Transarterial Chemoembolization versus Radiofrequency Ablation for Small Hepatocellular Carcinomas with Discrepant Features on Computed Tomography and Magnetic Resonance Imaging

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Background/Aims: This study compared the outcomes of patients with small hepatocellular carcinomas (HCCs) who were treated using transarterial chemoembolization (TACE) or radiofrequency ablation (RFA).

Methods: This was a post-hoc analysis of a prospective study that evaluated the diagnostic efficacy of magnetic resonance imaging (MRI) and computed tomography (CT). We analyzed 41 small hepatic nodules in 32 patients that showed typical radiologic hallmarks on both CT and gadoxate-enhanced MRI (typical nodules) and 25 small hepatic nodules from 22 patients that showed atypical radiologic hallmarks on CT and typical radiologic hallmarks on MRI (discrepant nodules).

Results: There were no significant differences in the baseline characteristics of the patients with typical and discrepant nodules. Complete response rates 1 month after TACE or RFA were 75.0% (18/24) and 94.1% (16/17; P=0.20), respectively, for the patients with typical nodules and 58.8% (10/17) and 100% (8/8; P=0.05), respectively, for the patients with discrepant nodules. Treatment failure rates after TACE or RFA were 33.3% (8/24) and 5.8% (1/17; P=0.15), respectively, for the patients with typical nodules and 47.0% (8/17) and 0.0% (0/8; P=0.02), respectively, for the patients with discrepant nodules. Among patients achieving complete response, there were no significant differences in the risk of marginal recurrence.

Conclusions: RFA provided higher complete response rates and significantly lower treatment
INTRODUCTION

Hepatocellular carcinoma (HCC) was the sixth most common cancer and the third most frequent cause of death worldwide in 2008. According to the recently revised guidelines of the American Association for the Study of Liver Diseases (AASLD), HCC can be diagnosed without biopsy. Typical radiologic hallmarks of HCC seen either on 1 or 2 dynamic studies, which include computed tomography (CT) and magnetic resonance imaging (MRI), can be used to establish the diagnosis of HCC in patients with chronic liver disease. Imaging surveillance of high-risk patients using ultrasonography or advanced CT or MRI has increased the detection rate of hepatic nodules smaller than 20 mm. However, the diagnosis of nodules smaller than 20 mm with nonspecific imaging characteristics and without signs of arterial hypervascularity remains difficult. The new paramagnetic contrast agent, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (gadoxate), which was developed to provide both dynamic and hepatobiliary MRI images, has been shown to improve the diagnosis of hepatic lesions.

Patients with conserved liver function (Child-Pugh class A) and HCCs smaller than 20 mm are classified as having very early (stage 0) HCC, according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Curative treatments such as hepatic resection, radiofrequency ablation (RFA), and liver transplantation are recommended for these patients. Transarterial chemoembolization (TACE) is not recommended for early HCC, but if the imaging diagnosis is not definitive, or if a patient cannot undergo resection or local ablation therapy, or the HCC is multinodular, TACE can be considered as a treatment option. In addition, if a patient has multiple hepatic lesions, including 1 or more nodules smaller than 20 mm that appear discrepant on contrast-enhanced CT and MRI, the correct diagnosis is even more important, because the finding of a positive nodule could change the clinical stage of the disease to intermediate-stage HCC (BCLC stage B).

To the best of our knowledge, there have not been any studies comparing RFA and TACE for early-stage HCC patients with discrepant contrast-enhanced CT and MRI findings. The aim of this post-hoc study was to compare the complete response rates and treatment failure rates of TACE and RFA for patients with small hepatic nodules that had atypical radiologic hallmarks on contrast-enhanced CT and typical features on gadoxate-enhanced MRI.

