Liver Stiffness Measured by Two-Dimensional Shear-Wave Elastography: Prognostic Value after Radiofrequency Ablation for Hepatocellular Carcinoma

Dong Ho Lee\textsuperscript{a}    Jeong Min Lee\textsuperscript{a, b}    Jung-Hwan Yoon\textsuperscript{c}    Yoon Jun Kim\textsuperscript{c}
Jeong-Hoon Lee\textsuperscript{c}    Su Jong Yu\textsuperscript{c}    Joon Koo Han\textsuperscript{a, b}

\textsuperscript{a}Department of Radiology, \textsuperscript{b}Institute of Radiation Medicine, Seoul National University College of Medicine, and \textsuperscript{c}Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Keywords
Hepatocellular carcinoma · Radiofrequency ablation · Overall survival · Two-dimensional supersonic shear-wave elastography · Liver stiffness measurement

Abstract
Purpose: To evaluate the prognostic value of liver stiffness (LS) measured using two-dimensional (2D) shear-wave elastography (SWE) in patients with hepatocellular carcinoma (HCC) treated by radiofrequency ablation (RFA). Methods: The Institutional Review Board approved this retrospective study and informed consent was obtained from all patients. A total of 134 patients with up to 3 HCCs \( \leq 5 \) cm who had undergone pre-procedural 2D-SWE prior to RFA treatment between January 2012 and December 2013 were enrolled. LS values were measured using real-time 2D-SWE before RFA on the procedural day. After a mean follow-up of 33.8 ± 9.9 months, we analyzed the overall survival after RFA using the Kaplan-Meier method and Cox proportional hazard regression model. The optimal cutoff LS value to predict overall survival was determined using the minimal \( p \) value approach. Results: During the follow-up period, 22 patients died, and the estimated 1- and 3-year overall survival rates were 96.4 and 85.8\%, respectively. LS measured by 2D-SWE was found to be a significant predictive factor for overall survival after RFA of HCCs, as was the presence of extrahepatic metastases. As for the optimal cutoff LS value for the prediction of overall survival, it was determined to be 13.3 kPa. In our study, 71 patients had LS values \( \geq 13.3 \) kPa, and the estimated 3-year overall survival was 76.8\% compared to 96.3\% in 63 patients with LS values <13.3 kPa. This difference was statistically significant (hazard ratio = 4.30 [1.26–14.7]; \( p = 0.020 \)). Conclusion: LS values measured by 2D-SWE was a significant predictive factor for overall survival after RFA for HCC.
Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death worldwide [1, 2]. Among the various treatment options available for patients with HCCs, radiofrequency ablation (RFA) has emerged as an effective local treatment option with curative intent in patients with cirrhosis and small HCCs <3 cm in diameter [2–4]. Indeed, according to several management guidelines for HCC such as those of the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD), RFA is recommended for the treatment of patients with small, early-stage HCCs and portal hypertension [2, 4–8]. Recently, with surveillance tests using ultrasound (US) on the rise for patients at high risk of developing HCCs such as those with cirrhosis or chronic hepatitis B viral infection, increased detection of small HCCs and a concordant increase in RFA treatment of HCCs has been documented [5, 6].

Previous studies investigating the clinical outcome of RFA for HCCs have shown that a patient’s underlying liver function can significantly affect overall survival, with many studies reporting that Child-Pugh class B liver function is a significant determinant of poor overall survival after RFA for early-stage HCCs [2, 4, 9, 10]. The presence of cirrhosis and the degree of liver fibrosis have also been shown to be negative factors for liver regeneration [11, 12]. With recent advances in US technology, various elastography techniques including transient elastography (TE) (Fibroscan; Echosense, Paris, France), point shear-wave elastography (SWE) and two-dimensional (2D)-SWE by Aixplorer® have been confirmed to be effective tools for the staging of liver fibrosis and the diagnosis of liver cirrhosis [13–17]. In addition, a recent study reported that liver stiffness (LS) measurements using TE have also shown the capability to predict the 5-year survival of patients with chronic hepatitis C [18]. According to one recent study comparing the accuracies of various US elastography techniques for the staging of liver fibrosis, TE, acoustic radiation force impulse imaging, and 2D-SWE were shown to be comparably effective methods for the noninvasive assessment of liver fibrosis [16]. However, in contrast to TE, point SWE and 2D-SWE can provide real-time B-mode US imaging which can aid in the planning and guidance of interventional procedures including RFA, and LS measurements obtained through SWE can easily be linked to RFA procedures [19]. Moreover, 2D-SWE allows real-time bidimensional assessment of LS in larger regions, and therefore LS values measured by 2D-SWE can provide information regarding the degree of liver fibrosis [15, 16, 19]. We therefore hypothesized that LS values measured by 2D-SWE might be a significant predictive factor for the clinical outcome of RFA in patients with HCCs. Thus, the purpose of this study was to evaluate the value of LS measured by 2D-SWE as a predictor of the clinical outcome in HCC patients treated by RFA.

