ULTRA SONO GRAPHY

Percutaneous radiofrequency ablation of hepatocellular carcinoma in a recent cohort at a tertiary cancer center: incidence and factors associated with major complications and unexpected hospitalization events

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Purpose: This study aimed to assess the incidence of and factors associated with major complications, delayed discharge, and emergency room (ER) visits or readmission after percutaneous radiofrequency ablation (RFA) for single hepatocellular carcinoma (HCC) <3 cm in a recent cohort at a tertiary cancer center.

Methods: A total of 188 patients with treatment-naïve single HCCs <3 cm who underwent RFA between January 2018 and April 2021 were included in the analysis. Univariable and multivariable logistic regression analyses were performed to identify the factors associated with major complications, delayed discharge, and ER visits or readmission. Local tumor progression (LTP) and overall survival were estimated using the Kaplan-Meier method and Cox proportional-hazards regression analysis.

Results: Major complications occurred in 3.2% (6/188) of the patients. The longest diameter of the ablation zone was significantly larger in patients with major complications (P=0.023). Delayed discharge occurred in 5.8% (9/188) of the patients, for which albumin-bilirubin grade 3 was identified as an important determinant. No variables other than major complications were significantly associated with ER visits or readmission, which occurred in 7.0% (13/188) of the patients. Major complications, delayed discharge, and ER visits or readmission were not substantially related to the post-treatment outcomes of LTP and overall survival.

Conclusion: This study confirmed RFA as a highly safe procedure for single HCCs <3 cm, despite the rapidly changing RFA techniques in the most recent cohort. A large ablation zone and poor liver function were predictors of major complications and delayed discharge, respectively.

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Complications

Key points: The incidence of major complications after radiofrequency ablation for hepatocellular carcinoma <3 cm was similar to previously reported values, despite rapidly changing ablation techniques. A large ablation zone and poor liver function were predictors of major complications and delayed discharge after percutaneous radiofrequency ablation, respectively. Major complications, delayed discharge, and emergency room visits or readmission were not substantially related to local tumor progression and overall survival after percutaneous radiofrequency ablation.

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Introduction

Both surgical resection and radiofrequency ablation (RFA) are widely accepted as first-line treatments for hepatocellular carcinomas (HCCs) smaller than 3 cm in diameter [1,2]. RFA has advantages over surgical resection in terms of procedure-related complications owing to its less invasive nature. The common complications after RFA reported in earlier studies include collateral thermal injury around the liver, hemorrhage, bile duct injury, hepatic infarction, and hepatic abscess [3,4]. Due to increases in the available data and operators' experience, the mortality and major complication rates associated with RFA have been minimized by the application of more meticulous techniques and proper selection of patients. Furthermore, additional modifications have been made, such as creation of artificial ascites or pleural effusion when indicated, which can minimize the risk of thermal damage to adjacent structures [5,6].

Meanwhile, with technical developments, RFA has been performed using perfusion electrodes or multiple electrodes to produce larger ablation zones [7,8]. In addition, no-touch RFA has recently been implemented, which offers better local tumor control by effectively producing sufficient ablative margins without puncturing the tumor through the insertion of multiple electrodes around it [9,10]. These recent technical advances may lead to a higher risk of complications, as larger ablation zones are being created with much more ease than before.

Therefore, considering the rapidly changing environment of the RFA technique and its various modifications, information related to the incidence of complications and clinical outcomes of RFA should be updated based on the most recent data. Furthermore, no studies have analyzed the factors associated with delayed discharge and emergency room (ER) visits or readmission after RFA from complications or side effects. Therefore, this study aimed to assess the incidence of and the factors associated with major complications, delayed discharge, and ER visits or readmission after percutaneous RFA for single HCCs <3 cm in a recent cohort at a tertiary cancer center.

Materials and Methods

Compliance with Ethical Standards

The Institutional Review Board (2022-02-002) of the Samsung Medical Center approved this retrospective study, and the requirement for obtaining written informed consent from patients was waived.

Patients

Between January 2018 and April 2021, 1,787 patients underwent percutaneous RFA for HCC. Among them, 1,599 patients (1) who were previously treated for HCC (n=1,453), (2) with multiple HCCs (n=75), (3) with a single tumor of <1 cm (n=12), (4) with single nodular HCC >3 cm (n=4), (5) with previous or concomitant malignancies other than HCC (n=14), and (6) who underwent combined transarterial chemoembolization and RFA (n=41) were excluded. Thus, 188 patients with treatment-naïve single HCCs of <3 cm were included in this study (Fig. 1). The diagnosis of HCC was made based on either the typical imaging features on multiphase liver computed tomography (CT) or gadoxetic acid-enhanced liver magnetic resonance imaging (n=181) or percutaneous biopsy (n=7) [10].

RFA Procedures and Follow-up

Percutaneous RFA was performed by one of five radiologists with >3 years of experience in local ablation therapy for hepatic tumors on an inpatient basis under fusion imaging guidance (volume navigation, LOGIQ E9 or LOGIQ E10, GE Healthcare, Chicago, IL, USA) [11]. When the lesion conspicuity was insufficient for fusion imaging-guided electrode placement, contrast-enhanced ultrasonography (US) was performed in addition to fusion imaging [12]. Artificial ascites or pleural effusion was induced to enhance sonographic window or to avoid collateral thermal injury whenever necessary, using 5% dextrose in water solution [13]. Various electrodes were utilized according to tumor size, shape, and location: active tip length-adjustable internally cooled tip

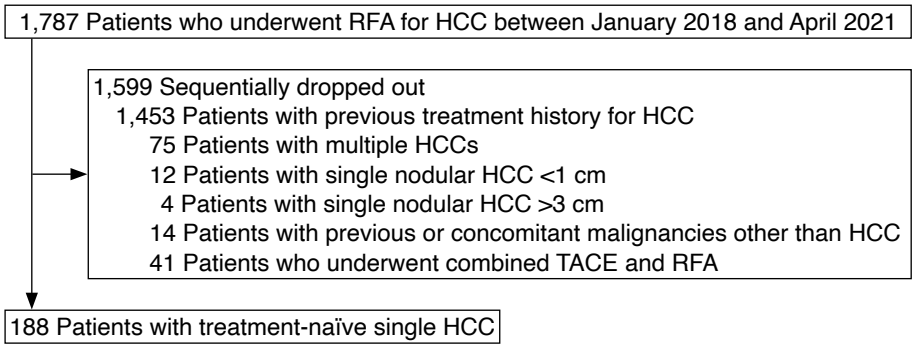


Fig. 1. Flow diagram of the patient selection process. RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

