 9	8.6	14.2	NA	OS, 70.3 (5 years)†
Cherqui[31]	Resection	18*	NA	NA	NA	OS, 70 (5 years)	OS, 72 (5 years); RFS, 44 (5 years)
Cucchetti et al.[21]	Mixed	315	Median, 10	16.5	10.2	OS, 74.3 (5 years)	NA
Current study	RFA	121	Mean, 10.2	7.4	5.6	OS, 79.7 (3 years), 75.8 (5 years), 71.3 (8 years), 42.2 (10 years), RFS, 78.3 (3 years), 71.1 (5 years), 66.9 (8 years), 39.6 (10 years)	OS, 67.2 (3 years), 63.5 (5 years), 60.0 (8 years), 41.2 (10 years), RFS, 65.4 (3 years), 60.8 (5 years), 54.8 (8 years), 37.7 (10 years)

NA, not applicable.
*Out of the entire study population (n = 67), only 18 patients underwent LT.
†Patients within Milan criteria at the time of listing.

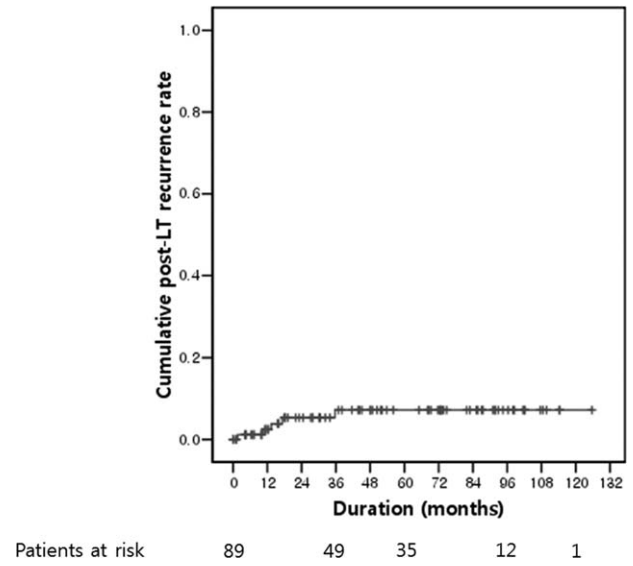

FIG. 2. Cumulative rates of tumor recurrence after LT were estimated using the Kaplan-Meier method in patients who underwent LT (n = 89). Cross-marks (+) indicate censored data.

DISTANT TUMOR RECURRENCE

Before LT, a total of 91 remote intrahepatic tumor recurrences (mean ± SD, 2.1 ± 1.9; median, 1; range, 1-9) were identified in 44 (36.4%) patients. Extrahepatic tumor recurrence eventually developed in 3 (2.5%) patients, including lymph node, bone, and peritoneum. Treatment for intrahepatic recurrence included additional thermal ablation (n = 23), combined RFA and chemoembolization (n = 3), combined RFA and percutaneous ethanol injection (n = 1), chemoembolization (n = 1), and radioembolization (n = 1). The remaining 15 patients did not receive specific treatment because of medical comorbidities.

COMPLICATIONS

No mortality occurred after RFA. Five (2.9%) early major complications occurred in 171 RFA procedures. These consisted of hemoperitoneum requiring transfusion (n = 2), nonocclusive thrombus in the left portal vein and large amount of right pleural effusion (n = 1), severe transaminitis (n = 1), and massive right pleural effusion (n = 1). All five patients required prolonged hospitalization but eventually recovered. There was one late complication in the form of probable tumor seeding in the chest wall, though this complication occurred only after transplantation and in the setting of widespread metastasis.