METHODS

1. Patient selection

The original study was a prospective study that evaluated the diagnostic accuracy of CT and MRI for small hepatic nodules (10–20 mm) in cirrhotic patients. Between February 2010 and October 2011, 100 patients with 117 hepatic nodules smaller than 20 mm on enhanced CT at a university-affiliated hospital were enrolled in that study, and underwent gadoxate-enhanced MRI within 1 month after CT. All participants had provided written informed consent. This current study was a post-hoc analysis of that original study. We studied patients with nodules that had atypical radiologic hallmarks on dynamic multidetector computed tomography (MDCT) and typical features on dynamic gadoxate-enhanced MRI (discrepant nodules) and patients with nodules that had typical radiologic hallmarks on both dynamic MDCT and dynamic MRI (typical nodules) as controls. The
inclusion criteria were as follows: (a) age >18 years, (b) underlying chronic liver disease, and (c) underwent either TACE or RFA for those small hepatic target nodules. Typical radiologic hallmarks on MRI were defined as high signal intensity (SI) in the arterial phase and low SI in the hepatobiliary phase. Typical radiologic hallmarks on MDCT were defined as high attenuation in the arterial phase and low attenuation in the equilibrium phase. Atypical features on dynamic MDCT included high attenuation in the arterial phase and iso attenuation in the equilibrium phase, iso attenuation in the arterial phase and iso-/low attenuation in the equilibrium phase, and low attenuation in both the arterial phase and equilibrium phase. Typical MDCT and MRI images of a discrepant nodule meeting inclusion criteria are shown in Figure 1. The exclusion criteria were as follows: (a) hepatic nodule showing an atypical enhancement pattern on both dynamic MDCT and gadoxate-enhanced MRI, or (b) hepatic nodule with no definitive enhancement pattern on gadoxate-enhanced MRI. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was also approved by the Institutional Review Board of our institute.

2. Patient characteristics

The patient selection process is summarized in Figure 2. There were 100 patients with a total of 117 nodules ranging from 10-20 mm. Of these nodules, 50 showed typical radiologic hallmarks on dynamic MDCT and all 50 nodules showed hypervascularity on dynamic MRI; these nodules

Figure 1. 60-year-old man with hepatocellular carcinoma (HCC). Example of HCC with discrepant findings on dynamic multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI). Dynamic MDCT showed no definite enhancement during the arterial phase (A) and low attenuation (arrow) during the delayed phase (B). Gadoxate-enhanced MRI showed high signal intensity (arrow) during the arterial phase (C) and low signal intensity (arrow) during the hepatobiliary phase (D).
were termed "typical nodules". Among 67 nodules showing atypical radiologic hallmarks on contrast-enhanced CT, 27 nodules appeared hypervascular on dynamic MRI; these nodules were termed "discrepant nodules". A total of 41 typical nodules and 25 discrepant nodules fulfilling the inclusion criteria were enrolled. Among the patients with typical nodules, 16 patients with 24 nodules underwent TACE and 16 patients with 17 nodules underwent RFA. Among the patients with discrepant nodules, 14 patients with 17 nodules underwent TACE and 8 patients with 8 nodules underwent RFA. Nodules not treated by TACE and RFA were treated by hepatic resection, percutaneous ethanol injection, and some nodules were observed with serial CT or MRI.

Baseline characteristics of patients showing typical radiologic hallmark on CT and hypervascularity on MRI are summarized in Table 1, and baseline characteristics of patients showing atypical radiologic hallmark on CT and hypervascularity on MRI are summarized in Table 2. Hepatitis B virus infection was the predominant etiology of underlying liver disease. There were no significant differences between the 2 treatment groups, except for history of liver biopsy in the patients with discrepant nodules. Significantly more patients undergoing RFA underwent a liver biopsy before enrollment in the original study than patients undergoing TACE (50.0% versus 0.0%, respectively; \( P = 0.01 \)). For those undergoing TACE in the original study, previous treatment before study included the following: TACE only for 9 patients, RFA only for 1 patient, hepatic resection for 2 patients, both TACE and RFA for 4 patients, and percutaneous ethanol injection for 2 patients. Previous treatment before study for those patients undergoing RFA in the original study included the following: TACE only for 4 patients and RFA only for 3 patients, and 1 patient underwent both TACE and RFA.

3. Imaging methods

We performed contrast-enhanced CT scans on 1 of the 3 CT scanners: Lightspeed Ultra 8 (GE Healthcare, Milwaukee, WI, USA), Somatom Sensation 16 (Siemens Medical Solutions, Forchheim, Germany) or Brilliance 64 (Philips Medical Systems, Cleveland, OH, USA). After performing unenhanced CT scan, patients received 1.5 mL/kg of iopromide (Ultravist 370, Schering, Berlin, Germany) at a rate of 3 to 5 mL/s for 30 seconds intravenously. The scanning delay for the arterial phase was 15 to 19 seconds, and 30 to 33 seconds for the portal phase. We performed all magnetic resonance imaging studies with 4.0 T or higher field strength.
(MR) examinations with a 3 Tesla MR scanner (Signa Horizon, GE Healthcare) with a 8-channel torso-phased-array coil. After baseline imaging patients received 10 mL of gadoxate (Primovist, Schering, Berlin, Germany) at a rate of 1.5 mL/s.