(Proteus RF Electrode, STARmed, Goyang, Korea), internally cooled wet-tip perfusion electrode (Jet-tip, RF Medical, Seoul, Korea), or clustered separable electrodes with an internally cooled tip (Octopus Electrode, STARmed). When using multiple electrodes, centripetal ablation with peripheral tumor-puncturing or no-touch RFA was preferred to achieve a sufficient ablative margin. Overlapping ablation was performed when required, regardless of the number of electrodes. Based on the US findings, the index tumor was covered entirely by the ablation zone with an ablative margin of at least 5–10 mm. The tract was cauterized after RFA during electrode removal.

Multiphase liver CT was performed immediately after RFA. If a residual tumor was identified on CT, a second RFA session was performed within 24 hours after the initial treatment. Follow-up liver CT and laboratory tests, including tumor markers and liver function tests, were performed 1 month after discharge, followed by routine checkups every 3 months for the first 2 years and every 4–6 months thereafter.

Assessment of Study Outcomes

The primary outcomes of this study were unexpected relevant events after RFA, including major complications, delayed discharge, and ER visits or readmission within 1 month after RFA. Major complications were defined as events that lead to substantial morbidity and disability that increase the level of care, result in hospital admission, or substantially lengthen the hospital stay in accordance with the standardization of terminology and reporting criteria [14]. Minor complications and side effects were also assessed based on the definitions in the standardization paper [14].

Delayed discharge was defined as a hospital stay exceeding 1 day after the procedure, considering the typical 3-day RFA protocol of the authors' center: admission the day before and discharge the day after the procedure. ER visits or readmission within 1 month after the procedure were considered relevant events after discharge.

The secondary outcomes were local tumor progression (LTP) and overall survival. LTP was defined as the appearance of tumor foci adjacent to the ablation zone after technique efficacy has been achieved. Overall survival was defined as the time from RFA until death or the last follow-up visit before December 31, 2021, for patients who survived. Patients who underwent liver transplantation were censored for analysis at the time of transplantation.

Definition of Tumor Locations

Tumor location was described in terms of proximity to the vessels and the liver capsule. A perivascular tumor was defined as a tumor adjacent to the portal or hepatic vein branches with a lumen caliber of ≥3 mm [15]. A subcapsular tumor was referred to as a tumor whose nearest margin was within 1 mm of the liver capsule [16]. A subcapsular location beneath the diaphragm was described as subphrenic [17].

Statistical Analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Variables with a normal distribution were presented as mean±standard deviation and were analyzed using the two-sample t-test. By contrast, variables that did not follow a normal distribution were presented as median (interquartile range) and were analyzed using the Wilcoxon rank-sum test. Categorical variables were expressed as counts (percentage) and were analyzed using the Fisher exact test.

Univariable logistic regression analysis was performed to screen for potential factors associated with unexpected relevant events, including major complications, delayed discharge, and ER visits or readmission. The factors significantly related to each relevant event in the univariable analysis were selected for further multivariable regression analysis.

The cumulative rates of LTP and overall survival over time were estimated using the Kaplan-Meier method. The log-rank test was used to compare the treatment outcomes between patients with and without each unexpected relevant event. Univariable and multivariable Cox proportional-hazard regression analyses were performed to assess the effects of relevant events on LTP and overall survival. Multivariable Cox proportional-hazards regression analyses were performed to adjust for variables associated with each relevant event in the logistic regression analysis.

The differences were considered significant at a two-sided P-value of <0.05. All analyses were performed using R version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics and Clinical Characteristics of the Patients

The demographic and clinical characteristics of the 188 patients included in this study are summarized in Table 1. A total of 188 patients (age, 60.3±9.4 years; 132 men and 56 women) with treatment-naïve single HCCs <3 cm who underwent RFA were included in the analysis. The median tumor size was 1.5 cm (1–2.7 cm). Slightly more than half (52.1%; 98/188) of the patients underwent no-touch RFA, and the remaining 47.9% (90/188) underwent tumor-puncturing RFA. Artificial fluid was introduced in 29.8% (56/188) of the patients during ablation: artificial ascites (n= 42), artificial pleural effusion (n=12), and both (n=2). Contrast-enhanced US was used in 11.7% (22/188) of the patients during the RFA procedures.

Table 1. Demographics and clinical characteristics of patients with and without major complications