Patients and Methods

Patients

Our Institutional Review Board approved this retrospective analysis of prospectively collected pre-RFA SWE data and written informed consent was obtained from all patients. From January 2012 to December 2013, 151 patients with HCCs were treated by RFA and met the following eligibility criteria for inclusion in this study. The eligibility criteria for this study were: (a) fewer than 3 HCC nodules without extrahepatic metastasis or macrovascular invasion; (b) largest diameter of the tumor ≤5 cm; (c) well-compensated Child-Pugh class A liver function; (d) prothrombin activity >40% and a platelet count >5 × 10^9/L; (e) successfully measured LS values using 2D-SWE prior to RFA; (f) patients who underwent liver transplantation after RFA for HCC during the follow-up period; and (g) available follow-up imaging study and/or medical records to assess the clinical outcome of RFA. Of the 151 patients, 17 patients were excluded from the study due to either technical failure to obtain LS value measurements using 2D-SWE (n = 3), immediate follow-up loss after RFA (n = 3), or undergoing liver transplantation during the follow-up period (n = 11). The remaining
Child-Pugh class A patients who underwent RFA for less than 3 HCCs between January 2012 and December 2013 (n = 151)

Excluded due to technical failure of liver stiffness value measurement by using Supersonic shear-wave elastography (n = 3)
Immediate follow-up loss after RFA (n = 3)
Undergoing liver transplantation after RFA during follow-up (n = 11)

134 patients with fewer than 3 HCC nodules, and Supersonic shear-wave elastography before RFA

With liver stiffness value ≥13.3 kPa (n = 71)
With liver stiffness value <13.3 kPa (n = 63)

Fig. 1. Flow diagram summarizing the patient enrollment process of this study. RFA, radiofrequency ablation.

Table 1. Baseline characteristics of 134 patients with 161 HCCs treated by RFA

| Characteristic                              | Value                                      |
|--------------------------------------------|--------------------------------------------|
| Age, years                                 | 61.7±8.3 [38–84]                          |
| Gender                                     |                                            |
| Males                                      | 99 (73.9)                                  |
| Females                                    | 35 (26.1)                                  |
| Etiology of liver disease                  |                                            |
| HBV-related                                | 112 (83.6)                                 |
| HCV-related                                | 12 (9.0)                                   |
| Alcoholic                                  | 6 (4.5)                                    |
| Others1                                    | 4 (2.9)                                    |
| Prothrombin activity (INR)                 | 1.09±0.10 [0.91–1.58]                     |
| Serum albumin, g/L                         | 37.7±3.9 [29–47]                          |
| Total bilirubin level, mg/dL               | 0.89±0.35 [0.20–1.90]                     |
| Serum AFP level, ng/mL                     | 252.8±1,279.0 [1.0–10,650.0]              |
| FIB-4 index                                | 4.76±3.38 [0.79–22.77]                    |
| Tumor number                               |                                            |
| 1                                          | 112 (83.6)                                 |
| 2                                          | 17 (12.7)                                  |
| 3                                          | 5 (3.7)                                    |
| Tumor size (largest one), cm               | 1.7±0.65 [1.0–3.6]                        |
| Previous treatment history for HCC         |                                            |
| No                                         | 53 (39.6)                                  |
| Surgical resection                         | 10 (7.5)                                   |
| Ablation                                   | 12 (9.0)                                   |
| Transarterial chemoembolization            | 33 (24.6)                                  |
| More than two modalities                   | 26 (19.3)                                  |
| Antiviral therapy                          |                                            |
| Yes                                        | 97 (72.4)                                  |
| No                                         | 37 (27.6)                                  |

Values are presented as mean ± SD [range] or n (%). HCC, hepatocellular carcinoma; SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; AFP, alpha-fetoprotein. 1 Cryptogenic in 4 patients.
134 patients (M:F = 99:35; mean age ± SD, 61.7 ± 8.3 years; age range, 38–84 years) were included in the final study population (Fig. 1). The baseline characteristics of the study population are summarized in Table 1. The FIB-4 index was also calculated by using the following equation: age (years) × AST [U/L] / (platelet counts [10⁹/L] × (ALT [U/L]¹/₂) [20].