4. TACE

After patients underwent hepatic angiography, TACE was performed using iodized oil (Lipiodol, Andre Guerbet, Aulnay-sous-Bois, France) and mixture of doxorubicin (Adriamycin RDF, Ildong Pharmaceutical, Seoul, Korea). Particle embolization was performed using Gelfoam (Upjohn, Kalamazoo, MI, USA). Chemoembolic material was injected through a 3-Fr microcatheter selected for tumor-feeding arteries, until reflux of lipiodol into the draining portal vein was seen. C-arm CT was routinely performed when performing superselective TACE. TACE was performed by interventional radiologists with >10 years experience.

5. RFA

Percutaneous RFA under sonographic guidance and monitoring was performed by an experienced attending physician (3 to 10 years of experience performing RFA). RFA was performed using either a 500-KHz monopolar radiofrequency (RF) generator (CC-1; Integra Radionics, Burlington, MA, USA) or a multichannel RF generator (Taewoong, Koyang, Korea). RFA was performed by radiologists with >10 years experience.

6. Follow-up

After the patients underwent RFA or TACE, dynamic liver

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**Table 1. Baseline characteristics of patients showing typical radiologic hallmark on CT and hypervascularity on MRI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TACE group (n=16)</th>
<th>RFA group (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>57.1 (±9.5)</td>
<td>61.0 (±6.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>13 (81.3%)</td>
<td>13 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (18.8%)</td>
<td>3 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>Cause of cirrhosis, n (%)</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>13 (81.3%)</td>
<td>13 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2 (12.5%)</td>
<td>1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (6.3%)</td>
<td>1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>LC Child-Pugh class, n (%)</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>A</td>
<td>15 (93.8%)</td>
<td>13 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0 (0.0%)</td>
<td>3 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1 (6.3%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL), mean</td>
<td>3.9±0.5</td>
<td>4.0±0.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Bilirubin (mg/mL), mean</td>
<td>1.5±1.2</td>
<td>1.4±0.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Prothrombin time (sec), mean</td>
<td>12.0±1.62</td>
<td>13.1±1.9</td>
<td>0.97</td>
</tr>
<tr>
<td>Platelet count (x10³ /mm³), mean</td>
<td>108.0±39.2</td>
<td>103.4±57.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/mL), mean</td>
<td>40.3±579</td>
<td>184.2±565.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Hepatic nodule in CT, n (%)</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Solitary</td>
<td>7 (43.8%)</td>
<td>12 (75.0%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>9 (56.2%)</td>
<td>4 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Tumor diameter (mm), mean</td>
<td>1.5±0.5</td>
<td>1.5±0.5</td>
<td>0.95</td>
</tr>
<tr>
<td>Previous history of treatment, n (%)</td>
<td>9 (56.2%)</td>
<td>6 (37.5%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Biopsy proven HCC, n(%)</td>
<td>0 (0.0%)</td>
<td>3 (18.8%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CT, computed tomography; MRI, magnetic resonance imaging; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; LC, liver cirrhosis; HCC, hepatocellular carcinoma.
MDCT was performed within 1 month to evaluate the efficacy of treatment. Follow-up contrast-enhanced CT scans were repeated every 3 to 4 months to identify marginal recurrence of the treated nodules and new hepatic nodules.

### 7. Study Endpoints

The primary endpoints of this study were rates of complete response and treatment failure. Complete response was defined as complete tumor ablation and disappearance of the target lesion on contrast-enhanced CT within 1 month after treatment, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Treatment failure was defined as incomplete tumor ablation at 1 month follow-up or marginal recurrence within 12 months of follow-up.

Secondary endpoints included marginal recurrence and time-to-marginal recurrence (TTR). Marginal recurrence was defined as recurrence within 2 cm of the original tumor nodule that had been completely ablated at 1 month. TTR was measured from the date of initial treatment until the date of the imaging study showing marginal recurrence of tumor.