Characteristic	Major complications (n=6)	No major complications (n=182)	P-value
Age at RFA (year)	60.7±6.0	60.3±9.5	0.893
Sex			0.181
Male	6 (100)	126 (69.2)	
Female	0	56 (30.8)	
Etiology			0.197
HBV	3 (50.0)	136 (74.7)	
HCV	1 (16.7)	9 (4.9)	
Others	2 (33.3)	37 (20.2)	
ALBI grade			>0.99
1	5 (83.3)	122 (75.3)	
2	1 (16.6)	35 (21.6)	
3	0	5 (3.1)	
Platelet count ($\times10^9$/L)	135.5 (125–169)	120 (85–162)	0.324
PT (INR)	1.08 (1.02–1.12)	1.07 (1.01–1.15)	0.855
AFP (ng/mL)	2.9 (2.4–23.1)	6.35 (3.42–14.3)	0.711
PIVKA-II (mAU/mL)	34 (19–40)	24 (20–31)	0.641
Tumor location (segment)			0.140
I	0	1 (0.5)	
II	0	5 (2.8)	
III	1 (16.7)	8 (4.4)	
IV	2 (33.3)	18 (9.9)	
V	1 (16.7)	28 (15.4)	
VI	1 (16.7)	32 (17.6)	
VII	1 (16.7)	27 (14.8)	
VIII	0	63 (34.6)	
Peritumoral vessel			
Portal vein			0.418
No	5 (83.3)	167 (91.8)	
Yes	1 (16.7)	15 (8.2)	
Hepatic vein			>0.99
No	6 (100)	166 (91.2)	
Yes	0	16 (8.8)	
Subcapsular and subphrenic location			0.703
Non-subcapsular	115 (63.2)	4 (66.7)	
Non-subphrenic, subcapsular	44 (24.2)	2 (33.3)	
Subphrenic	23 (12.6)	0	
Tumor size (cm)	1.35 (1.07–1.4)	1.5 (1.2–1.8)	0.123
No-touch technique			0.214
No	1 (16.7)	89 (48.9)	
Yes	5 (83.3)	93 (51.1)	
Needle count	2 (1.25–2)	2 (1–3)	0.531
Number of needle positions	3 (2.25–3)	3 (2–4)	0.741
Ablation time (min)	7 (7–7.75)	9 (8–12)	0.098
Ablation energy (kcal)	5.5 (5.08–5.92)	7 (4.95–10.1)	0.082
Ablation zone size (cm)[a]			
Dx	4.68±0.85	3.57±0.73	0.023
Dy	3.25±0.79	2.77±0.66	0.197
Dz	3.4 (2.8–3.8)	3.0 (2.5–3.5)	0.336
Ablation volume (cm^3)[b]	22.7 (16.6–43.9)	15.0 (10.6–21.4)	0.058
Ascites and pleural effusion			>0.99
None	4 (66.7)	120 (65.9)	
Artificial	2 (33.3)	54 (29.7)	
Native	0	8 (4.4)	
CEUS			0.535
No	5 (83.3)	159 (88.3)	
Yes	1 (16.7)	21 (11.7)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

RFA, radiofrequency ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI grade, albumin-bilirubin grade; PT (INR), prothrombin time (international normalized ratio); AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence II; CEUS, contrast-enhanced ultrasonography.

[a]The size of the ablation zone was measured on post-RFA computed tomography (CT) images in three perpendicular directions. Dx refers to the longest diameter of the ablation zone on the axial section of the CT images, while Dy represents the perpendicular diameter of Dx on the same axial section. Dz refers to the longest vertical diameter from the coronal or sagittal images. [b]The ablation volume was calculated using the following formula: ablation volume=π(Dx×Dy×Dz)/6 [8].

Treatment Response after RFA

Technical success was achieved in 187 of 188 patients (99.5%). One patient showed viable residual tumor on immediate post-RFA CT imaging; therefore, a second RFA session was performed. Technical efficacy was achieved in 188 patients (100%) based on the CT examination results at the 1-month follow-up.

Major Complications

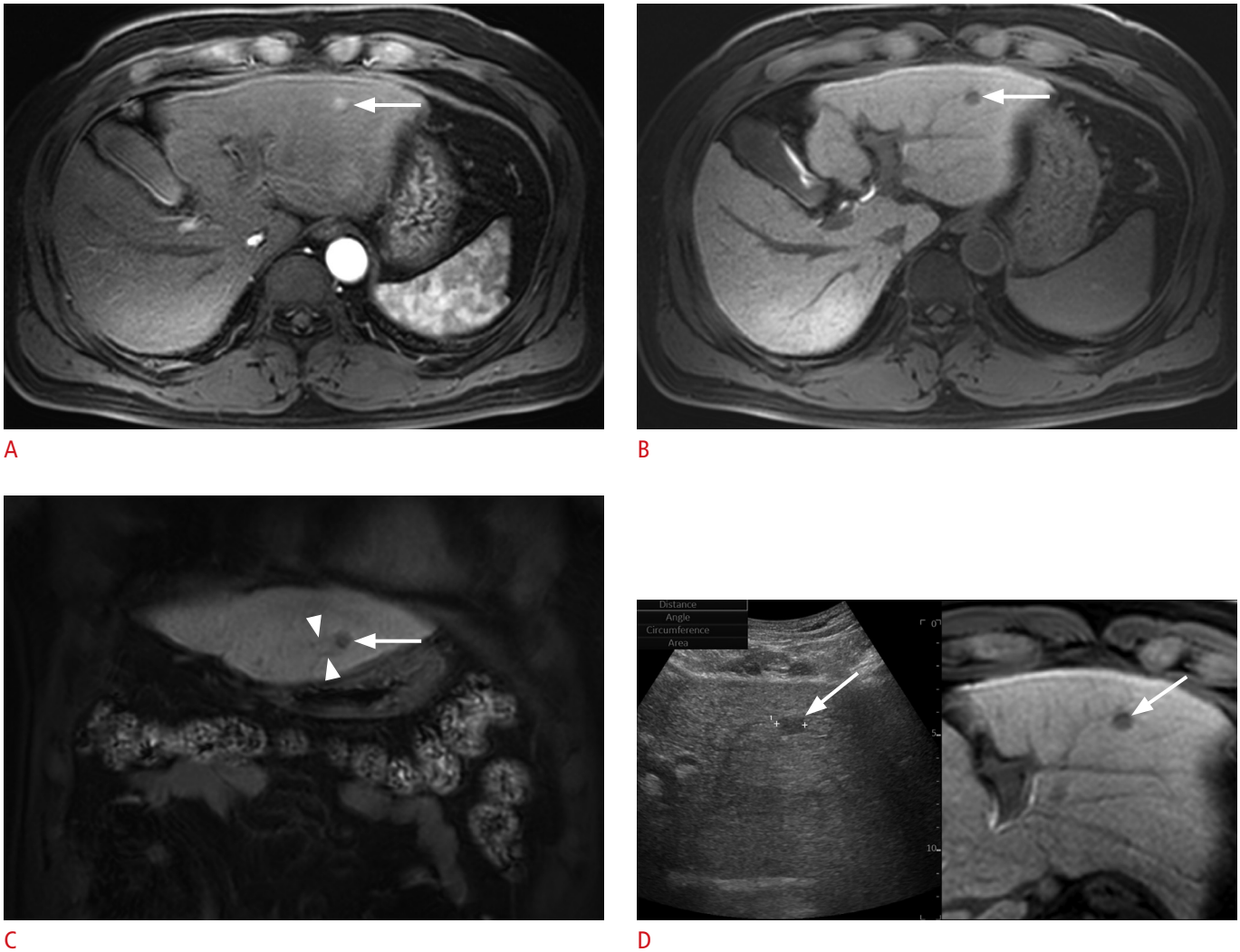
Major complications occurred in 3.2% (6/188) of the patients, and included ablation zone infection (n=2), liver infarction (n=2) (Fig. 2), gallbladder perforation (n=1), and biloma with infection (n=1). The patient and tumor characteristics were not significantly different between the major complication group and the no major complication group (Table 1). In terms of ablation parameters, the size of the ablation zone on the X-axis (defined as the longest

diameter on the axial section of the post-RFA CT) was significantly larger in the major complication group than in the no major complication group (P=0.023). No significant difference was observed in the other ablation parameters, including no-touch RFA, number of electrodes, total number of needle positions, ablation time, and ablation energy, between the two groups (Table 1).

