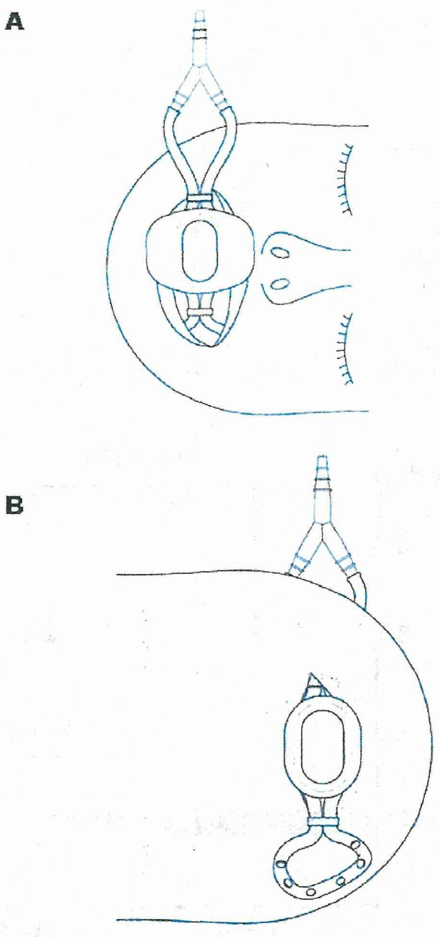

Figure 2 Schema for using the continuous suction mouthpiece (CSM). (A) View from outside of the body while using the CSM. Solid lines show the extra-oral part and broken lines show the intra-oral part. (B) View from inside of the body while using the CSM. Solid lines show the visible part and broken lines show the invisible part.

Procedures for PEG and exchange of a gastrostomy button or tube

Percutaneous endoscopic gastrostomy was carried out using a percutaneous endoscopic gastrostomy kit with a Funada-style fixture (Create Medic Co., Yokohama, Japan), whereas for the exchange of a gastrostomy button or tube, the new catheter (Kangaroo Button™ II; Nippon Sherwood Co., Tokyo, Japan) was placed after pulling the old button or tube out of the gastrocutaneous fistula. At each procedure, a conventional gastrointestinal videoscope (GIF-XP260N; Olympus) was orally inserted into the stomach to observe the upper gastrointestinal tract and to identify the site of insertion of the tube by transillumination and palpation of the abdominal wall. The endoscope was left in the stomach throughout the procedure. The procedures for all patients were carried out by one endoscopist and one assistant doctor.

Premedication with anticholinergic agents or glucagon was not used. Lidocaine 8% was sprayed into the posterior pharynx before insertion of the endoscope to reduce the gag reflex in all patients. Then, midazolam (1–5 mg) was given i.v. for sedation. During insertion of the endoscope, the patient was placed on his or her left side and, after the scope reached the inside of the stomach, the patient was shifted to the supine position, with only the patient's face facing to the left. Adequate monitoring of vital signs and oxygen saturation was carried out throughout the procedure.

Outcome assessment and evaluation

Primary outcome was occurrence of aspiration pneumonia. Secondary outcomes were extent of salivary flow, frequency of saliva suction, and the number of choking episodes during the procedure. Adverse events during and after the procedure were also examined. In addition, the oral cavity was meticulously examined after the procedure to determine whether blood blisters or any suction tube fragments were present in the oral cavity.

The duration of procedures using the CSM included the time required for biting down on the mouthpiece with the intra-oral loop placed inside the left cheek. The level of sedation was defined as follows: non, no use of sedatives; mild, conscious sedation; moderate, between conscious sedation and deep sedation; and deep, deep sedation. The extent of salivary flow was defined as follows: grade 1, no flow of saliva out of the mouth; grade 2, flow extending to the cheek; grade 3, flow extending to the ear; and grade 4, flow extending to the hair or clothing. When a rumbling sound was heard in the oropharyngeal region, the assistant suctioned the saliva during the procedure using the suction catheter (NIPRO SUCTION CATHETER® 14-Fr; NIPRO). Choking episodes were counted each time they occurred during the procedure, whereas consecutive coughs or chokes were counted as one choking episode.

