

Figure 2 Recurrence-free survival curves according to B-mode ultrasound classification. Recurrence-free survival was significantly shorter for type 2c hepatocellular carcinoma than for other types. $P = 0.0454$ type 1 vs type 2c; $P = 0.0005$ type 2b vs type 2c.

in type 2c than in other types. Mean AFP-L3 level was higher in type 2c than in other types.

Recurrence-free survival curves according to B-mode ultrasound classification are compared in Figure 2. Recurrence-free survival was significantly shorter for type 2c HCC than for other types.

Survival curves according to B-mode ultrasound classification are compared in Figure 3. Survival was significantly longer for type 2b than for other groups. No significant difference in survival was evident between types 1 and 2c.

Results of univariate analysis of background variables associated with tumor recurrence are shown in Table 2. Number of tumors, tumor stage, AFP-L3 levels and B-mode ultrasound classification were identified as significant contributing factors for recurrence after RFA. These significant variables were then entered into multivariate analysis. The results of multivariate analysis are shown in Table 3, with type 2c of B-mode ultrasound classification identified as the only independent factor contributing to tumor recurrence.

The results of univariate analysis of background variables associated with survival are shown in Table 4. Tumor stage and B-mode ultrasound classification were identified as significant contributing factors for survival. All significant variables on univariate analysis were then entered into multivariate analysis. The results of multivariate analysis are shown in Table 5, with type 1 of B-mode ultrasound classification identified as the only independent factor contributing to survival.

DISCUSSION

This review of a prospective database for patients who had undergone RFA for primary HCC found B-mode ultrasound image classification as an independent factor strongly influencing post-RFA recurrence and disease outcomes. This result supports the earlier finding that the B-mode ultrasound image classification we devised is capable of evaluating the malignant potential of HCC^[19].

The most common B-mode ultrasound image clas-

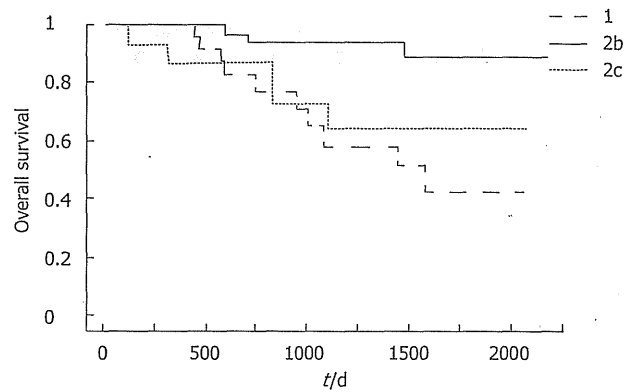


Figure 3 Survival curves according to B-mode ultrasound classification. Survival was significantly longer for type 2b than for other types. $P = 0.0006$ type 1 vs type 2b; $P = 0.0165$ type 2b vs type 2c; $P = 0.4473$ type 1 vs type 2c.

sification for primary HCCs ≤ 3 cm in diameter that had undergone RFA was type 2b, followed by types 1b, 2c and 2a, in that order. Substantial bias in the distribution of ultrasound types was thus evident. We have previously reported that type 2a HCC shows the smallest mean diameter in B-mode ultrasound classification and represents well-differentiated HCC with fat deposition^[19]. Type 2a can therefore be considered as the ultrasound classification associated with the lowest malignant potential. Our present database of patients with hypervascular HCC included only 9 type 2a patients and data for these cases were excluded from analyses due to insufficient numbers. However, type 2a HCC seems likely to represent the patient group associated with the best prognosis.

Type 2b showed a longer interval until recurrence and better outcomes compared with types 1 and 2c. Of course, mean tumor diameter is smaller in type 2b than in types 1 and 2c and tumor stage also shows a higher proportion of early-stage cases. Outcomes for type 2b could thus be due to these reasons. However, multivariate analysis identified ultrasound categorization as an independent factor exerting greater influence on recurrence and survival than either tumor diameter or stage. For that reason, the malignant potential of type 2b HCC can be considered lower than that of types 1 and 2c.

Type 1 in the B-mode ultrasound image classification represents HCC with a clear margin accompanied by a halo. The halo represents a fibrous capsule, a finding commonly seen in dedifferentiated and moderately differentiated HCCs during the course of multistep carcinogenesis. In contrast, a type 2c ultrasound image is commonly seen in poorly differentiated HCCs, showing no halo and irregular or unclear margins^[19]. In addition, a type 2c ultrasound image is frequently seen in HCCs that are positive for AFP-L3 and type 2c HCCs thus have higher malignant potential than type 1 HCCs^[19]. When the recurrence-free curve following RFA was stratified for types 2b, 1 and 2c, type 2c was seen to include the most cases of early recurrence. This difference can be thought to reflect the malignant potential of HCC. Conversely, we found no difference in survival rates between

