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Microvascular invasion of single small hepatocellular carcinoma ≤3 cm: Predictors and optimal treatments

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Abstract

Background: Small hepatocellular carcinomas (HCC ≤3 cm) are generally considered to have low malignant potential; however, some of them display pathological microvascular invasion (MVI).

Methods: Between 1991 and 2013, 414 patients with a single HCC ≤3 cm underwent curative hepatic resection (HR). Predictors for MVI were identified. Using another cohort (149 patients during 2000-2014), our predictors for MVI in HCC ≤3 cm were validated. In 428 patients with a single HCC ≤3 cm who had predictors for MVI, survival was compared among anatomical HR (n = 149), partial HR (n = 227), and radiofrequency ablation (RFA) (n = 52).

Results: The positive rate of MVI reached 40.6% (168/414 patients). Independent predictors for MVI were as follows: tumor diameter ≥2 cm (odds ratio 1.84, $P = .0052$), alpha-fetoprotein (AFP) ≥200 ng/mL (odds ratio 1.82, $P = .0466$), and des-gamma-carboxy prothrombin (DCP) ≥40 mAU/mL (odds ratio 1.79, $P = .0126$). Matching at least one predictor among these three could predict MVI in HCC ≤3 cm well (sensitivity 82.8%, positive predictive value [PPV] 48.7%). This criterion could also predict MVI in HCC ≤3 cm well in another cohort (sensitivity 82.8%, PPV 30.3%). In patients with single HCC ≤3 cm matching our criterion for predicting MVI, anatomical HR led to significantly better survival in both disease-free (hazard ratio 0.689, $P = .0231$) and overall (hazard ratio 0.589, $P = .0316$) survivals.

Conclusion: Matching at least one factor among three (tumor diameter ≥2 cm, AFP ≥200 ng/mL, or DCP ≥40 mAU/mL) can predict MVI in HCC ≤3 cm. In such patients, anatomical HR would be recommended to improve survival.

KEYWORDS
alpha-fetoprotein, anatomical hepatic resection, des-gamma-carboxy prothrombin, hepatocellular carcinoma, microvascular invasion

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. Its incidence has doubled in the past 20 years, making it the second leading cause of cancer death.[1] It is estimated that by 2020 the number of HCC cases in Europe and the USA will reach 78 000 and 27 000, respectively.[2] Management of HCC has significantly improved over the last decade as a result of better knowledge of HCC behavior, improvements in staging systems and treatment algorithms, and emerging therapeutic options.[3] One of the most reliable and widely adopted methods for staging HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which stratifies patients according to the characteristics of the tumor, underlying liver disease and performance status.[4]

HCC diameter value "3 cm or less (≤3 cm)" has a major impact for treatment choice in both the BCLC system and the 3rd Japan Society of Hepatology (JSH)-HCC guidelines.[5] Percutaneous ablation therapy such as radiofrequency ablation (RFA) and hepatic resection (HR) are equally recommended for HCC ≤3 cm. The reason why HCC ≤3 cm would be proposed for RFA was not clear, although two reasons can be considered. One is that HCC ≤3 cm is thought to have low malignant potential, and the other is the limitation of the safety margin for ablation.

Many reports have noted the heterogeneity of small HCC ≤3 cm, and some of these tumors display microvascular invasion (MVI) ranging from 18.1% to 37.0%, which indicated locally advanced HCC.[6–8] We previously reported that HR with a wide margin (>0.5 cm) led to better survival in patients with solitary HCC ≤2 cm that displayed MVI. To realize personalized treatment for small HCC, the establishment of reliable predictions for MVI in HCC ≤3 cm is very important.

Here, we present a retrospective analysis of predictors of MVI in single HCC ≤3 cm, and of survival in patients with single HCC ≤3 cm matching predictors for MVI who underwent anatomical HR, partial HR, or RFA.

2 | METHODS

2.1 | Patients

Four hundred and fourteen patients with initial solitary HCC ≤3 cm underwent HR at the Department of Surgery and Science, Kyushu University Hospital, between 1991 and 2013. Maximum tumor diameter of ≤3 cm was confirmed by cutting the surface after HR. In all cases, sufficient non-cancerous lesions were collected for analysis of MVI. Medical records of these 414 patients were followed up through March 2015. Median follow-up period in this series was 71 months. Predictors for MVI in HCC ≤3 cm were identified in this cohort.

One hundred and forty-nine patients with initial solitary HCC ≤3 cm underwent HR at the Department of Gastroenterological Surgery, Kumamoto University Hospital, between 2000 and 2014. The medical records of these 149 patients were also followed up through March 2017. Median follow-up period in this series was 62 months. Predictors for MVI in HCC ≤3 cm, identified in the former cohort, were validated in this next cohort.