Statistical analysis

Data were expressed as medians with ranges. Data were analyzed using the unpaired Mann–Whitney *U*-test and Fisher's exact test. The level of statistical significance was $P < 0.05$. All analyses were carried out using the SPSS 11.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

A TOTAL OF 72 subjects (22 men and 50 women, median age 80.5 years [range 49–98]) were recruited during the study period, and all patients were considered

Table 1 Characteristics of patients assigned to the CSM group or to the conventional (MB-142) mouthpiece group

	CSM	MB-142	*P*-value
Sex, male/female	14/22	8/28	0.125
Age, years median (range)	80 (49–92)	81 (58–98)	0.310
PEG procedure, placement/exchanging	4:32	4:32	1.000
Duration of procedure, minutes median (range)	8.5 (5–20)	8 (4–33)	0.258
Sedation, non/mild/moderate/deep	1/4/6/25	1/2/14/19	0.166
Underlying disease, brain/neurological/dementia/temporomandibular joint disorder/disuse syndrome/psychiatric disorder	23/2/6/1/4/0	24/1/6/0/4/1	0.798

CSM, continuous suction mouthpiece; MB-142, MB-142 mouthpiece (Olympus, Tokyo, Japan); PEG, percutaneous endoscopic gastrostomy.

eligible. Of the 72 patients enrolled, 66 (92%) could not express his or her will to participate in this study. In such cases, the next of the kin provided the consent. Of the patients, 36 were assigned to the CSM group, and the remaining 36 were allocated to the conventional mouthpiece group. The patients' characteristics are summarized in Table 1. There were no significant differences between the two groups in sex, age, procedure type, duration of procedure, depth of sedation, and indication for the procedure.

Aspiration pneumonia was not observed in any of the participating patients. The grade of salivary flow was significantly lower in patients with the CSM than in patients with the conventional mouthpiece ($P < 0.001$) (Fig. 3). Significantly fewer suctions and choking episodes were observed in patients with the CSM than in patients with the conventional mouthpiece ($P = 0.013$, and $P = 0.015$, respectively) (Figs 4,5). Complete obstruction of the holes, blood blisters or fragments of the PVC suction tubes were not observed in patients with the CSM. No other significant adverse events were observed in any of the patients.

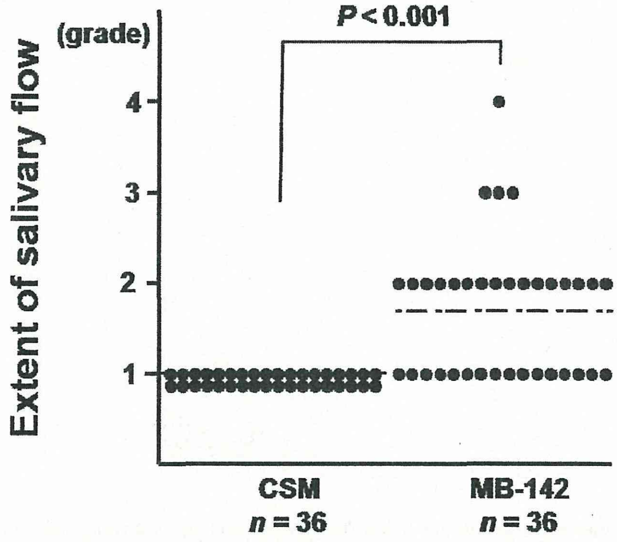

Figure 3 Extent of salivary flow. Grade of salivary flow is significantly lower in patients with the continuous suction mouthpiece (CSM) than in patients with the conventional mouthpiece (MB-142; Olympus, Tokyo, Japan) ($P < 0.001$). •, each value for each case; ——, mean value for CSM; -·-·-, mean value for MB-142.