Discussion

In patients with HCC awaiting LT, locoregional treatment is recommended when wait times are

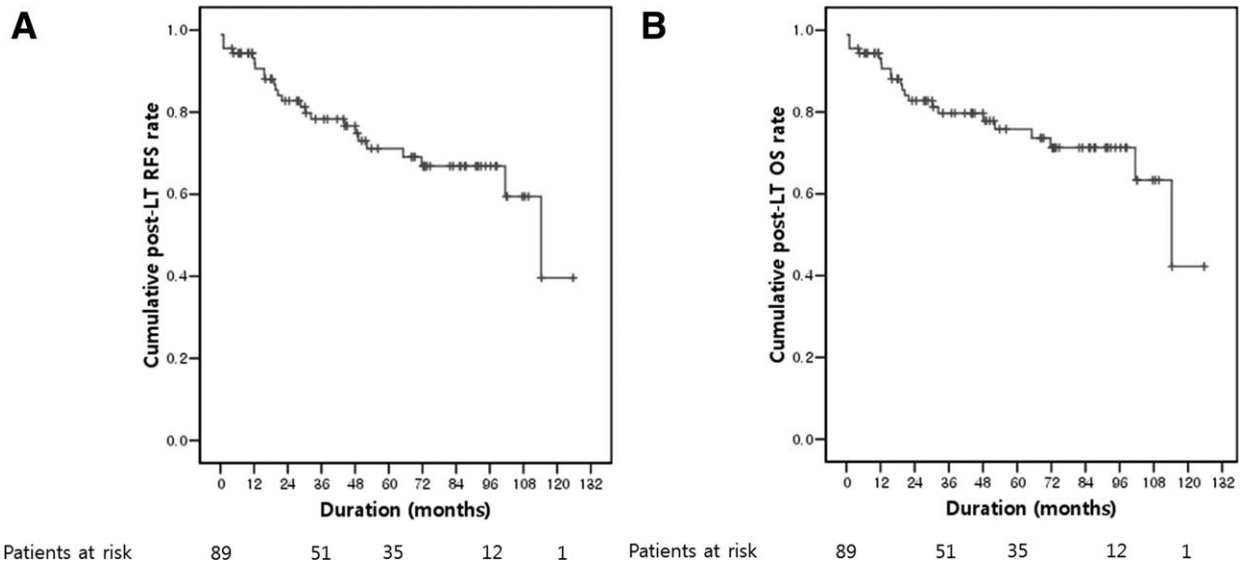

FIG. 3. (A) Cumulative rates of post-LT RFS and (B) OS were estimated using the Kaplan-Meier method in patients who underwent LT (n = 89). Cross-marks (+) indicate censored data.