2.2 | Surgical techniques and follow-up methods

Thorough intraoperative ultrasonography was carried out to determine the extent of disease and the line of parenchymal transection. A decision was then made regarding the type of liver resection to carry out, such as anatomical or partial HR, while considering the patient's liver function.[9] Anatomical resection included hemi-hepatectomy, segmentectomy, and subsegmentectomy or more, based on Couinaud's classification.[10] In almost all HR, intermittent Pringle's maneuvers consisting of clamping the portal triad for 15 minutes and then releasing the clamp for 5-minute intervals were applied. The CUSA system (Valley Lab, Boulder, CO, USA) was mainly used to transect the liver parenchyma. Our standard skin incision for HCC ≤3 cm was an upper midline and/or right subcostal incision. Forty-one patients (9.9%) underwent laparoscopic hepatic resection.[11] Any death that occurred in the hospital after treatment was recorded as a mortality. Complications were evaluated by Clavien's classification, and those with a score of Grade II or more were defined as positive.[12]

Gross classification of HCC ≤3 cm was made according to the general rules for clinical and pathological study of primary liver cancer established by the Liver Cancer Study Group of Japan,[13] as non-invasive gross type (vaguely nodular type, n = 7; and single nodular type, n = 315) and invasive gross type (single nodular type with extranodular growth, n = 42; and confluent multinodular type, n = 50). Pathological diagnoses were carried out by two or three certified experts in the individual institute according to the above general rules for pathological diagnosis.[13]

After discharge, all patients were examined for recurrence by ultrasonography, using tumor markers such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) every month, and by computed tomography (CT) or magnetic resonance imaging (MRI) every 3 months. When recurrence was suspected, we treated the recurrent HCC by repeat HR,[14] RFA, or lipiodolization.[15]

2.3 | Statistics

Continuous variables are expressed as the means ± standard deviations (SD) and were compared using Student's *t*-test. Categorical variables were compared using the χ^2-test. Survival curves were generated by the Kaplan-Meier method and compared using the log-rank test. Variables at $P < .05$ on univariate analysis were subjected to stepwise logistic regression analysis to identify independent predictors for MVI in HCC ≤3 cm. To identify better prognostic factors after treatments in patients with single HCC ≤3 cm matching our criterion for predicting MVI, 11 clinical, surgical, and tumor-related variables were included in a Cox proportional hazard model in accordance with the findings of previous reports:[5,6,9,14] age (older vs

younger than 65); preoperative total bilirubin (T-bil) level (> vs ≤1 mg/dL); preoperative albumin level (> vs ≤3.5 mg/dL); indocyanine green retention rate at 15 minutes (ICGR15) (> vs ≤20%); liver damage[13] (A vs B and C); preoperative AFP level (≥ vs <200 ng/mL); preoperative DCP level (≥ vs <40 mAU/mL); tumor diameter (≥ vs <2 cm); anatomical resection (yes vs no); surgical blood loss (> vs ≤1000 mL), and intraoperative blood cell transfusion (yes vs no). All analyses were carried out with JMP Pro 12.2.0 (SAS Institute, Cary, NC, USA). *P*-values < .05 were considered significant.

3 | RESULTS

3.1 | Details of MVI in HCC ≤3 cm

Microvascular invasion was found in 168 patients (40.6%) among 414 patients with HCC ≤3 cm. Most of these patients (160/168 patients; 95.2%) had portal venous infiltration (vp), and two patients (0.5%) had hepatic venous infiltration (vv). Six patients (1.4%) had intrahepatic metastasis (im) without vp/vv, and one patient (0.2%) had bile duct infiltration (b).

3.2 | Clinical characteristics of HCC ≤3 cm with and without MVI

Comparisons of background characteristics between the MVI (−) group (n = 246) and the MVI (+) group (n = 168) are summarized in Table 1. No variables showed significant differences between the two groups in background characteristics such as age, BMI, and liver function tests.

Comparisons of surgical factors between the two groups are summarized in Table 2. Resected volume was significantly larger in the MVI (+) group (99 vs 73 g, *P* = .0071), and the rate of anatomical HR was higher in the MVI (+) group (36 vs 28%, *P* = .0993). Mean duration of hospital stay was significantly longer in the MVI (+) group (18 vs 16 days, *P* = .0414).

Comparisons of tumor-related factors between the two groups are summarized in Table 3. Variables of the MVI (+) group more often showed features of advanced tumor stage, such as tumor diameter (2.2 vs 2.0 cm; *P* < .0001), invasive gross type (46 vs 6%; *P* < .0001), poorly differentiated (33 vs 13%; *P* < .0001), fc-inf (+) (63 vs 31%; *P* < .0001), and higher DCP level (124 vs 48 mAU/mL; *P* = .0031).