DISCUSSION

ALTHOUGH ENDOSCOPY-RELATED COMPLICATIONS associated with salivary flow can be quite troublesome, little attention has been paid to these complications. To the best of our knowledge, this is the first attempt to control salivary flow by continuous suctioning during endoscopic procedures. The present study showed that, during PEG procedures, salivary flow was less extended in patients with the CSM than in patients with the conventional mouthpiece. Moreover, significantly fewer suctioning and choking episodes were observed in patients with the CSM.

The present results suggest that the CSM has many advantages during endoscopic procedures. First, the CSM may decrease complications of aspiration during endoscopic procedures, because use of the CSM reduced the frequencies of saliva suction and choking episodes. It has been reported that there is considerable risk of aspiration during the PEG procedure in elderly patients and in patients with brain infarction, neurological disease, or dementia, because these patients cannot gag or choke adequately.[2] Therefore, although no aspiration pneumonia was observed in patients in either group in the present study, perhaps due to the small number of patients, use of the CSM in PEG procedures is recommended. Second, a nurse's time and effort can be saved during endoscopic procedures, because the frequency of suctioning is reduced. Third, the CSM could prevent exposure of the patient's body, clothing or operating bed to saliva. This advantage might reduce patient discomfort, as well as the time and cost required for clean-up. Fourth, continuous

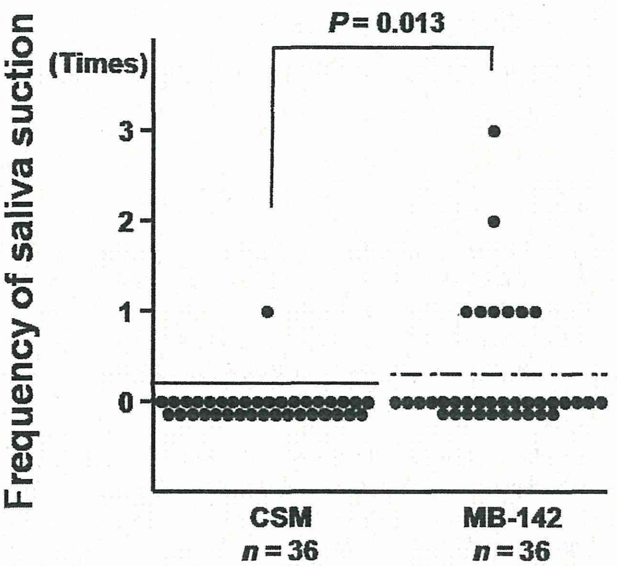

Figure 4 Frequency of saliva suction. Significantly fewer suctions were observed in patients with the continuous suction mouthpiece (CSM) than in patients with the conventional mouthpiece (MB-142; Olympus, Tokyo, Japan) ($P = 0.013$). •, each value for each case; —, mean value for CSM; -·-·-, mean value for MB-142.

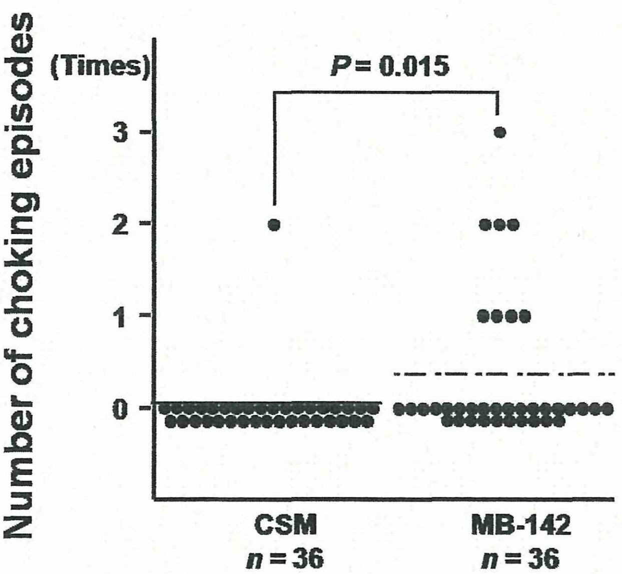

Figure 5 Number of choking episodes. Significantly fewer choking episodes were observed in patients with the continuous suction mouthpiece (CSM) than in patients with the conventional mouthpiece (MB-142; Olympus, Tokyo, Japan) ($P = 0.015$). •, each value for each case; —, mean value for CSM; -·-·-, mean value for MB-142.