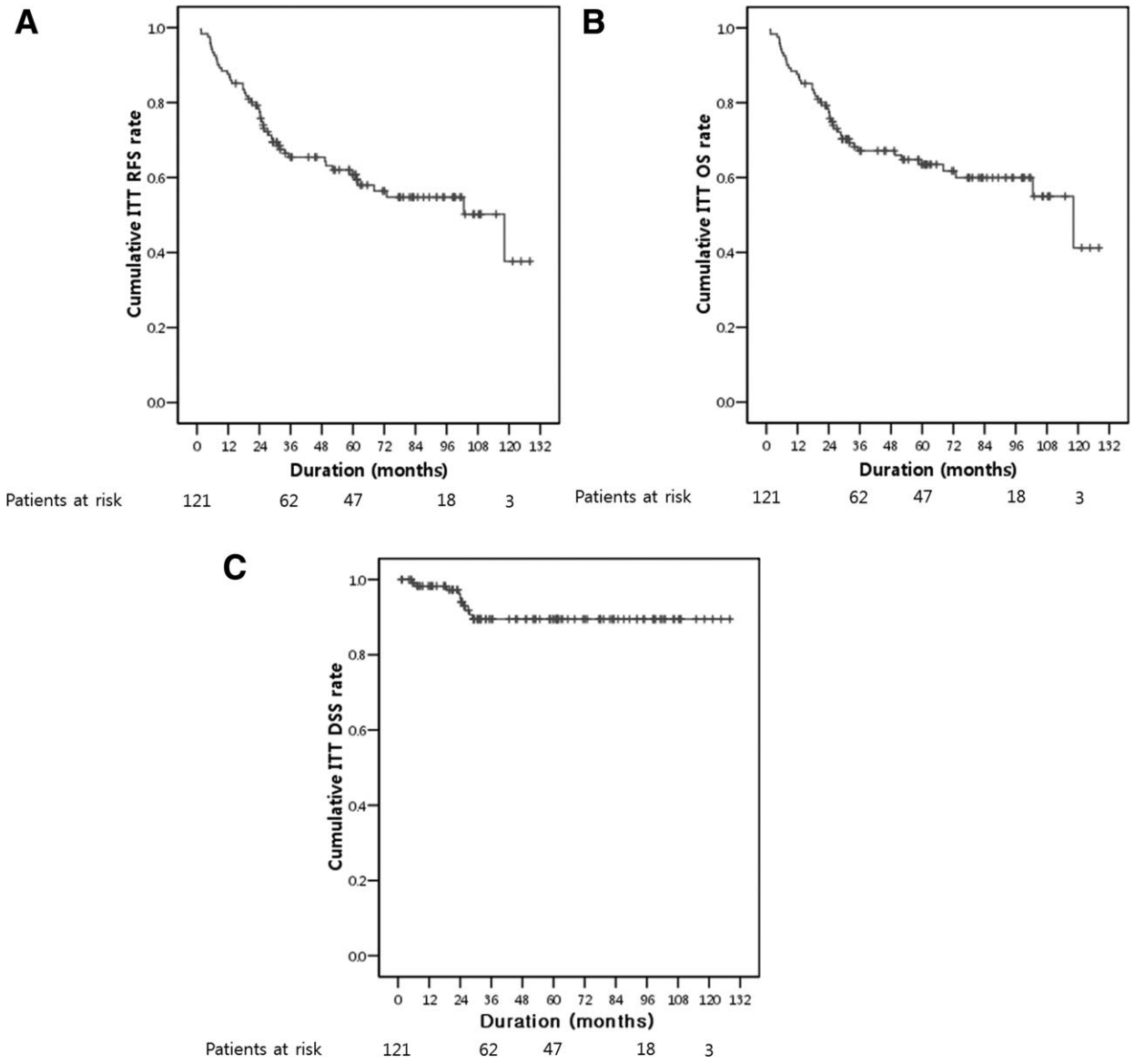

FIG. 4. (A) Cumulative rates of intention-to-treat (ITT) RFS, (B) OS, and (C) DSS were estimated using the Kaplan-Meier method in entire study population (n = 121). Cross-marks (+) indicate censored data.

predicted to exceed 6 months.[19] Because RFA can provide higher rate of complete necrosis of target tumor than other locoregional therapies, RFA has played a pivotal role in locoregional bridging therapies to LT.[20] However, even though RFA can be highly effective as a stand-alone therapy, results from studies using RFA as the dominant or sole bridge therapy are rare, and previous studies have reported 5-year outcomes at most.[2,5,11] Furthermore, to our knowledge, there are no previous studies reporting all five relevant outcomes including therapeutic response to RFA, dropout rate from waitlist, post-LT HCC recurrence, post-LT survival, and intention-to-treat survival (Table 4).[14] Our study addresses these issues in a large cohort of patients undergoing RFA as the initial and dominant bridge therapy while awaiting LT, with up to 10 years of follow-up.

The most important role of a bridge therapy is to prevent dropout from the LT wait list because of tumor progression. In this study, 16 (13.2%) patients were delisted and tumor-specific dropout occurred in 9 (7.4%) patients (Fig. 1). In a cohort with an average

wait list time of 10.2 months and with many patients waiting up to 3 years, the low dropout rate from tumor progression clearly confirms the role of RFA as an effective bridging therapy. However, treatment failure after the initial RFA treatment course of 3 months was one of the independent predictors for tumor-specific dropout. Increased serum AFP level upon first RFA was also an independent predictor for tumor-specific dropout and this is not surprising, given that it is an indicator of tumor biology.

In addition to preventing waitlist dropout, bridging therapy for HCC must also confer excellent posttransplantation survival. Previous studies have shown good 5-year post-LT survival rates following locoregional therapy for HCC.[21,22] In our study, bridging therapy with RFA showed not only excellent overall 5-year post-LT survival, but continued with an 8-year survival rate of 71.3%. While 10-year survival was estimated at 42.2%, this result is less accurate due to the low sample size at the end of the study.[23] Moreover, causes of death at the latter follow-up period were not highly related to HCC progression, as reflected by a 10-year DSS rate of 89.5% (Figs. 2 and 4).