3.3 | Independent risk factors or predictors for MVI in HCC ≤3 cm

Results of multivariate analysis with stepwise logistic regression analysis are summarized in Table 4. Independent risk factors for MVI were invasive gross type (odds ratio 13.68), fc-inf (+) (odds ratio 4.11), and tumor diameter ≥2 cm (odds ratio 1.96). As for predictive factors for MVI which can be evaluated preoperatively, multivariate analysis (Table 5) showed that all three factors were independently significant predictors for MVI: tumor diameter ≥2 cm (odds ratio 1.84), AFP ≥200 ng/mL (odds ratio 1.82), and DCP ≥40 ng/mL (odds ratio 1.79).

3.4 | Criterion for predicting MVI in HCC ≤3 cm

Sensitivity and positive predictive value (PPV) of our predictors are summarized in Table 6. Matching at least one predictor among the three predictors could predict MVI well (sensitivity 82.8%, PPV 48.7%). Matching two predictors led to a higher PPV (55.6%);

TABLE 1 Comparisons of background characteristics between the MVI (−) group and the MVI (+) group

Variable	MVI (−) (n = 246)	MVI (+) (n = 168)	*P*-value
Age (y)	66 ± 9	66 ± 10	.6567
Male/Female	168/78	113/55	.8255
BMI (kg/m^2)	23.1 ± 3.0	23.2 ± 3.0	.7779
DM (+) (%)	76 (31%)	40 (24%)	.1071
HBs-Ag (+) (%)	36 (14.6%)	30 (17.9%)	.4108
HCV-Ab (+) (%)	182 (74.0%)	122 (72.6%)	.7578
Plt (× 10^4/μL)	19.3 ± 57.7	15.7 ± 17.8	.4325
T-bil (mg/dL)	0.8 ± 0.4	0.8 ± 0.4	.7817
Alb (g/dL)	3.9 ± 0.4	3.9 ± 0.4	.6978
AST (IU/L)	53 ± 45	48 ± 27	.1456
ALT (IU/L)	51 ± 40	49 ± 34	.3881
PT (%)	86 ± 15	87 ± 14	.5402
ICG15R (%)	18.0 ± 9.7	18.9 ± 11.3	.3865
Child A (%)	230 (93%)	156 (93%)	.7999
Liver damage A (%)	167 (68%)	126 (75%)	.1364

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; HBs-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C antibody; ICGR-15, indocyanine green retention rate at 15 min; MVI, microvascular invasion; Plt, platelet count; PT, prothrombin time; T-bil, total bilirubin.

TABLE 2 Comparisons of surgical factors between the MVI (−) group and the MVI (+) group

Variable	MVI (−) (n = 246)	MVI (+) (n = 168)	*P*-value
Intraoperative factors			
Operation time (min)	227 ± 93	219 ± 89	.3539
Bleeding (g)	436 ± 449	469 ± 626	.5233
Resected volume (g)	73 ± 75	99 ± 117	.0071
Transfusion (+) (%)	24 (9.8%)	15 (8.9%)	.7665
Anatomical resection (%)	69 (28%)	60 (36%)	.0993
Surgical margin (mm)	4.9 ± 5.7	5.7 ± 6.8	.2036
Postoperative factors			
Mortality (%)	1 (0.4%)	2 (1.2%)	.3606
Morbidity (%)	51 (21%)	45 (27%)	.1601
Hospital stay (days)	16 ± 9	18 ± 12	.0414

MVI, microvascular invasion.

TABLE 3 Comparisons of tumor-related factors between the MVI (−) group and the MVI (+) group

Variable	MVI (−) (n = 246)	MVI (+) (n = 168)	*P*-value
Tumor diameter (cm)	2.0 ± 0.6	2.2 ± 0.5	<.0001
Tumor diameter ≥2 cm (%)	129 (52%)	115 (68%)	.0011
Invasive gross type (%)	14 (6%)	78 (46%)	<.0001
Poorly differentiated (%)	32 (13%)	56 (33%)	<.0001
fc (+) (%)	113 (46%)	115 (68%)	<.0001
fc-inf (+) (%)	78 (32%)	106 (63%)	<.0001
AFP (ng/mL)	201 ± 1039	199 ± 515	.9756
AFP ≥200 ng/mL (%)	27 (11%)	30 (18%)	.0479
DCP (mAU/mL)	48 ± 86	124 ± 367	.0031
DCP ≥40 mAU/mL (%)	51 (21%)	60 (36%)	.0029
lc (+) (%)	135 (55%)	92 (55%)	.8894

AFP, alfa-fetoprotein; DCP, des-gamma-carboxy prothrombin; fc, fibrous capsule; fc-inf, fibrous capsule infiltration; lc, histological liver cirrhosis; MVI, microvascular invasion.