suction creates airflow in the oral cavity and may reduce discomfort in the oral cavity caused by the endoscopic procedure. Finally, ease in preparing the equipment with no particular materials and low cost would be advantageous.

To reduce salivary secretion during endoscopic procedures, a strategy using anticholinergic agents could be an alternative. However, there are drawbacks in using these agents. First, because the effect of anticholinergics is not maintained during prolonged examinations or procedures, the effect is limited during long-term endoscopic procedures. Next, there are many patients in whom anticholinergics cannot be used due to heart disease, glaucoma, or prostate enlargement. In particular, patients who undergo PEG are rarely allowed to receive anticholinergics, because they are likely to be elderly subjects with serious underlying diseases. In contrast, the CSM can be used for all patients because it is associated with no serious adverse effects. In addition, it works throughout the endoscopic procedure. Thus, the improved mouthpiece would be superior to anticholinergics in terms of controlling salivary secretion during endoscopic procedures.

During the course of constructing the mouthpiece, the detailed specifications, including loop size and the number, size, and locations of the holes were determined through a trial and error process. The prototype device with a single hole caused blood blisters on the mucosal membrane inside the cheek by focused suction pressure. Therefore, devices with multiple holes and a unique loop shape were made so as to not adhere to the mucosal membrane. However, in terms of the number and location of the holes, suction pressure, and loop size, there may be room for further improvement.

In this context, development of equipment in which the suctioning function is integrated into the body of the mouthpiece could be expected, although an external suctioning part was used in the present study. Integration of the suctioning function in the body would completely prevent adherence of a tube to the oral mucosa. In addition, concerns regarding increased saliva production associated with tube placement can be eliminated.

The CSM may also be effective in endoscopic procedures other than PEG. Recently, many kinds of upper endoscopic procedures taking a long time have become common, such as endoscopic submucosal dissection, peroral double-balloon enteroscopy, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, endoscopic hemostasis, and endoscopic procedures for gastroesophageal varices. Because these procedures are also associated with an increased risk of aspiration,[3,4] all patients who undergo these procedures may be candidates for the CSM. The usefulness of this item in various procedures should be evaluated in the future.

The present study had several limitations. First, neither the endoscopist nor the assistant was blinded as to which mouthpiece was used. Because the shapes of the mouthpieces were different, blinding was not possible. Second, the frequency of aspiration pneumonia, the primary outcome of this study, could not be evaluated due to the small number of patients, because the reported rate of the aspiration pneumonia with conventional methods in PEG was only approximately 2.3%.[2] Finally, there are problems with the time and cost of the CSM. However, construction of one CSM costs no more than 1 US dollar, in addition to the cost of the MB-142 mouthpiece.

CONCLUSION

THE CSM REDUCED the extent of salivary flow and the frequencies of suction and choking episodes during PEG-related procedures. This type of simple and inexpensive device is expected to reduce complications such as aspiration not only in PEG but also in other upper endoscopic procedures.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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ORIGINAL ARTICLE

Ultrasonogram of hepatocellular carcinoma is associated with outcome after radiofrequency ablation

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Abstract

AIM: To investigate the association between B-mode ultrasound classification of small hepatocellular carcinoma (HCC) and outcome after radiofrequency ablation (RFA).