**LS Measurements Using Supersonic Shear-Wave Imaging**

LS value measurements were performed six times using a convex broadband probe (Aixplorer SC6–1; Supersonic Imagine) by one abdominal radiologist (J.M.L.) with 20 years of experience in liver US imaging on the same day just before RFA (interval between SWE and RFA: 0.5–6 h). All patients had fasted for at least 6 h prior to the examination. LS value measurements were done with the patient in the supine position with the right arm extended above the head to stretch the intercostal muscles [21, 22]. LS value measurements were performed in the right lobe of the liver through the intercostal space in order to ensure a proper sonic window and to avoid any artifacts from cardiac motion as well as HCC lesions. The convex probe was kept still for 5–7 s during acquisition, and patients were asked to hold their breath during the examination for exact acquisition. A 2 × 2 cm SWE box was placed in the liver parenchyma to avoid large vessels, and the upper edge of the SWE box was placed 1.5–2.0 cm away from the Glisson capsule. LS values were obtained within a region of interest of 10 mm² in diameter that most clearly displayed homogeneous stiffness within the plane but showed no movement or pressure artifacts. The mean value of LS expressed in kilopascal was used as the representative measurement in each patient (Fig. 2) [17]. Measurements were considered to have failed when little or no signal was obtained in the SWE box after at least 6 trials [21].

**RFA Procedures and Follow-Up after Treatment**

All RFA procedures were performed percutaneously under conscious sedation (fentanyl citrate [Hana Pharm, Seoul, Korea], midazolam [Hana Pharm, Seoul, Korea], and ketamine [Huons, Hwaseong, Kyunggi, Korea]). RFA was performed using the switching monopolar technique with a separable clustered electrode (Octopus electrodes; STARmed, Goyang, Kyunggi, Korea) and a 200-W multichannel generator (VIVA RF System, STARmed).

Follow-up examinations, including contrast-enhanced, multiphasic liver computed tomography (CT) or MRI, liver function tests, and measurement of serum alpha-fetoprotein levels were done in all patients 1 month after RFA. According to the 1-month follow-up imaging results, the technical success of the RFA procedure was assessed for each patient. Treatment failure was defined as (1) failure of the ablation zone to completely encompass the tumor seen on CT or MRI obtained before the RFA procedure or (2) presence of an arterial enhancing foci of tissue showing washout at portal or delayed phase images at the site of the original tumor seen on 1-month follow-up imaging [23, 24]. For these patients, other possible treatment options including hepatic resection, repeated ablation, liver transplantation, and transarterial chemoembolization (TACE) were considered. Treatment success was defined as complete ablation observed on 1-month follow-up images. In cases of treatment success, follow-up contrast-enhanced, multi-phase liver CT or MRI.
and measurement of the serum alpha-fetoprotein level were performed every 3 months during the first year, and then every 3–6 months during the second year [25]. Thereafter, if no tumor recurrence was observed, patients were followed up based on the schedule set for the surveillance program for liver cirrhosis.

Development of tumor recurrence during the follow-up period was evaluated and was classified into three categories: local tumor progression (LTP), intrahepatic distant recurrence (IDR), and extrahepatic metastases (EM). LTP was defined as the reappearance of enhancing tumor tissue adjacent to the ablated zone after achievement of treatment success, and IDR as the emergence of 1 or more HCCs not adjacent to the treated site [23]. The appearance of EM was also assessed on follow-up imaging. When we observed LTP, IDR, or EM on follow-up imaging, the date of each type of recurrence was recorded.

Statistical Analysis

Categorical variables were compared using the Fisher exact test and continuous variables using the Mann-Whitney test for univariate analysis; a \( p \) value <0.05 was considered to indicate statistical significance. Overall survival was defined as the interval between RFA treatment and death or the date of the last follow-up visit before May 31, 2016. Patients who underwent liver transplantation during the follow-up period after RFA were excluded from this study at the date of their transplantation. Recurrence-free survival was defined as the interval between RFA treatment and the first date of any type of HCC recurrence (either local and/or distant) or the last follow-up date without recurrence.