The intention-to-treat survival analysis is an important measure of the HCC treatment strategy starting with RFA as bridging therapy to LT because it combines the success of bridging with the success of transplantation in eradicating HCC. In our study, 8-year intention-to-treat OS and DSS rates were 60.0% and 89.5%, respectively. 10-year intention-to-treat DSS was also 89.5%. This 10-year intention to treat survival rate for HCC patients bridged to LT by RFA is much higher than previously reported 10-year survival rates for RFA alone without subsequent LT.[24,25]

In our study, residual tumor was confirmed in 28.3% (32/113) of tumors on histopathologic examination. In comparison, a previous study by Mazzaferro et al.[5] showed residual tumor in 55% (33/60) of explants on histopathologic examination after RFA as a bridge therapy to LT. This difference can be explained by the following observations. First, tumor size was larger in the Mazzaferro et al. study (3.0 ± 1.3 cm versus 2.4 ± 1.0 cm). Second, unlike our study, a single RFA session was the sole treatment before LT.[5] However, it is generally accepted that RFA can be performed repeatedly, and this is one of the major advantages of RFA over surgical resection.[24,26,27] Third, we used dual guidance of CT and ultrasonography, whereas Mazzaferro et al. used ultrasonography alone. Accurate image guidance is the cornerstone of successful ablation therapy and the combined CT and ultrasonography approach likely improved outcomes. Fourth, the time period of the two studies did not overlap (1998-2003 versus 2004-2014), during which time new technology became available and evolution of interventional techniques may have contributed to the better outcomes in our study.

In our study, the rate of complete necrosis of HCC was lower in patients with post-LT HCC recurrence than those without recurrence. This result is in close agreement with a previous study in which complete tumor necrosis has been correlated with reduced risk of posttransplantation tumor recurrence.[6] Hence, complete tumor necrosis is the goal of any treatment modality, including emerging therapies such as microwave ablation and stereotactic body radiotherapy.[28-30] In order to achieve the so-called "holy grail" of complete necrosis, the treatment paradigm for RFA of liver tumors requires a sufficient ablation margin beyond the visible tumor margin to ensure ablation of infiltrative and/or microscopic disease that may not be visible by current imaging methods. However, this principle must be balanced against the need to preserve functional liver, which is by definition tenuous for someone awaiting LT. In our study, 55 (45.8%) patients on the waiting list were categorized as Child-Pugh class B or C. In this context, less-aggressive tumor control may be acceptable in patients with borderline liver reserve, as the primary goal is to bridge to LT, even if microscopic residual disease may be present.[11] Such microscopic disease would not be expected to be detectable by current imaging methods, and would be consistent with our finding of very low sensitivity for their detection (1/32 cases). This shortcoming is unavoidable and hence the rationale behind the necessary strict serial imaging follow-up in patients who underwent RFA for HCC.

In terms of complications, there was no mortality after RFA, and the major complication rate was low at 3.5% (6/171), in keeping with previous studies.[5,11] Although tract seeding occurred in one patient, it was found only after transplantation and in the setting of widespread metastasis. None of the complications after RFA precluded LT. Therefore, RFA can be considered as a safe bridge therapy for LT.

Our study has several limitations. First, it is a retrospective study, in which selection bias is unavoidable. Second, treatment outcome after RFA depends on patient population and the level of operator's experience. This is a single-center study in a tertiary hospital with a large volume of LT and RFA. Also, 75 (62.0%) of the study population has hepatitis C–related liver

disease and thus the results of our study may not be generalizable to other countries where hepatitis C may not be the dominant cause of HCC or end-stage liver disease. Third, for new HCCs after initial RFA, other treatments such as chemoembolization were also performed, even though RFA played a pivotal role in the management of recurrent tumors. Therefore, the effect of RFA for tumor control may have been diluted.[11] This outcome was inevitable, however, because HCCs are characterized by frequent intrahepatic recurrence, which is estimated up to 50% at 5 years after initial treatment due to either intrahepatic metastasis or *de novo* carcinogenesis.[19] In clinical practice, a multimodal treatment approach is generally applied to HCCs based on tumor size, location, and number.

In conclusion, in patients eligible for RFA as first line stand-alone therapy for naïve HCC, tumor-specific dropout rate after treatment while awaiting liver transplantation was low, despite long wait list times. Post-LT tumor recurrence and survival outcomes after RFA as a bridge therapy were excellent, with a 10-year intention-to-treat cancer-specific survival rate of 89.5%.

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