METHODS: Ninety-seven cases of HCC treated using RFA between April 2001 and March 2006 were reviewed. Ultrasound images were classified as follows: type 1, with halo (n = 29); and type 2, without halo (n = 68). Type 2 was further categorized into three subgroups: type 2a, homogenous hyperechoic (n = 9); type 2b, hypoechoic with smooth margins (n = 43); and type 2c (n = 16), hypoechoic with irregular or unclear margins. Patients with type 2a HCC were excluded from analysis due to the small number of cases.

RESULTS: Two year recurrence rates for type 2b, type 1 and type 2c were 26%, 42% and 69%, respectively, with significant differences between type 2b and type 2c (P < 0.01), and between type 1 and type 2c (P < 0.05). Five year survival rates were 89%, 43% and 65%, respectively. Survival was significantly longer for type 2b than for other types (type 1 *vs* type 2b, P < 0.01; type 2b *vs* type 2c, P < 0.05). On univariate analysis, factors contributing to recurrence were number of tumors, tumor stage, serum level of lens culinaris agglutinin-reactive alpha-fetoprotein and ultrasound classification (P < 0.05). Factors contributing to survival were tumor stage and ultrasound classification (P < 0.05). Multivariate analysis identified ultrasound classification as the only factor independently associated with both recurrence and survival (P < 0.05).

CONCLUSION: B-mode ultrasound classification of small HCC is a predictive factor for outcome after RFA.

Key words: B-mode ultrasound; Hepatocellular carcinoma; Radiofrequency ablation; Recurrence; Prognosis

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INTRODUCTION

Treatment strategies for hepatocellular carcinoma (HCC) are decided on the basis of tumor size and number, liver function and performance status[1,2]. Percutaneous local treatments that are less invasive than resection are performed for small HCCs that are unsuitable for resection, with the indications of ≤ 3 lesions, each with diameter ≤ 3 cm, in accordance with the Japanese guidelines[2] and the practice guidelines of the American Association for the Study of Liver Diseases[1].

Percutaneous radiofrequency ablation (RFA) is a well established local treatment for unresectable small HCC[3,4]. RFA is a curative treatment and achieves not only superior local control of the disease, but also better prognosis compared to percutaneous ethanol injection therapy (PEIT)[5,6]. Accordingly, RFA is now recommended over PEIT for the treatment of small HCC. Recently, RFA has also been adopted for patients with resectable early HCC, defined as single tumors > 2 cm in diameter or up to 3 nodules < 3 cm in diameter, with performance status 0 and Child-Pugh class A or B[7].

However, rapid aggressive recurrence with vascular invasion[8-10], intrahepatic dissemination[11,12], seeding or metastasis[13,14] has been reported after RFA. In particular, the risk of seeding is high in patients with poorly differentiated HCC[15]. Furthermore, the prognosis following RFA for poorly differentiated HCC is reportedly unfavorable[16,17]. A large proportion of patients with poorly differentiated HCC show microscopic vascular invasion and intrahepatic metastasis, even when the tumor is small[18]. As a result, curative treatment cannot be achieved using RFA alone and the procedure may thus cause dissemination or metastasis. Clinical diagnosis of poorly differentiated HCC with high-grade malignancy is therefore crucial when determining treatment strategies for small HCC.

Small HCCs show various images on B-mode ultrasound. However, the correlation between B-mode ultrasound image and prognosis has not been elucidated. We have previously reported that classification on B-mode ultrasonography of small hypervascular HCC correlated with histological differentiation and serum level of lens culinaris agglutinin-reactive alpha-feto protein (AFP-L3), an indicator of poor prognosis[19]. In particular, the presence of irregular or unclear margins was very important in screening for small, poorly differentiated HCC. The aim of this study was to determine whether B-mode ultrasound classification is associated with recurrence and survival after RFA.