Table 2 Univariate analysis of factors contributing to recurrence

Variables	HR	95%CI	P value
Age (yr)	1.007	0.972-1.043	0.717
Gender			
Female	1		
Male	1.036	0.577-1.859	0.906
HCV			
Negative	1		
Positive	1.176	0.527-2.625	0.693
Number of tumors	1.557	1.009-2.404	0.045
Size of tumor (mm)	1.035	0.980-1.092	0.214
Child-Pugh classification			
A	1		
B	1.481	0.838-2.617	0.177
Tumor stage			
I	1		
II	1.214	0.657-2.244	0.535
III	5.055	2.123-12.034	0.000
Activity grade			
A0, 1	1		
A2, 3	1.346	0.745-2.430	0.325
Fibrosis stage			
F0-2	1		
F3, 4	1.323	0.689-2.540	0.401
AFP (ng/mL)	1.000	1.000-1.001	0.318
AFP-L3 (%)	1.017	1.004-1.030	0.023
DCP (mAU/mL)	1.000	1.000-1.001	0.332
B-mode classification			
Type 2b	1		
Type 1	1.531	0.767-3.053	0.227
Type 2c	3.179	1.623-6.227	0.001

HR: Hazard ratio; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive alpha-fetoprotein; DCP: Des-gamma-carboxy prothrombin.

Table 3 Multivariate analysis of factors contributing to recurrence

Variables	HR	95%CI	P value
n	1.411	0.719-2.770	0.317
Tumor stage			
I	1		
II	0.645	0.283-1.467	0.296
III	2.540	0.784-8.224	0.120
AFP-L3			
Negative	1		
Positive	1.531	0.642-3.649	0.337
B-mode classification			
Type 2b	1		
Type 1	1.850	0.878-3.899	0.106
Type 2c	2.438	1.107-5.373	0.027

HR: Hazard ratio; AFP-L3: Lens culinaris agglutinin-reactive alpha-fetoprotein.

types 1 and 2c. HCC does not just show a high recurrence rate; it is a cancer that also undergoes repeated recurrence, as a result of which the level of compliance with the follow-up schedule and administration of treatment for recurrent lesions also greatly influence the outcome. The patient database used in the present study was prospective, in accordance with the predetermined

Table 4 Univariate analysis of factors contributing to survival

Variables	HR	95%CI	P value
Age (yr)	0.979	0.929-1.032	0.440
Gender			
Female	1		
Male	1.161	0.435-3.096	0.766
HCV			
Negative	1		
Positive	0.947	0.218-4.124	0.943
Number of tumors	1.700	0.840-3.440	0.140
Size of tumor (mm)	1.030	0.945-1.123	0.504
Child-Pugh classification			
A	1		
B	1.789	0.710-4.512	0.218
Tumor stage			
I	1		
II	1.588	0.551-4.579	0.392
III	3.847	1.081-13.690	0.037
Activity grade			
A0, 1	1		
A2, 3	1.978	0.698-5.606	0.200
Fibrosis stage			
F0-2	1		
F3, 4	1.292	0.425-3.930	0.652
AFP (ng/mL)	1.001	1.000-1.002	0.087
AFP-L3 (%)	1.012	0.995-1.031	0.212
DCP (mAU/mL)	1.000	0.999-1.001	0.919
B-mode classification			
Type 2b	1		
Type 1	6.911	1.897-25.176	0.003
Type 2c	4.466	1.066-18.709	0.041

HR: Hazard ratio; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive alpha-fetoprotein; DCP: Des-gamma-carboxy prothrombin.

Table 5 Multivariate analysis of factors contributing to survival

Variables	HR	95%CI	P value
Tumor stage			
I	1		
II	1.189	0.406-3.481	0.752
III	3.763	0.896-15.796	0.070
B-mode classification			
Type 2b	1		
Type 1	7.146	1.924-26.538	0.003
Type 2c	3.055	0.668-13.970	0.150

HR: Hazard ratio.

follow-up schedule. For that reason we think that compliance with the follow-up schedule exerted little effect on outcomes in this study. However, the possibility that treatment at the time of recurrence influenced the results cannot be ignored. We actively performed RFA for our patients, not only in cases where they satisfied the indications for RFA at the time of recurrence, but even when criteria of tumor size and number were not met, as long as the imaging findings were evaluated as suggesting that the lesions could be controlled. Radical re-treatment rates, including iterative RFA or resection for

type 1, type 2b and type 2c, were 93%, 95% and 80%, respectively. No significant differences were seen among radical re-treatment rates according to ultrasound classification. Our analysis of prognostic factors in this study did not include the treatment method at the time of recurrence. However, early detection of recurrence due to the prudent follow-up schedule and the effectiveness of our active treatment of recurrent lesions may have been reasons for the lack of significant differences in survival rate between types 1 and 2c.