Univariate and multivariate analyses were performed to determine significant clinical and biological parameters able to predict overall and recurrence-free survival. Survival curves were estimated using the Kaplan-Meier method and a univariate Cox proportional hazards model was fitted to each variable. All variables with a \( p \) value <0.05 were included in the multivariate analysis using a stepwise Cox hazards regression model in order to evaluate their value as independent predictors. All statistical analyses were performed using SPSS version 21 (SPSS, Chicago, IL, USA). To obtain the optimal cutoff LS value for predicting overall survival after RFA, the minimal \( p \) value approach based on the log-rank test statistic was used [26]. Thereafter, for internal validation of the optimal cutoff LS value, twofold cross-validation was performed [27]. Determination of the optimal cutoff LS value measured by SWE and the internal validation was done using SAS 9.2 version (SAS Institute Inc., Cary, NC, USA) after consultation with a biostatistician working at the Medical Research Collaborating Center of our institute. All authors had access to the study data and reviewed and approved the final manuscript.

Results

LS Measurements using Supersonic Shear-Wave Imaging

Among the 151 patients who initially underwent LS measurements using 2D-SWE, measurement success was achieved in 148 patients resulting in a technical success rate of 98.0% (148/151). In addition, 14 patients in whom successful LS value measurements were obtained using 2D-SWE were excluded from this study due to the lack of follow-up imaging studies (\( n = 3 \)) and undergoing liver transplantation after RFA during the follow-up period (\( n = 11 \)). Mean and median LS values for the final 134 patients measured by 2D-SWE were 14.6 ± 6.05 (SD) and 13.8 kPa (standard error [SE], 0.52), respectively, and ranged from 4.4 to 42.5 kPa.

Treatment Outcome of RFA

There were no procedure-related mortalities in this study. For the treatment of HCCs, a total of 141 RFA sessions were performed in 134 patients (1 session in 127 patients and 2 sessions in 7 patients). Treatment success assessed by 1-month follow-up CT or MRI obtained after RFA was achieved in 130 of 134 patients (97.0%, 130/134). Thus, treatment failure was observed in 4 of 134 patients and was retreated by repeat RFA (\( n = 1 \)) and TACE (\( n = 3 \)).

Survival Outcome after RFA

During a mean and median follow-up period of 33.8 ± 9.9 and 36.0 months (SE, 0.86), respectively, 22 (15.2%) patient deaths occurred due to the following causes: liver failure (\( n = \))
7); progression of HCC \( (n = 14) \); and pneumonia \( (n = 1) \). The estimated 1- and 3-year overall survival rates after RFA for HCCs in the 134 patients were 96.2 and 85.4\%, respectively (Fig. 3). We also found that LS values measured by 2D-SWE were a significant affecting factor for overall survival after RFA \( (p = 0.002) \). The optimal cutoff value was set at 13.3 kPa using the minimal \( p \) value approach, and twofold cross-validation results revealed that this cutoff LS value was internally valid \( (p = 0.020) \). Of the 63 patients with LS values less than 13.3 kPa measured by 2D-SWE, 3 patients died during the follow-up period due to the progression of HCCs, resulting in estimated overall 1- and 3-year survival rates of 98.3 and 96.3\%, respectively. Among the 71 patients with LS values \( \geq 13.3 \) kPa measured by 2D-SWE, 19 patients died due to liver failure \( (n = 7) \), progression of HCCs \( (n = 11) \) or pneumonia \( (n = 1) \), and the estimated overall 1- and 3-year survival rates were 94.4 and 76.8\%, respectively. This difference was statistically significant (hazard ratio = 4.30, 95% confidence interval = 1.26–14.7; \( p = 0.020 \), Fig. 4).