In the univariable logistic regression analysis, the longest diameter of the ablation zone (odds ratio [OR], 8.47; 95% confidence interval [CI], 2.19 to 32.76) and ablation volume (OR, 1.08; 95% CI, 1.02 to 1.14) were the factors associated with the occurrence of major complications. Results of the multivariable analysis revealed that the longest diameter of the ablation zone (OR, 15.30; 95% CI, 2.08 to 112.60) was the only significant factor associated with the occurrence of major complications (Table 2).

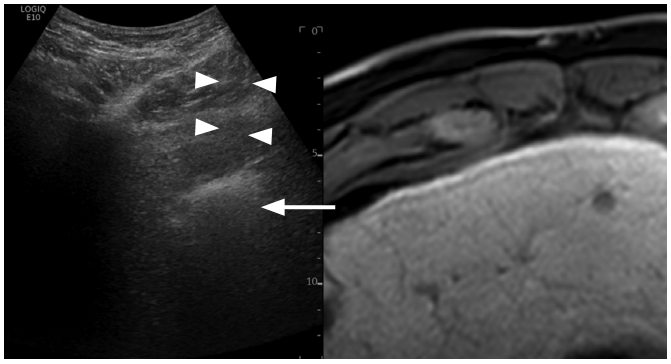
Delayed Discharge

Delayed discharge occurred in 5.8% (9/188) of the patients. Among them, 55.6% (5/9) exhibited RFA-related events: periprocedural side effects (mild fever or pain) (n=2), uncontrolled ascites (n=1), poor general condition (n=1), and technical failure of initial RFA (n=1). These five patients needed additional hospital stays after the RFA procedures (median, 2 days; interquartile range, 1 to 4 days). Mild fever and pain without radiologic evidence of extensive damage after RFA are generally transient and self-limited; thus, these were



A B C D

Fig. 2. A 61-year-old man with a single hepatocellular carcinoma.
A. Arterial-phase magnetic resonance image (MRI) shows a 1.0-cm hepatocellular carcinoma (arrow) in segment 3 of the liver. B. The tumor is seen as a nodule with hypointensity on hepatobiliary phase (HBP) MRI (arrow). C. On the coronal HBP image, fine portal vein branches (arrowheads) are visible around the tumor (arrow). D. The tumor (arrows) appears as a low-echoic lesion (left figure) at the corresponding site on the fused MRI.



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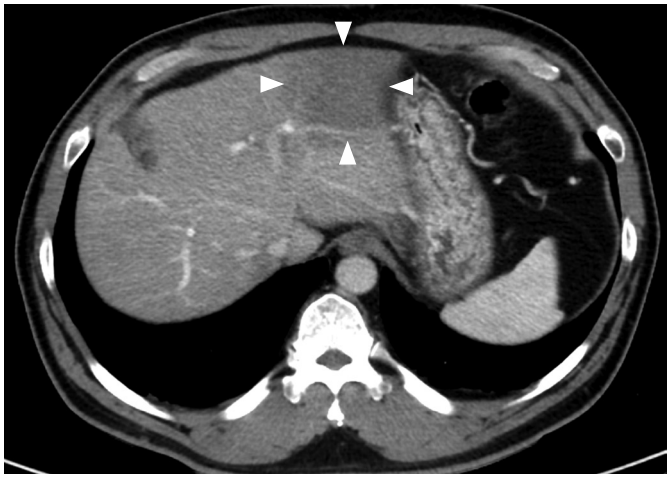

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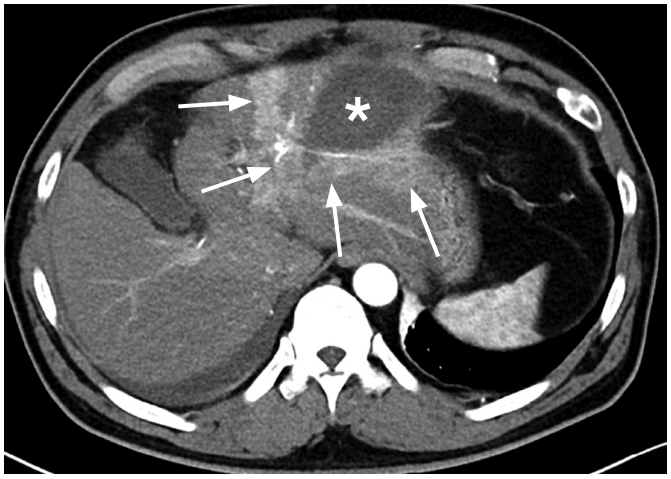

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Fig. 2. E. No-touch radiofrequency ablation (RFA) was performed after placing two internally cooled wet-tip electrodes (arrowheads) with a 1.5-cm exposed tip placed in parallel with each other. After ablation, a large echogenic zone (arrow) was observed, which was large enough to cover the entire tumor. F. An immediate post-RFA computed tomography shows that the tumor was completely ablated with a sufficient ablative margin. However, areas with decreased perfusion (arrowheads) were noted due to infarction by peritumoral vessel injury. G. Owing to abdominal pain, the patient visited the emergency room 8 days after undergoing RFA. On computed tomography images obtained during the emergency room visit, hepatic infarction (asterisk) is seen in segment 3. Hyperemia (arrows) was present around the infarcted liver, suggestive of infection. The patient was managed conservatively using analgesics.

classified as side effects. Two patients with uncontrolled ascites or poor general condition had poor liver function (albumin-bilirubin [ALBI] grade 2 or 3; platelet counts of 61,000/μL or 67,000/μL, respectively). One of them needed to receive a transfusion to correct thrombocytopenia before the RFA procedure. The patient needed to take diuretics to control ascites as he gained 3 kg of weight due to transfusion. These events may be related to the RFA procedure, but may not be entirely attributable to the RFA procedure only; likewise, they do not involve substantial morbidity and disability that increase the level of care. Therefore, these patients were not categorized as having major complications. Delayed discharge due to RFA-independent events occurred in the remaining four cases: adverse reactions to the CT contrast agent (n=2), persistent fever prior to RFA (n=1), and esophageal variceal ligation (n=1).