MATERIALS AND METHODS

Patients

Our prospective database of 97 patients with initial hypervascular HCC (≤ 3 tumors, all ≤ 3 cm in diameter) who had undergone RFA between April 2001 and March 2006 was reviewed. Diagnosis of hypervascular HCC was based on the findings of tumor staining during the arterial phase of contrast-enhanced computed tomography (CT), dynamic magnetic resonance imaging (MRI) or contrast ultrasonography. If any of these diagnostic imaging techniques showed tumor stain in the arterial phase that was washed out in the equilibrium phase, imaging diagnosis was considered definitive. In all patients, tumor stage (tumor-node-metastasis classification as described by the Liver Cancer Study of Japan), etiology of hepatitis, Child-Pugh classification, levels of tumor markers (AFP, AFP-L3 and des-gamma-carboxy prothrombin), fibrosis stage and activity grade of the biopsied liver tissue using the new Inuyama classification[20] were evaluated before RFA. Eligibility criteria for RFA were as follows: (1) no vascular invasion on imaging diagnosis; (2) no severe ascites; (3) platelet count ≥ 5 × $10^4/mm^3$; (4) prothrombin time ≥ 50%; (5) total bilirubin < 3 mg/dL; (6) no distant metastases; and (7) in principle, ≤ 3 tumors, all ≤ 3 cm in diameter. No exclusion criteria were set in terms of tumor location (i.e., near main vessels, adjacent organs). Furthermore, all patients with recurrent HCC underwent iterative RFA even when the above criteria for tumor size and number were not met, as long as complete ablation was considered achievable. Written informed consent was obtained from each enrolled patient and the protocol was approved by our institutional review board.

RFA technique

Percutaneous RFA using the Cool-tip RF system (Valleylab, Boulder, CO, United States) was performed under ultrasound guidance in all patients. Artificial pleural effusion or artificial ascites was produced using saline when necessary[21]. The impedance control mode was used with a 17-gauge, cooled-tip electrode with a 2 or 3 cm exposed tip. Ablation was started at 40 W for the 2 cm exposed tip and 60 W for the 3 cm exposed tip. Power was increased at a rate of 10 W/min. When a rapid increase in impedance occurred, output was automatically stopped and ablation was restarted after a short time at an output 10 W lower. Duration of a single ablation was 6 min for the 2 cm electrode and 12 min for the 3 cm electrode. After RF exposure, temperature of the needle tip was measured. When the temperature was below 65 ℃, additional ablation was performed. The electrode track was not treated by thermo-coagulation in any patients, to prevent seeding or hemorrhage.

Assessment of response and follow-up

Treatment response was assessed by contrast-enhanced CT or MRI at 1-3 d after the final session. Complete response was defined as no enhancement in the entire lesion with a safety margin on imaging. Additional ablation was performed until complete ablation was confirmed in each nodule. All patients were followed up on an outpatient basis every 3-4 mo using contrast-enhanced CT or MRI and measurement of tumor marker levels.

B-mode ultrasound imaging

We used either a SONOLINE Elegra™ Ultrasound Platform (Siemens Medical Systems, Erlangen, Germany)