The prognostic factors affecting overall survival after RFA of HCCs are summarized in Table 2. According to univariate analysis, serum albumin level \( >36 \) g/L, FIB-4 index \( >5.29 \), doing antiviral therapy, the appearance of extrahepatic metastasis and LS values \( \geq 13.3 \) kPa measured by 2D-SWE were significant predictors of overall survival. However, only the appearance of extrahepatic metastasis and LS values \( \geq 13.3 \) kPa measured by 2D-SWE were revealed to be significant predictive factors for overall survival at multivariate analysis. The survival outcome according to the previous history of HCC treatment and etiology of HCC were given in supplementary material.
**Table 2.** Cox survival analysis of the predictors of overall survival in 134 patients with 161 HCCs after RFA

| Characteristic                                      | Univariate         | Multivariate       |
|-----------------------------------------------------|---------------------|--------------------|
|                                                     | HR | 95% CI | p value | HR | 95% CI | p value |
| Gender (male)                                       | 0.65 | 0.22–1.94 | 0.439 |     |        |        |
| Age (per 1 year)                                    | 1.04 | 0.99–1.09 | 0.152 |     |        |        |
| Tumor number                                        | 0.54 | 0.15–1.92 | 0.340 |     |        |        |
| Tumor size (cm)                                     | 1.50 | 0.84–2.66 | 0.168 |     |        |        |
| Total bilirubin (mg/dL)                             | 1.58 | 0.50–5.04 | 0.437 |     |        |        |
| Serum albumin >36 g/L                               | 0.27 | 0.12–0.63 | 0.002 | 0.91 | 0.30–2.76 | 0.866 |
| Prothrombin activity (INR)                          | 18.7 | 0.67–521 | 0.084 |     |        |        |
| Platelet count (K)                                  | 1.00 | 0.98–1.01 | 0.104 |     |        |        |
| Serum AFP (ng/mL)                                   | 1.00 | 0.99–1.01 | 0.057 |     |        |        |
| FIB-4 index >5.29                                   | 3.61 | 1.51–8.63 | 0.004 | 1.65 | 0.60–4.54 | 0.330 |
| Previous treatment for HCC (no vs. yes)             | 2.96 | 0.99–8.79 | 0.051 |     |        |        |
| LS value ≥13.3 kPa by 2D-SWE                         | 5.09 | 1.50–17.3 | 0.009 | 4.30 | 1.26–14.7 | 0.020 |
| Antiviral therapy                                   | 0.42 | 0.18–0.98 | 0.045 | 0.65 | 0.25–1.69 | 0.378 |
| Intrahepatic distant recurrence                     | 1.65 | 0.64–4.25 | 0.301 |     |        |        |
| Local tumor progression                              | 2.71 | 0.99–7.44 | 0.052 |     |        |        |
| Extrahepatic metastasis                             | 8.24 | 3.52–19.3 | <0.001 | 7.24 | 3.08–17.0 | <0.001 |

Values in italics are significant. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; HR, hazard ratio; INR, international normalized ratio; AFP, alpha-fetoprotein (per 100 units); LS, liver stiffness; SWE, supersonic shear-wave elastography.

**Table 3.** Cox survival analysis of the predictors of recurrence-free survival in 134 patients with 161 HCCs after RFA

| Characteristic                                      | Univariate         | Multivariate       |
|-----------------------------------------------------|---------------------|--------------------|
|                                                     | HR | 95% CI | p value | HR | 95% CI | p value |
| Gender (male)                                       | 0.70 | 0.41–1.18 | 0.179 |     |        |        |
| Age (per 1 year)                                    | 1.01 | 0.99–1.04 | 0.339 |     |        |        |
| Tumor number                                        | 1.05 | 0.69–1.61 | 0.812 |     |        |        |
| Tumor size (cm)                                     | 1.06 | 0.76–1.48 | 0.741 |     |        |        |
| Total bilirubin (mg/dL)                             | 1.02 | 0.55–1.90 | 0.950 |     |        |        |
| Serum albumin >36 g/L                               | 0.65 | 0.40–1.05 | 0.077 |     |        |        |
| Prothrombin activity (INR)                          | 2.02 | 0.30–13.8 | 0.472 |     |        |        |
| Platelet count (K)                                  | 1.00 | 0.99–1.01 | 0.556 |     |        |        |
| Serum AFP (ng/mL)                                   | 1.00 | 0.99–1.01 | 0.820 |     |        |        |
| FIB-4 index >5.29                                   | 1.22 | 0.77–1.92 | 0.403 |     |        |        |
| Previous treatment for HCC (no vs. yes)             | 3.26 | 1.98–5.40 | <0.001 | 2.98 | 1.79–4.95 | <0.001 |
| LS value ≥13.3 kPa by 2D-SWE                         | 1.30 | 0.84–2.01 | 0.242 |     |        |        |
| Antiviral therapy                                   | 1.52 | 0.89–2.60 | 0.124 |     |        |        |
| Local tumor progression                              | 4.54 | 2.50–8.25 | <0.001 | 3.64 | 2.00–6.61 | <0.001 |