In the univariable logistic regression analysis, ALBI grade 3 (OR, 46.13; 95% CI, 5.95 to 357.46), prothrombin time (international normalized ratio) (OR, 73.48; 95% CI, 1.20 to 491.24), and the longest diameter of the ablation zone (OR, 0.35; 95% CI, 0.14 to 0.93) were identified as risk factors for delayed discharge. Of these factors, only ALBI grade 3 was significant in the multivariate analysis (OR, 66.58; 95% CI, 2.10 to 2,115.26) (Table 3).

ER Visits or Readmission

Approximately 7.0% (13/188) of patients visited the ER or were readmitted within 1 month after RFA treatment. Six patients had RFA-related events, and all of these events were major complications. The other patients had RFA-independent events: admission for liver transplantation workup (n=1), constrictive pericarditis surgery (n=1), disorientation from hepatic encephalopathy exacerbated by pneumonia and constipation (n=1), gastroesophageal reflux disease (n=1), neurosurgical issues (n=1), an obstetric emergency (n=1), and resection of lung chondroid hamartoma (n=1).

Results of the univariable logistic regression analysis showed that the major complications were the only factor associated with ER

Table 2. Factors associated with major complications after RFA for HCC

Characteristic	Univariable odds ratio (95% CI)	Multivariable odds ratio (95% CI)
Age at RFA (year)	1.00 (0.92–1.10)	–
Sex		
Male	Reference	
Female	0.17 (0.01–3.19)	–
Etiology		
HBV	Reference	
HCV	6.16 (0.76–50.12)	–
Others	2.60 (0.49–13.92)	–
ALBI grade		
1	Reference	
2	0.94 (0.15–6.08)	–
3	2.02 (0.08–54.10)	–
Log[platelet count ($\times 10^9$/L)]	2.64 (0.33–20.87)	–
PT (INR)	0.80 (0.00–440.59)	–
Log[AFP (ng/mL)]	0.88 (0.41–1.88)	–
Log[PIVKA-II (mAU/mL)]	1.07 (0.26–4.35)	–
Tumor location (segment)		
I	Reference	
II	0.27 (0.00–68.55)	–
III	0.53 (0.00–69.84)	–
IV	0.41 (0.00–45.67)	–
V	0.16 (0.00–19.66)	–
VI	0.14 (0.00–17.19)	–
VII	0.16 (0.00–20.40)	–
VIII	0.02 (0.00–4.85)	–
Peritumoral vessel		
Portal vein		
No	Reference	
Yes	2.23 (0.24–20.32)	–
Hepatic vein		
No	Reference	
Yes	0.78 (0.04–15.66)	–
Subcapsular and subphrenic location		
Non-subcapsular	Reference	
Non-subphrenic, subcapsular	1.57 (0.28–8.85)	–
Subphrenic	0.52 (0.03–10.15)	–
Tumor size (cm)	0.13 (0.01–2.03)	–
No-touch technique		
No	Reference	
Yes	4.78 (0.55–41.77)	–
Needle count	0.71 (0.24–2.08)	–
No. of needle positions	0.82 (0.39–1.72)	–
Ablation time (min)	0.81 (0.59–1.10)	–
Ablation energy (kcal)	0.77 (0.56–1.08)	–
Ablation zone size (cm)[a]		
Dx	8.47 (2.19–32.76)[b]	15.30 (2.08–112.60)[b]
Dy	2.96 (0.85–10.37)	–
Dz	1.71 (0.58–5.00)	–
Ablation volume (cm^3)[c]	1.08 (1.02–1.14)[b]	0.96 (0.86–1.07)
Ascites and pleural effusion		
None	Reference	
Artificial	1.23 (0.25–6.02)	–
Native	1.58 (0.07–37.48)	–
CEUS		
No	Reference	
Yes	1.51 (0.17–13.60)	–

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI grade, albumin-bilirubin grade; PT (INR), prothrombin time (international normalized ratio); AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence II; CEUS, contrast-enhanced ultrasound.
[a]The size of the ablation zone was measured on post-RFA computed tomography (CT) images in three perpendicular directions. Dx refers to the longest diameter of the ablation zone on the axial section of the CT images, while Dy represents the perpendicular diameter of Dx on the same axial section. Dz refers to the longest vertical diameter from the coronal or sagittal images. [b]Statistically significant. [c]The ablation volume was calculated using the following formula: ablation volume=π(Dx×Dy×Dz)/6 [8].

visits or readmission, as expected by definition (Table 4). By contrast, side effects and minor complications had no significant association with ER visits or readmission.

Recurrence and Survival Outcomes

Seven patients underwent liver transplantation for liver failure and/or recurrent HCC. The median follow-up period after RFA was 22.4 months (range, 0.7 to 46.4 months). During follow-up, LTP was observed in five of 188 patients (2.7%), while six patients (3.2%) died. The cumulative LTP and overall survival rates at 1 and 3 years were 1.2% and 3.1%, and 97.0% and 95.9%, respectively.