Studies to date have identified various risk factors for recurrence following RFA for HCC, including tumor diameter^[22-27], tumor number^[28-30], tumor stage^[24], histological poor differentiation^[24], insufficient safety margin^[25,29,31], a tumor location^[25,27] that is problematic for RFA, such as adjacent to a large blood vessel or the liver surface, hepatitis C virus^[23] and/or hepatitis B virus infection^[23], AFP level^[22,25,28], liver fibrosis and platelet count^[23,30]. Santambrogio *et al.*^[32] recently reported that intraoperative ultrasound score can predict recurrent HCC after radical treatment. However, no previous reports have identified B-mode ultrasonogram for small HCC using external ultrasound as a risk factor for recurrence. The present study identified that risk factors for recurrence included, not only the previously reported tumor number, tumor stage and tumor markers, but also ultrasound image type. Moreover, multivariate analysis identified ultrasound image type 2c as the only significant independent risk factor. Ultrasound image type thus seems more closely associated with recurrence of HCC after RFA than previously reported risk factors.

On the other hand, the prognostic factors for RFA that have been reported to date are similar to the risk factors for recurrence; in addition to factors such as tumor diameter, tumor number, tumor stage, tumor differentiation grade and tumor markers, patient age and hepatic function (Child's classification) have also been cited^[33-37]. The present study found that tumor stage and B-mode ultrasound image type all represented significant prognostic factors and multivariate analysis identified ultrasound image type as the only significant independent risk factor. Accordingly, B-mode ultrasound image type appears more closely associated with the outcome of RFA than the previously reported risk factors for both recurrence and prognosis. When deciding therapeutic strategies for small HCC in the future, the greatest attention and importance should be placed on the B-mode ultrasound image type.

Ultrasound achieves superior spatial resolution compared with CT and MRI and is the most capable modality for depicting the morphological details of tumors. For that reason, ultrasound is considered to closely reflect the gross morphology of tumors. The gross morphology of HCC is a prognostic factor. With regard to the nodular type, the contiguous multi-nodular type and the single nodular type with extra-nodular growth are reportedly less histologically differentiated than the single nodular type and, because they show higher inci-

dences of vascular invasion and intrahepatic metastasis, recurrence following resection is an early indicator of poor prognosis^[38-40]. We think that the reason ultrasound image type is strongly associated with recurrence and outcomes following RFA is that the B-mode ultrasound classification we devised closely reflects the macroscopic type of HCC and enables identification of small HCC with poorer differentiation and higher malignant potential.

Some limitations of the present study were the design as a small-scale retrospective study, with a large degree of bias in the distribution of B-mode ultrasound image types. This prevented us from analyzing post-RFA recurrence and prognosis in relation to type 2a small HCC. We were also unable to investigate the effects of therapy on hepatitis, which presumably influences the recurrence and outcomes of small HCC, or the effects of treatments administered at the time of recurrence. However, even with those limitations, we were able to generate very interesting results indicating that the B-mode ultrasound image type is strongly associated with outcomes following RFA.

In conclusion, this study demonstrated B-mode ultrasound image classification type as a factor that strongly influences outcomes following RFA of small HCC. This new knowledge is likely to influence the therapeutic strategies of physicians treating patients with small HCC. That is, even if a patient satisfies the indications for RFA, the malignant potential of lesions should be evaluated on the basis of B-mode ultrasound image classification and tumor marker levels. Since type 1 and type 2c small HCC have high malignant potential, potentially more effective therapeutic strategies that include other treatment methods, such as resection or concurrent transcatheter arterial chemoembolization *etc.*, should be carefully devised rather than simply selecting RFA by default.

COMMENTS

Background

Percutaneous radiofrequency ablation (RFA) is a minor invasive and radical treatment for small hepatocellular carcinomas (HCCs). However, rapid aggressive recurrence with vascular invasion, intrahepatic dissemination, seeding or metastasis has been reported after RFA. The risk of seeding is high in patients with poorly differentiated HCC. Furthermore, the prognosis following RFA for poorly differentiated HCC is reportedly unfavorable. Clinical diagnosis of poorly differentiated HCC with high-grade malignancy is therefore very important when selecting treatment for small HCC.

Research frontiers

Small HCCs show various images on B-mode ultrasound. However, the correlation between B-mode ultrasound image and prognosis has not been elucidated. In the present study, the authors investigated the association between B-mode ultrasound image of small hypervascular HCC and outcome after RFA. The authors have previously reported that classification on B-mode ultrasonography of small hypervascular HCC correlated with histological differentiation.

Innovations and breakthroughs

This is the first study to report that B-mode ultrasound image of small hypervascular HCC is a predictive factor for outcome after RFA. Nodules with a halo and halo-free hypoechoic nodules with irregular or unclear margins have higher malignant potential and treatment for such lesions should be selected with care.

Applications

B-mode ultrasound image of small HCC is likely to influence the therapeutic strategies of physicians treating patients with small HCC.

Terminology

The halo sign is a hypoechoic band around the tumor, corresponding to a thin fibrous capsule around the HCC.

Peer review

The authors report a series of 97 patients affected by HCC undergoing RFA. They demonstrated that the ultrasonographic pattern of HCC predicts the risk of recurrence after RFA. It is an interesting and innovative issue.

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