Figures in italics are significant. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; HR, hazard ratio; INR, international normalized ratio; AFP, alpha-fetoprotein (per 100 units); LS, liver stiffness; SWE, supersonic shear-wave elastography.
Recurrence Outcome after RFA

Of the 130 patients with HCCs in whom treatment success was achieved after RFA, LTP developed in 15 patients (15/130, 11.5%). For the treatment of LTP, 5 patients underwent repeated RFA, 2 patients underwent percutaneous ethanol injection, 6 patients underwent TACE, and the remaining 2 patients underwent hepatic resection. Of the 134 patients with HCCs treated by RFA, 79 patients (79/134, 59.0%) experienced IDR during follow-up and initial IDR was treated with the following modalities: percutaneous ethanol injection (n = 8); RFA (n = 17); TACE (n = 53); and best supportive care (n = 1). During follow-up, EM developed in 16 out of 134 patients with HCCs (16/134, 11.9%). The location of initial EM was: peritoneal seeding (n = 2), lymph node (n = 8), lung (n = 5), and adrenal gland (n = 1). Of these 16 patients, 9 were treated with systemic chemotherapy, 3 with radiation therapy, 3 with best supportive care, and 1 with surgery.

The estimated 1- and 3-year recurrence-free survival rates after RFA in the 134 patients with 161 HCCs were 63.4 and 37.6%, respectively. The predictive factors for recurrence-free survival are summarized in Table 3. The development of LTP and previous treatment history for HCC were significant predictors of recurrence-free survival.

Discussion

According to our study results, LS measured by 2D-SWE in patients with HCCs treated by RFA was a significant predictive factor for overall survival, with the optimal cutoff LS value for the prediction of overall survival determined as 13.3 kPa (hazard ratio = 4.30, 95% confidence interval 1.26–14.7; p = 0.020). In addition, on multivariate analysis, conventional fibrosis markers calculated by using serum biochemical test such as FIB-4 index was not a significant affecting factor for overall survival after RFA for HCC, which could mean that the FIB-4 index was not enough to predict overall survival and addition of 2D-SWE might be helpful to predict patient outcome. Our study results well correlate with the results of a previous study by Vergniol et al. [18], which also reported that LS values measured by TE were able to predict the 5-year survival of patients with chronic hepatitis C. This similarity in our study results is surprising given the significant differences between our study populations (i.e., patients with HCCs in our study vs. patients with chronic hepatitis C) and LS value measurement methods (i.e., 2D-SWE in our study vs. TE). As for the optimal cutoff value for the prediction of overall survival after RFA, our calculated value of 13.3 kPa was similar to the cutoff value of 15.4 kPa previously proposed as the optimal cutoff LS value for the diagnosis of clinically significant portal hypertension [28]. Indeed, several studies have previously reported that LS values measured by TE or 2D-SWE were moderately correlated with the hepatic vein pressure gradient (HVPG), which is considered to be the standard method of diagnosing portal hypertension [29, 30]. In addition, regarding surgical resections for patients with HCCs, the presence of portal hypertension is a well-known risk factor for both the development of posthepatectomy liver failure and overall survival outcome after treatment [31–33]. Therefore, considering these previous study results and our own, it is possible that the poor overall survival rate after RFA of HCCs in patients with higher LS values could be due to the presence of portal hypertension. In addition, increased LS value measured by 2D-SWE can indicate the presence of more advanced stage of fibrosis/cirrhosis, and the presence of advanced stage of fibrosis/cirrhosis has been a well-known negative factor for liver regeneration. Therefore, the negative effect on liver regeneration of increased LS value measured by 2D-SWE might also explain our study result of poor overall survival outcome after RFA for HCCs in patients with increased LS value measured by 2D-SWE [11, 12].
From a clinical point of view, the survival estimates obtained in our study may have an impact on the choice of the appropriate treatment modality in patients with HCCs. According to our study results, in patients with LS values less than 13.3 kPa determined by 2D-SWE, the estimated 3-year survival rate was 96.3%, which is comparable to that of liver transplantation. Therefore, in those patients in whom surgical resection is not possible due to concerns of posthepatectomy liver failure or other comorbidities which preclude major surgery, RFA may be the best therapeutic option. Conversely, in patients with LS values ≥13.3 kPa, the estimated 3-year survival rate was 76.8% which is significantly lower than that in patients with an LS value <13.3 kPa. Therefore, in those cases, liver transplantation would be the better choice if and when a donor’s liver becomes available. However, larger studies with a prospective design are warranted to more confirmatively assess whether LS values measured by 2D-SWE could be used to determine the optimal treatment modality for HCC.