Fig. 3 shows the Kaplan-Meier curves for LTP and overall survival according to the incidence of major complications, delayed discharge, and ER visits or readmission. Patients whose discharge was delayed showed poorer overall survival than those without delayed discharge (P<0.01). Delayed discharge was also associated with poor overall survival in the univariable Cox regression analysis (P=0.003). However, multivariable Cox regression analysis revealed

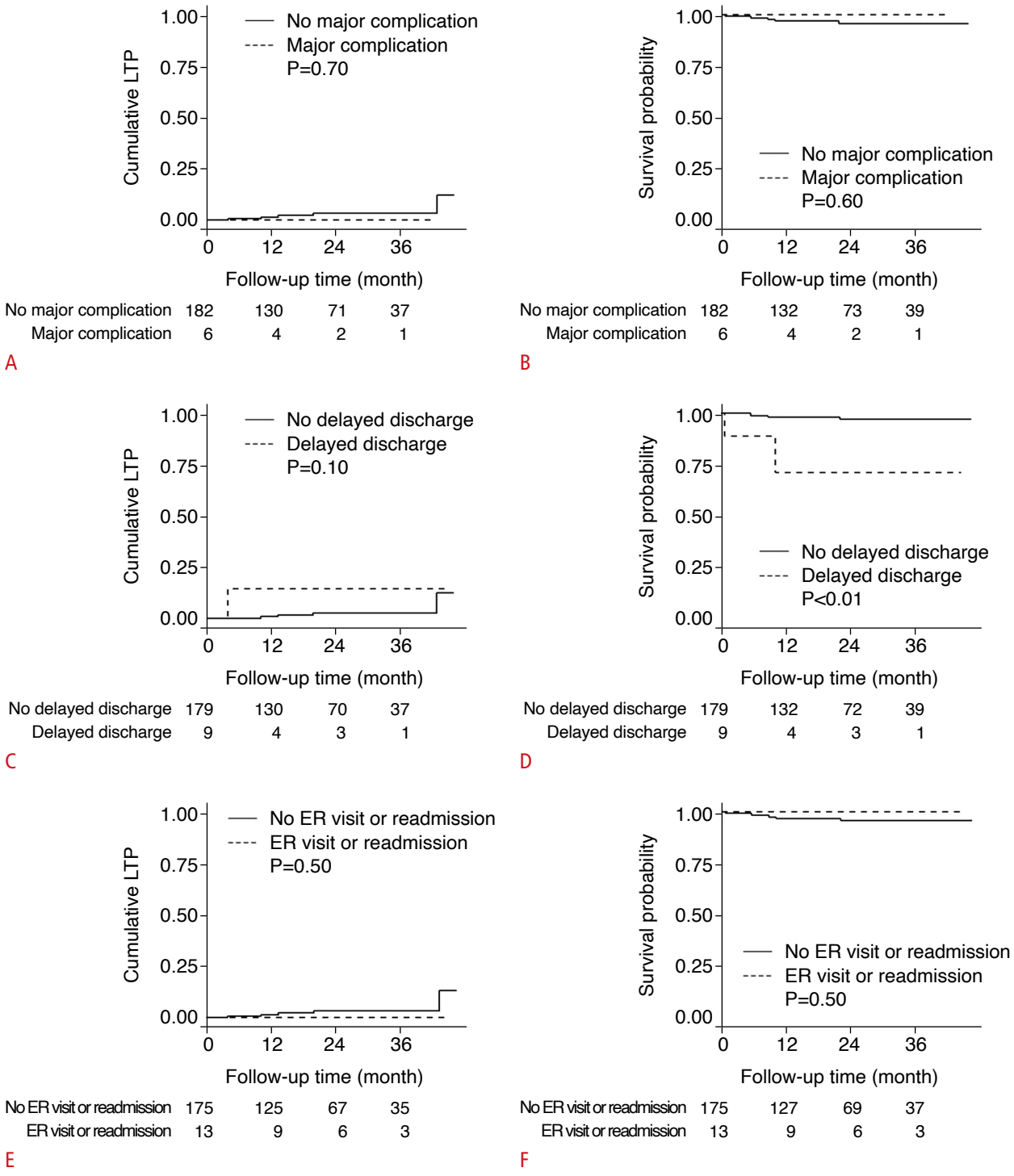

Fig. 3. Kaplan-Meier curves for local tumor progression (LTP) and overall survival of patient groups based on the incidence of major complications, delayed discharge, and emergency room (ER) visits or readmission.
A. The cumulative LTP rate was not significantly different between the no major complication group and the major complication group. B. Overall survival was not significantly different between the no major complication group and the major complication group. C. The cumulative LTP rate was not significantly different between the delayed discharge group and the non-delayed discharge group. D. Overall survival was higher in the non-delayed discharge group than in the delayed discharge group. However, the difference was not significant based on the multivariable Cox regression analysis. E. The cumulative LTP rate was not significantly different according to whether patients visited the ER or were readmitted. F. Overall survival was not significantly different according to whether patients visited the ER or were readmitted.

Table 3. Factors associated with delayed discharge after RFA for HCC

Characteristic	Univariable odds ratio (95% CI)	Multivariable odds ratio (95% CI)
Age at RFA (year)	0.99 (0.92–1.06)	–
Sex		
Male	Reference	
Female	3.14 (0.81–12.15)	–
Etiology		
HBV	Reference	
HCV	0.841 (0.04–18.04)	–
Others	1.178 (0.27–5.24)	–
ALBI grade		
1	Reference	
2	1.81 (0.32–10.30)	2.95 (0.50–17.43)
3	46.13 (5.95–357.46)[a]	66.58 (2.10–2,115.26)[a]
Log[platelet count ($\times 10^9$/L)]	0.32 (0.05–1.93)	–
PT (INR)	73.48 (1.20–491.24)[a]	0.04 (0.00–53.90)
Log[AFP (ng/mL)]	1.15 (0.64–2.05)	–
Log[PIVKA-II (mAU/mL)]	1.86 (0.66–5.26)	–
Tumor location (segment)		
I	Reference	
II	0.27 (0.00–68.55)	–
III	0.16 (0.00–35.99)	–
IV	0.41 (0.00–45.67)	–
V	0.05 (0.00–10.66)	–
VI	0.24 (0.00–26.48)	–
VII	0.05 (0.00–11.05)	–
VIII	0.28 (0.00–28.38)	–
Peritumoral vessel		
Portal vein		
No	Reference	
Yes	1.37 (0.16–11.67)	–
Hepatic vein		
No	Reference	
Yes	3.37 (0.64–17.77)	–
Subcapsular and subphrenic location		
Non-subcapsular	Reference	
Non-subphrenic, subcapsular	0.15 (0.01–2.73)	–
Subphrenic	0.89 (0.11–7.48)	–
Tumor size (cm)	0.52 (0.08–3.23)	–
No-touch technique		
No	Reference	
Yes	0.72 (0.19–2.78)	–
Needle count	0.51 (0.20–1.30)	–
No. of needle positions	0.66 (0.34–1.30)	–
Ablation time (min)	1.08 (0.92–1.26)	–
Ablation energy (kcal)	0.93 (0.78–1.11)	–
Ablation zone size (cm)[b]		
Dx	0.35 (0.14–0.93)[a]	0.58 (0.21–1.60)
Dy	0.42 (0.14–1.25)	–
Dz	0.71 (0.26–1.93)	–
Ablation volume (cm^3)[c]	0.92 (0.83–1.02)	–
Ascites and pleural effusion		
None	Reference	
Artificial	0.30 (0.04–2.53)	–
Native	2.39 (0.26–22.20)	–
CEUS		
No	Reference	
Yes	0.93 (0.11–7.80)	–
Complications		
None	Reference	
Side effect	2.33 (0.50–10.79)	–
Minor complication	0.91 (0.04–19.54)	–
Major complication	1.47 (0.06–35.86)	–