### 8. Statistical analysis

The complete response rates of the RFA- and TACE-treated nodules were compared using the chi-square test. The Student t-test was used to compare pairs of independent continuous variables, and the Mann-Whitney test was used for dependent continuous variables. TTRs were calculated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using
PASW Statistics, version 19.0 (SPSS Inc., Chicago, IL, USA), and a two-sided $P$-value $<0.05$ was considered statistically significant.

**RESULTS**

1. Reasons for TACE treatment

Among the 30 patients who underwent TACE, more hepatic nodules consistent with HCC were found on gadoxate-enhanced MRI compared to contrast-enhanced CT (median 2.0 [range 1-8] versus median 1.0 [range, 1-5], respectively; $P<0.01$). We administered TACE to 13 patients because there were more than 3 nodules on gadoxate-enhanced MRI, and to the other patients because the target nodule was adjacent to major vessels or the capsule of the liver, or ultrasonographic images were too inadequate to perform RFA.

2. Rates of complete response and treatment failure

At the 1-month follow-up using contrast-enhanced CT, the complete response rates were lower in patients with either typical nodules or discrepant nodules who were treated with TACE than in those treated with RFA. Complete response rates after TACE or RFA were 75.0% (18/24) and 94.1% (16/17; $P=0.20$), respectively, for the patients with typical nodules and 58.8% (10/17) and 100% (8/8; $P=0.05$), respectively, for the patients with discrepant nodules (Fig. 3).

Treatment failure rates were higher in patients with either typical nodules or discrepant nodules who were treated with TACE than in those treated with RFA. Treatment failure rates after TACE or RFA were 33.3% (8/24) and 5.8% (1/17; $P=0.15$), respectively, for the patients with typical nodules and 47.0% (8/17) and 0.0% (0/8; $P=0.02$), respectively, for the patients with discrepant nodules (Fig. 4). RFA provided better tumor response for both the typical and the discrepant nodules, although the difference was larger and significant only for the discrepant nodules. For 14 nodules that showed incomplete response, we administered additional RFA for 3 nodules and additional TACE for 11 nodules.

3. Marginal recurrence after complete response

The median follow-up periods for nodules showing complete response were as follows: all nodules, 31.0 months (range, 6-47 months); typical nodules, 27.5 months (range, 6-47 months); and discrepant nodules, 31.0 months (range, 6-47 months).

Figure 3. Complete response rates of patients treated with transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). TACE provided a lower complete response rate than RFA for patients with hepatocellular carcinoma nodules with a typical enhancement pattern on dynamic magnetic resonance imaging but not on dynamic computed tomography (CT) ($P=0.05$) (A) and for patients with nodules with typical enhancement patterns on both dynamic and dynamic CT ($P=0.20$) (B).
Among the typical nodules, there were 4 marginal recurrences observed at a median of 13.5 months in the TACE patients and 4 marginal recurrences at a median of 19.5 months in the RFA patients. Among the discrepant nodules, there was 1 marginal recurrence observed at a median of 7 months in the TACE patients and there were 3 marginal recurrences observed at a median of 18 months in the RFA patients. There were no significant differences between the 2 treatments in TTR for both the typical nodules and the discrepant nodules ($P=0.80$ and $P=0.23$, respectively, Fig. 5).
DISCUSSION

To our knowledge, this is the first study to compare the efficacy of TACE and RFA for small (10-20 mm) hepatic nodules that had discrepant features on dynamic MDCT and MRI. Our analysis included patients with nodules with discrepant CT and MRI features who underwent TACE or RFA, and we compared these patients with patients undergoing TACE or RFA who had typical nodules that showed hyper-vascularity on both MDCT and MRI. We found that RFA provided better complete response rate and treatment failure rate for the patients with either discrepant nodules or typical nodules, although these differences were only significant for treatment failure rate of discrepant nodules. For the patients with discrepant nodules, RFA provided a marginally significant higher complete response rate than TACE, and provided a significantly lower treatment failure rate. There were no differences in the risks of marginal recurrence for patients with either typical or discrepant nodules who achieved complete response after undergoing either TACE or RFA.