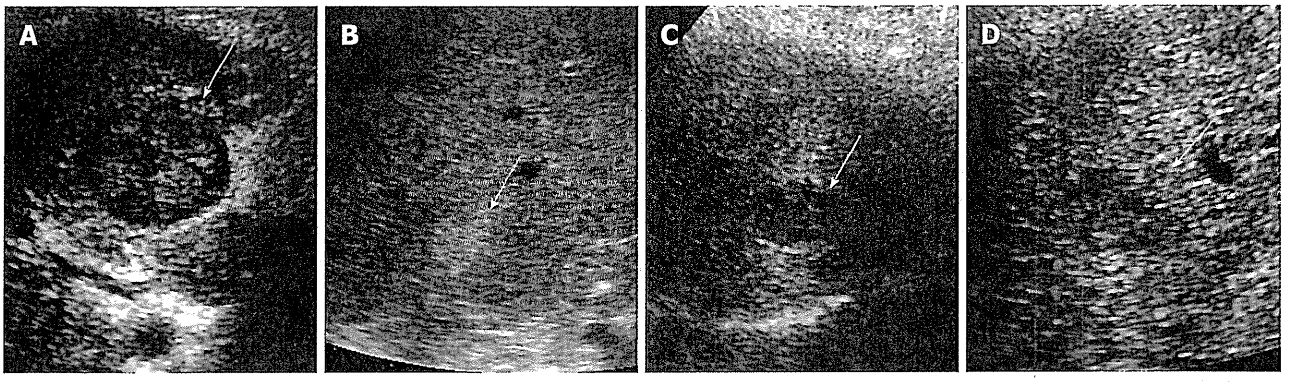

Figure 1 Classification of B-mode ultrasonographic images of small hepatocellular carcinoma. A-D: Hepatocellular carcinoma nodules < 3 cm in diameter were classified into two groups using B-mode ultrasonography: Type 1 with halo (A) and type 2 without halo. Type 2 was then further categorized into three subgroups: Type 2a, homogenous hyperechoic (B); Type 2b, hypoechoic with smooth margins (C); Type 2c, hypoechoic with irregular or unclear margins (D). Hepatocellular carcinoma nodules are indicated by arrows.

Table 1 Comparison of patient characteristics according to B-mode ultrasound-based classification

	Type 1 (n = 29)	Type 2b (n = 43)	Type 2c (n = 16)	P value
Age (yr)	66.4 ± 9.5	66.9 ± 8.7	69.3 ± 6.8	0.554
Gender (male/female)	23/6	25/18	8/8	0.085
HCV (positive/negative)	28/1	36/7	14/2	0.241
Number of tumors	1.2 ± 0.4	1.2 ± 0.5	1.6 ± 0.7	0.046
Size of tumor (mm)	22.5 ± 3.8	19.0 ± 5.2	23.1 ± 5.6	0.003
Child-Pugh classification (A/B)	16/13	31/12	9/7	0.272
Tumor stage (Ⅰ/Ⅱ/Ⅲ)	10/15/4	28/13/2	4/7/5	0.006
Activity grade (A0, 1/2, 3)	7/22	14/29	10/6	0.032
Fibrosis stage (F0-2/3, 4)	8/21	10/33	7/9	0.298
AFP (ng/mL)	124 ± 246	118 ± 274	207 ± 406	0.564
AFP-L3 (%)	7.3 ± 17.0	5.8 ± 16.5	17.5 ± 25.5	0.098
DCP (mAU/mL)	223 ± 489	210 ± 482	299 ± 486	0.817

Data are presented as mean ± SD or n/N. HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive alpha-fetoprotein; DCP: Des-gamma-carboxy prothrombin.

with a 3.5C40 convex probe or a SSA-770A ultrasound system (Toshiba Medical Systems, Tochigi, Japan) with a PVT-674BT ultrasound probe. Tissue harmonic imaging was performed in B-mode.

B-mode ultrasound classification

The B-mode ultrasound classification of small HCC we reported previously was used[19]. Nodules with a halo were regarded as type 1 and halo-free nodules were regarded as type 2. In addition, type 2 nodules were further classified based on the internal echo level and marginal features; uniform hyperechoic nodules were evaluated as type 2a, hypoechoic nodules with regular margins as type 2b and hypoechoic nodules with irregular or unclear margins as type 2c. B-mode ultrasound images were obtained within 1 mo before RFA. All recorded ultrasound images were analyzed by two skilled hepatologists (10 and 19 years of experience in abdominal ultrasonography) who were blinded to patient names. When a discrepancy existed in interpretation between the two hepatologists, a consensus was reached through discussion. If HCCs comprised two or three nodules, the largest nodule was selected and classified using our B-mode classification. B-mode ultrasound classified 29 cases as type 1, 9 as type 2a, 43 as type 2b, and 16 as type 2c. Given the small number of patients with type 2a HCC, these cases were excluded from analysis (Figure 1).