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI grade, albumin-bilirubin grade; PT (INR), prothrombin time (international normalized ratio); AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence II; CEUS, contrast-enhanced ultrasonography.
[a]Statistically significant. [b]The size of the ablation zone was measured on post-RFA computed tomography (CT) images in three perpendicular directions. Dx refers to the longest diameter of the ablation zone on the axial section of the CT images, while Dy represents the perpendicular diameter of Dx on the same axial section. Dz refers to the longest vertical diameter from the coronal or sagittal images. [c]The ablation volume was calculated using the following formula: ablation volume=π(Dx×Dy×Dz)/6 [8].

the effect of ALBI grade as a confounder rather than there being a true independent association between delayed discharge and overall survival (Table 5). No significant differences were observed in the cumulative LTP rate and overall survival for other relevant events after RFA treatment (Fig. 3).

Discussion

In this study, the incidence of and factors associated with unexpected relevant events (major complications, delayed discharge, and ER visits or readmission within 1 month) were evaluated after percutaneous RFA treatment for single nodular HCC <3

Table 4. Factors associated with emergency room visits or readmission after RFA for HCC

Characteristic	Univariable odds ratio (95% CI)
Age at RFA (year)	1.00 (0.94–1.06)
Sex	
Male	Reference
Female	0.69 (0.18–2.61)
Etiology	
HBV	Reference
HCV	2.095 (0.23–18.94)
Others	2.773 (0.83–9.28)
ALBI grade	
1	Reference
2	1.35 (0.34–5.38)
3	3.72 (0.37–37.29)
Log[platelet count ($\times 10^9$/L)]	1.45 (0.34–6.14)
PT (INR)	24.32 (0.56–1053.32)
Log[AFP (ng/mL)]	0.90 (0.53–1.56)
Log[PIVKA-II (mAU/ml)]	1.21 (0.42–3.47)
Tumor location (segment)	
I	Reference
II	0.27 (0.00–68.55)
III	0.53 (0.00–69.84)
IV	0.60 (0.01–64.45)
V	0.40 (0.00–42.12)
VI	0.24 (0.00–26.48)
VII	0.16 (0.00–20.40)
VII	0.17 (0.00–18.2)
Peritumoral vessel	
Portal vein	
No	Reference
Yes	0.89 (0.11–7.31)
Hepatic vein	
No	Reference
Yes	0.89 (0.11–7.31)
Subcapsular and subphrenic location	
Non-subcapsular	Reference
Non-subphrenic, subcapsular	1.41 (0.41–4.80)
Subphrenic	0.24 (0.01–4.44)
Tumor size (cm)	1.09 (0.27–4.44)
No-touch technique	
No	Reference
Yes	1.08 (0.35–3.33)
Needle count	0.72 (0.34–1.51)
No. of needle positions	0.95 (0.59–1.51)
Ablation time (min)	0.97 (0.83–1.14)
Ablation energy (kcal)	0.95 (0.83–1.09)
Ablation zone size (cm)[a]	
Dx	1.75 (0.83–3.70)
Dy	1.20 (0.52–2.80)
Dz	1.44 (0.67–3.08)
Ablation volume (cm^3)[b]	1.03 (0.99–1.08)
Ascites and pleural effusion	
None	Reference
Artificial	0.42 (0.09–1.99)
Native	1.63 (0.18–14.59)
CEUS	
No	Reference
Yes	0.60 (0.07–4.88)
Complications	
None	Reference
Side effect	0.43 (0.02–8.19)
Minor complication	0.91 (0.04–19.54)
Major complication	248.73 (10.21–6,060.03)[c]
Delayed discharge	1.74 (0.20–15.08)

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI grade, albumin-bilirubin grade; PT (INR), prothrombin time (international normalized ratio); AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence II; CEUS, contrast-enhanced ultrasonography.
[a]The size of the ablation zone was measured on post-RFA computed tomography (CT) images in three perpendicular directions. Dx refers to the longest diameter of the ablation zone on the axial section of the CT images, while Dy represents the perpendicular diameter of Dx on the same axial section. Dz refers to the longest vertical diameter from the coronal or sagittal images. [b]The ablation volume was calculated using the following formula: ablation volume=π(Dx×Dy×Dz)/6 [8]. [c]Statistically significant.

cm in a recent cohort at a tertiary cancer center. Owing to the experience of the operators in treating the complications after RFA and in applying several techniques that help overcome collateral thermal injury, serious morbidity and mortality after RFA may have been avoided. However, the clinical environment of RFA has substantially changed over the past decade; in particular, a larger ablation zone can now be easily created using more powerful RFA devices. Therefore, the present study is expected to provide insights regarding the complications of percutaneous RFA as treatment for small HCCs using these recent techniques, which may be beneficial for interventional oncologists performing local ablation therapy for HCCs, ultimately leading to a safer RFA strategy.