For early HCC, hepatic resection is considered to be the treatment of choice, and if hepatic resection is unfeasible, RFA is an alternative option. If curative treatments are unavailable, TACE can be performed as salvage treatment. Since HCC has a high recurrence rate, less emphasis is placed on the initial treatment than for other solid tumors. The few studies that have compared the efficacy of TACE and RFA for small HCC showed that TACE may provide an overall survival comparable to RFA. A recent study showed that the overall survival rates of patients with small HCCs (<30 mm) who were treated using TACE, RFA, or surgical resection were comparable after adjustment for baseline characteristics with inverse-probability-of-treatment weighting, although recurrence-free survival was shorter after TACE. Another study that compared RFA vs TACE for small HCCs (<20 mm), found that TACE provided overall survival similar to RFA, but that RFA provided longer time to progression and higher rates of tumor regression. This study showed that RFA provided superior complete response rates and treatment failure rates than TACE. Although only for the discrepant nodules, which are thought to have low arterial vascularity, RFA provided a significantly lower treatment failure rate than TACE.

According to the revised AASLD guidelines, the typical radiologic hallmarks of a single imaging modality are sufficient for the diagnosis of HCC, but more evidence is needed to validate this diagnostic criterion and the diagnosis of 10-20 mm nodules remains challenging. When 2 dynamic imaging modalities show discrepant findings, a definite diagnosis cannot be made, and consequently treatment will be difficult to plan. TACE can be performed for patients who have discrepant findings on CT and MRI, to confirm the diagnosis and treat the nodule simultaneously. Although angiography is not listed as a diagnostic tool in the current AASLD guidelines, a previous study has shown that angiography was more accurate for diagnosis than dynamic CT. Angiography can increase the sensitivity of the diagnostic evaluation of 10-20 mm hepatic nodules. However, since our study showed that the rate of complete response and treatment failure rate was inferior in the TACE patients; TACE may not be better for these lesions. It may be preferable to perform liver biopsy when the diagnosis is uncertain, and treat patients with these lesions using surgical resection or local ablation therapy such as RFA.

In practice, the diagnosis of small hepatic nodules can lead to a change from very early-stage HCC (BCLC stage 0) to intermediate-stage HCC (BCLC stage B) if more than 4 multiple small HCCs are diagnosed on additional imaging. For these cases, the recommendation for first-line treatment might be changed from resection or RFA to TACE. In our study, we performed TACE for 13 patients because more than 4 nodules were seen on MRI; if the patients had not undergone MRI we may have treated them by surgical resection or RFA, which would have been inadequate. Because of this staging difficulty, we only evaluated the complete response rates of individual nodules and followed the patients to identify marginal recurrence of the treated nodules, instead of overall recurrence, including de novo nodules.

Serste et al. used liver biopsy to evaluate the accuracy of CT and MRI for the diagnosis of small HCC. CT and/or MRI showed 98% sensitivity and 81% specificity for the diagnosis of histologically confirmed HCC, not including dys-

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plastic nodules. However, CT and/or MRI showed 96% sensitivity and 100% specificity for the diagnosis of HCC or high-grade dysplastic nodule. This result suggests that some small hepatic nodules having discrepant CT and MRI findings might be high-grade dysplastic nodules. High-grade dysplastic nodules have less arterial vascularity, which might account for both the discrepant findings on CT and MRI and an incomplete response to TACE.

This study has several limitations. First, the study population was too small for definitive conclusions, and additional stratification based on important clinical variables such as tumor volume could not be performed. Second, an appropriate comparison of TACE and RFA could not be made because the baseline characteristics were different in the 2 groups of patients undergoing TACE or RFA. Although marginally significant, the TACE patients with discrepant nodules had undergone more treatment before study enrollment, and the biology of the tumors of that group might have been different from the biology of the tumors in the RFA patients.

In order to overcome this problem, we evaluated complete response and marginal recurrence of the treated hepatic nodules. Third, few hepatic nodules were confirmed histologically, although they met the AASLD noninvasive diagnostic criteria.

In conclusion, RFA provided higher complete response rates and significantly lower treatment failure rates than TACE for patients with discrepant nodules of HCC. Therefore, a treatment modality such as RFA may be preferable for small HCCs which show discrepancy on two imaging modalities.

**REFERENCES**


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