Statistical analysis

One factor analysis of variance and the Scheffe test were used to analyze continuous variables. Fisher's exact test or the χ^2 test were used to analyze categorical variables. Cumulative recurrence-free survival rates and cumulative survival rates according to B-mode ultrasound classification were constructed using Kaplan-Meier methods and compared using the log-rank test. Uni- and multivariate analyses using a Cox proportional hazard regression model were performed for factors contributing to tumor recurrence and survival. Results were expressed as hazard ratio with 95%CI. $P < 0.05$ was considered statistically significant for all analyses using SPSS Statistics Version 19 software (IBM, Tokyo, Japan).

RESULTS

The median follow-up interval was 1018 d. Two year recurrence rates for type 2b, type 1 and type 2c were 26%, 42% and 69%, respectively. Significant differences were seen between type 2b and type 2c ($P < 0.01$), and between type 1 and type 2c ($P < 0.05$). Five year survival rates were 89%, 43% and 65%, respectively. Survival was significantly longer for type 2b than for other groups (type 1 *vs* type 2b, $P < 0.01$; type 2b *vs* type 2c, $P < 0.05$).

Patient background variables at baseline according to B-mode ultrasound classification are compared in Table 1. Significant differences were evident among groups in terms of number of tumors, tumor size, tumor stage and activity grade of hepatitis. Mean tumor size was smaller in type 2b than in other types. Mean number of tumors was smaller in type 2b than in type 2c. High tumor stage was more frequent in type 2c than in other types. Severe activity grade of hepatitis was likewise more frequent

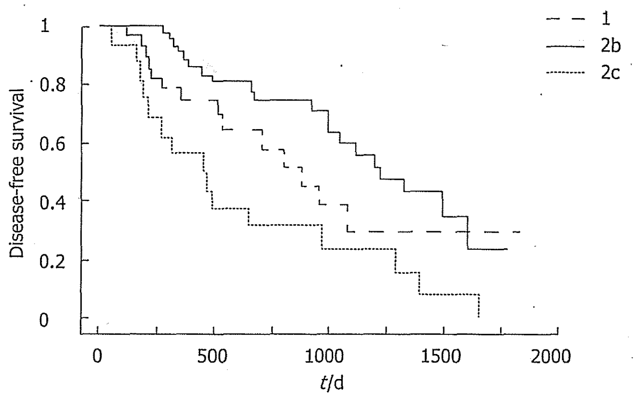

Figure 2 Recurrence-free survival curves according to B-mode ultrasound classification. Recurrence-free survival was significantly shorter for type 2c hepatocellular carcinoma than for other types. $P = 0.0454$ type 1 *vs* type 2c; $P = 0.0005$ type 2b *vs* type 2c.

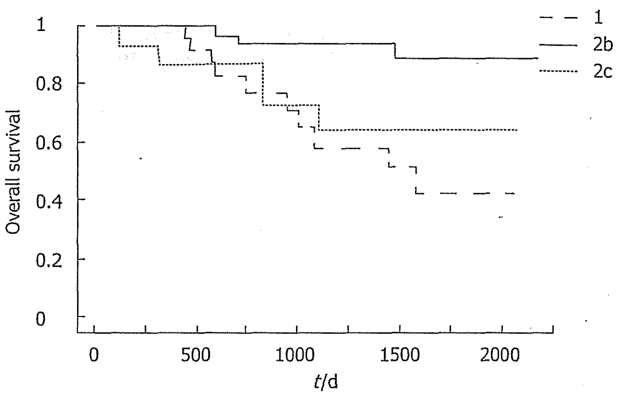

Figure 3 Survival curves according to B-mode ultrasound classification. Survival was significantly longer for type 2b than for other types. $P = 0.0006$ type 1 *vs* type 2b; $P = 0.0165$ type 2b *vs* type 2c; $P = 0.4473$ type 1 *vs* type 2c.

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 classification 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.

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.

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 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[28] 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 incidences 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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