To the authors' knowledge, this study was the first to analyze quantitative variables on post-RFA CT to assess the occurrence of

Table 5. Univariable and multivariable analyses of overall survival after RFA for HCC in patients with delayed discharge

Characteristic	Hazards ratio (95% CI)	P-value
Univariable Cox regression analysis		
Delayed discharge	12.96 (2.37–71.00)	0.003[a]
Multivariable Cox regression analysis		
Delayed discharge	2.98 (0.31–28.56)	0.344
ALBI grade		
1	Reference	
2	6.82 (0.82–56.46)	0.075
3	21.17 (0.98–458.38)	0.052
Ablation zone size (cm)		
X-axis	0.50 (0.12–2.10)	0.347

ALBI grade and ablation zone size (suspected confounding variables) associated with delayed discharge were included in the multivariable Cox regression analysis of overall survival.

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; CI, confidence interval; ALBI grade, albumin-bilirubin grade.

[a]Statistically significant.

major complications. The longest ablation zone diameter was the only factor significantly associated with the occurrence of major complications. In a previous study, Child-Pugh B status was the only predictor of complications based on an analysis of patients' demographics, laboratory data, and tumor variables [18]. However, a high ALBI grade in this study was not associated with any major complications. Instead, poor liver function was associated with delayed discharge after RFA. It is possible that the operators in this study might have intentionally performed less aggressive ablation in patients with impaired liver function to prevent liver failure after treatment. This assumption is supported by the results of the univariable analysis of delayed discharge, in which ALBI grade 3 was identified as an associated risk factor, whereas the longest diameter of the ablation zone showed a negative correlation. ALBI grade 3 was the only factor associated with delayed discharge in the multivariable analysis, as delayed discharge was generally related to poor liver function, such as uncontrolled ascites or esophageal varices, and technical failure of RFA from an attempt to preserve remnant liver function by performing less aggressive ablation. No significant factor other than the major complications was associated with ER visits or readmission.

Previous studies have reported collateral thermal injury around the liver, hemorrhage, bile duct injury, hepatic infarction, and hepatic abscess as common and important complications of RFA. However, recent advances in RFA techniques, modifications, and image-guiding modalities may have changed its aspects [3,4]. A Japanese multicenter study involving 9,411 patients compared the incidence of complications after RFA in two periods (1999–2010 and 2011–2015) and concluded that the incidence of liver infarction and bile duct injury decreased in the recent period; meanwhile, no significant change was observed in the frequency of hemorrhagic complications [19]. Consistent with these results, in the present study, no bile duct injury was observed because patients with peritumoral bile ducts were more strictly screened out from the RFA candidates in recent years. However, different trends were observed in terms of the incidence of liver infarction and hemorrhagic complications. In this study, liver infarction and infection were the primary causes of major complications (83.3%, 5/6), whereas hemorrhagic complications were not observed. This result may be attributed to the use of more aggressive RFA techniques (no-touch RFA, 52.1% [98/188]; median number of needle positions, 3) that created larger ablation zones, whereas fusion imaging guidance made it possible to avoid major vessels during electrode insertion.

Major complications occurred in 3.2% (6/188) of the patients, similar to the complication rates reported in previous studies, suggesting that RFA is a safe and effective procedure [20]. Several previous studies have reported that the complication rates between no-touch RFA and conventional tumor-puncturing RFA were similar despite the larger ablative zone and the use of multiple electrodes in the no-touch technique [10,19]. However, although not statistically significant, no-touch RFA was used in a greater percentage of patients who developed major complications (83.3%, 5/6) than in those without major complications (51.1%, 93/182). This finding is explained by the fact that no-touch RFA generally creates larger ablation zones, which may lead to more collateral damage to peritumoral vessels, bile ducts, or any abutting structures. As expected, in the present study, major complications included ablation-zone infection (n=2), liver infarction (n=2), gallbladder perforation (n=1), and biloma with infection (n=1). A possible explanation for why no-touch RFA was not found to be a risk factor for major complications might be that no-touch RFA is not always feasible, and tumors abutting the liver capsule or hepatic vessels with a larger caliber might have been treated using tumor-puncturing RFA rather than no-touch RFA [10].

Although statistically insignificant, the risk of LTP was higher in patients without major complications, likely because the ablation zone was larger in those with major complications. Larger ablative margins are required to reduce LTP, but may increase the risk of developing complications [21]. Therefore, an ideal ablative margin should be targeted to simultaneously minimize the risk of LTP and complications.

The univariable analysis showed that patients with delayed discharge after RFA showed poorer overall survival than those with no delayed discharge. However, a high ALBI grade was the

strongest confounding factor that resulted in death of patients with delayed discharge, rather than the delayed discharge itself (Table 5). Therefore, the relationship between delayed discharge after RFA and overall survival should be cautiously interpreted.

This study has several limitations. First, selection bias was unavoidable as this was a retrospective cohort study conducted at a single tertiary cancer center. Second, patients who experienced delayed discharge were strictly described as those who were not discharged the day after the RFA procedure based on the RFA protocol of the authors' institution, which may differ from that of other institutions. Third, the number of events (major complications, 6; delayed discharge, 9; and ER visits or readmission, 13) was relatively small compared with the total number of patients (n=188). Therefore, the 95% CIs of the statistical analyses tended to be large, and results of the multivariable analysis may mask potentially associated variables [22]. However, considering (1) the intrinsically low complication rates of RFA as a safe procedure, (2) the rigorous inclusion criteria established to conduct a nodule-based analysis and avoid the confounding effects of previous treatment history in this study population, and (3) continuous advances in RFA techniques that make long-term analysis under controlled circumstances difficult, the present study provides valuable information regarding complications after RFA, and the data may reflect the status of the current RFA technique used in clinical practice.

In conclusion, this study confirmed RFA as a highly safe procedure for single HCCs of <3 cm, even with rapidly changing RFA techniques in the most recent cohort. The largest ablation zone diameter was identified as a predictive factor for major complications after RFA. In addition, an ALBI grade of 3 was identified as an independent variable associated with delayed discharge. Major complications were the only factors associated with ER visits or readmission. The occurrence of the three relevant events of interest in this study (major complications, delayed discharge, and ER visit or readmission) was not substantially related to the post-treatment outcomes of LTP and overall survival.

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Conflict of Interest

Min Woo Lee is a consultant for the STARmed company.

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