Until now, TE has been the most widely used modality to assess the degree of liver fibrosis, and its diagnostic and prognostic values have been extensively evaluated and validated [13, 14, 17, 18]. Nonetheless, 2D-SWE has several clear advantages over TE. First, the diagnostic performance of 2D-SWE in assessing the degree of liver fibrosis is more favorable than with TE [17, 34]. Second, unlike TE, the US equipment of 2D-SWE can provide real-time B-mode imaging of the liver. Therefore, US equipment of 2D-SWE can easily be used in conjunction with interventional procedures such as RFA. To the contrary, 2D-SWE might be more limited by factors such as operator variability compared to TE, as 2D-SWE embedded in a conventional scanner allows the choice of where to place the region of interest within the color stiffness box and whether to confirm or exclude each single measurement when determining the final value, while these choices are not available with TE [15]. In addition to US elastography including 2D-SWE and TE, magnetic resonance elastography (MRE) of the liver is another noninvasive method which can be used to measure the viscoelastic properties of the liver, providing a quantitative method for the diagnosis of liver fibrosis and cirrhosis as well as accurate liver fibrosis staging [35–40]. However, although the reproducibility of MRE for liver fibrosis has been reported to be even better than that of US elastography, the cost of MRE is much higher than that of SWE [41, 42]. In addition, MRE requires a longer acquisition time, and claustrophobia and the presence of iron overload in the liver are other limitations of MRE in assessing the degree of fibrosis at present [34].

Our study has several limitations. First, even though our cutoff LS value of 13.3 kPa for predicting overall survival after RFA of HCCs was internally validated, our study results need to be validated by other studies. It would be especially important to validate these results in Western populations, as the etiology of liver cirrhosis and HCC is different between Asian populations (i.e., hepatitis B virus infection) and Western populations (i.e., hepatitis C virus infection or alcohol related). Therefore, further studies including patients with other etiologies of liver disease are warranted for the generalization of our results. Second, as HVPG measurements were not performed prior to RFA in our study, we could not correlate the LS values measured by 2D-SWE with the presence of portal hypertension. However, according to most current guidelines, RFA is recommended for early-stage HCCs in patients with portal hypertension who cannot undergo liver transplantation mainly due to the shortage of donor livers [5–7]. In addition, a recent guideline has recommended RFA as the first-line treatment modality for very early-stage HCCs regardless of the presence of portal hypertension [7]. Therefore, HVPG measurements before RFA has generally not been recommended in the current management guidelines for HCCs.

In conclusion, LS values measured by 2D-SWE were a significant predictive factor for overall survival after RFA of HCCs.
Disclosure Statement

We have no conflicts of interest to disclose.

Funding Sources

The authors received no financial support for this study.

References

1. Parkin DM, Bray F, Ferlay J, et al: Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94: 153–156.
2. 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 2014; 270: 900–909.
3. Chen MS, Li JQ, Zheng Y, et al: A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006; 243: 321–328.
4. 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. Hepatology 2009; 50: 1475–83.
5. Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208–1236.
6. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012; 56: 908–943.
7. Former A, Llovet JM, Bruix J: Hepatocellular carcinoma. Lancet 2012; 379: 1245–1255.
8. Cucchetti A, Piscaglia F, Cescon M, et al: Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol 2013; 59: 300–307.
9. Shina S, Tateishi R, Arano T, et al: Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012; 107: 569–577; quiz 578.
10. Kim YS, 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; 58: 89–97.
11. Farges O, Malassagne B, Flejou JF, et al: Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999; 229: 210–215.
12. Ishikawa M, Yogita S, Miyake H, et al: Clarification of risk factors for hepatectomy in patients with hepatocellular carcinoma. Hepatogastroenterology 2002; 49: 1625–1631.
13. Castera L, Vergniol J, Foucher J, et al: Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005; 128: 343–350.
14. Foucher J, Chanteloup E, Vergniol J, et al: Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006; 55: 403–408.
15. Piscaglia F, Salvatore V, Mulazzani L, et al: Ultrasound shear wave elastography for liver disease. A critical appraisal of the many actors on the stage. Ultraschall Med 2016; 37: 1–5.
16. Gerber L, Kasper D, Fitting D, et al: Assessment of liver fibrosis with 2-D shear wave elastography in comparison to transient elastography and acoustic radiation force impulse imaging in patients with chronic liver disease. Ultrasound Med Biol 2015; 41: 2350–2359.
17. Cassinotto C, Lapuyade B, Mouties A, et al: Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan®. J Hepatol 2014; 61: 550–557.
18. Vergniol J, Foucher J, Terrebonne E, et al: Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011; 140: 1970–1979, 1979.e1–3.
19. Hong Ek, Choi YH, Cheon JE, et al: Accurate measurement of liver stiffness using shear wave elastography in children and young adults and the role of the stability index. Ultrasonography 2017, Epub ahead of print.
20. Vallet-Pichard A, Mallet V, Nalpas B, et al: FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. Hepatology 2007; 46: 32–36.
21. Yoon JH, Lee JM, Joo I, et al: Hepatic fibrosis: prospective comparison of MR elastography and US shear-wave elastography for evaluation. Radiology 2014; 273: 772–782.
22. Woo H, Lee JY, Yoon JH, et al: Comparison of the reliability of acoustic radiation force impulse imaging and supersonic shear imaging in measurement of liver stiffness. Radiology 2015; 277: 881–886.
23. Goldberg SN, Grassi CJ, Cardella JF, et al: Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 2005; 235: 728–739.
24. Kim SH, Lim HK, Kim MJ, et al: Radiofrequency ablation of high-grade dysplastic nodules in chronic liver disease: comparison with well-differentiated hepatocellular carcinoma based on long-term results. Eur Radiol 2008; 18: 814–821.
25. Lee DH, Lee JM, Lee JY, et al: Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. J Hepatol 2015; 62: 1122–1130.
Contal C, O’Quigley J: An application of change point methods in studying the effect of age on survival in breast cancer. Comput Stat Data Anal 1999;30:253–270.

Faraggi D, Simon R: A simulation study of cross-validation for selecting an optimal cut-point in univariate survival analysis. Stat Med 1996;15:2203–2213.

Procopet B, Berzigotti A, Abraldes JG, et al: Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015;62:1068–1075.

Llop E, Berzigotti A, Reig M, et al: Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol 2012;56:103–108.

Choi SY, Jeong WK, Kim Y, et al: Shear-wave elastography: a noninvasive tool for monitoring changing hepatic venous pressure gradients in patients with cirrhosis. Radiology 2014;273:917–926.

Bruix J, Castells A, Bosch J, et al: Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018–1022.

Llovet JM, Fuster J, Bruix J: Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–1440.

Berzigotti A, Reig M, Abraldes JG, et al: Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology 2015;61:526–536.

Ferraioli G, Tinelli C, Dal Bello B, et al: Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56:2125–2133.

Huwart L, Sempoux C, Salameh N, et al: Liver fibrosis: noninvasive assessment with MR elastography versus aspartate aminotransferase-to-platelet ratio index. Radiology 2007;245:458–466.

Chung S, Breton E, Mannelli L, et al: Liver stiffness assessment by tagged MRI of cardiac-induced liver motion. Magn Reson Med 2011;65:949–955.

Mannelli L, Wilson GJ, Dubinsky TJ, et al: Assessment of the liver strain among cirrhotic and normal livers using tagged MRI. J Magn Reson Imaging 2012;36:1490–1495.

Godfrey EM, Mannelli L, Griffin N, et al: Magnetic resonance elastography in the diagnosis of hepatic fibrosis. Semin Ultrasound CT MR 2013;34:81–88.

Loomba R, Wolfson T, Ang B, et al: Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology 2014;60:1920–1928.

Monti S, Palma G, Ragucci M, et al: Optimization of tagged MRI for quantification of liver stiffness using computer simulated data. PLoS One 2014;9:e111852.

Huwart L, Sempoux C, Vicaut E, et al: Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008;135:32–40.

Van Beers BE, Daire JL, Garteiser P: New imaging techniques for liver diseases. J Hepatol 2015;62:690–700.