TABLE 4 Independent risk factors for MVI in HCC ≤3 cm

Variable	Odds ratio	95% CI	*P*-value
Invasive gross type	13.68	6.47-31.76	<.0001
fc-inf (+)	4.11	1.77-10.51	.0008
Tumor diameter ≥2 cm	1.96	1.16-3.33	.0113
Poorly differentiated	1.43	0.91-3.22	.1985
DCP ≥40 mAU/mL	1.39	0.80-2.42	.2424
fc (+)	1.65	0.69-4.32	.2674
AFP ≥200 ng/mL	1.08	0.50-2.36	.8533

AFP, alpha-fetoprotein; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; fc, fibrous capsule; fc-inf, fibrous capsule infiltration; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

TABLE 5 Independent predictors for MVI in HCC ≤3 cm

Variable	Odds ratio	95% CI	*P*-value
Tumor diameter ≥2 cm	1.84	1.20-2.85	.0052
AFP ≥200 ng/mL	1.82	1.01-3.32	.0466
DCP ≥40 mAU/mL	1.79	1.13-2.83	.0126

AFP, alpha-fetoprotein; CI, confidence interval; DCP, des-gamma- carboxy prothrombin; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

however, sensitivity decreased (36.2%). Matching all three predictors also led to a higher PPV (69.2%); however, sensitivity decreased drastically (5.8%). According to these results, our criterion for predicting MVI in HCC ≤3 cm was defined as follows: matching at least one predictor among tumor diameter ≥2 cm, AFP ≥200 ng/mL, and DCP ≥40 ng/mL.

3.5 | Validation of our criterion for predicting MVI in HCC ≤3 cm using another cohort

Our criterion for predicting MVI in HCC ≤3 cm was validated using another cohort consisting of 149 patients with an initial single HCC ≤3 cm. MVI was found in 30 patients (20.1%). Among those with HCC ≤3 cm with MVI, most patients (22/30; 73.3%) had vp, and five (16.7%) had vv. Three patients (10.0%) had im without vp/vv, and three patients (10%) had b.

TABLE 6 Diagnostic value of our predictors for MVI in HCC ≤3 cm

Variable	Sensitivity (%)	Positive predictive value (%)
Matching one predictor	82.8	48.7
Matching two predictors	36.2	55.6
Matching three predictors	5.8	69.2

HCC, hepatocellular carcinoma; MVI, microvascular invasion.

Sensitivity and PPV of our criterion for predicting MVI in this next cohort are summarized in Table 7. Matching at least one predictor among three predictors could also predict MVI well (sensitivity 82.8%, PPV 30.3%). Matching two predictors led to a higher PPV (38.9%); however, sensitivity decreased (72.4%). Matching all three predictors also led to a higher PPV (41.2%); however, sensitivity dropped markedly (24.1%). Thus, in a separate cohort, our criterion for predicting MVI in HCC ≤3 cm also worked well.

3.6 | Survival of patients matching the criterion for predicting MVI in HCC ≤3 cm

In 563 patients, comprising both cohorts with initial single HCC ≤3 cm, 376 patients (67%) matched our criterion for predicting MVI. Anatomical HR was carried out in 149 patients, partial HR in 227 patients, and survivals were compared to 52 patients matched our criterion who underwent RFA. Disease-free survival (DFS) and overall survival (OS) curves of these three groups are shown in Figure 1A and 1B, respectively. There were significant differences in both DFS and OS curves ($P = .0478$ and $P = .0358$, respectively). The 5-year DFS of the anatomical HR group reached 55%; however, the 5-year DFS of the RFA group was 28%. The 5-year OS of the anatomical HR group reached 61%, whereas that of the RFA group was 36%.

Multivariate analysis using Cox proportional hazard models identified five better prognostic factors (absence of transfusion, T-bil ≤1.0 mg/dL, age ≤65 years, ICGR15 ≤20%, and anatomical HR) influencing DFS, and three better prognostic factors (ICGR15 ≤20%, anatomical HR, and age ≤65 years) influencing OS (Table 8). Anatomical HR led to significantly better survival in both disease-free

TABLE 7 Diagnostic value of our predictors for MVI in HCC ≤3 cm in another cohort

Variable	Sensitivity (%)	Positive predictive value (%)
Matching one predictor	82.8	30.3
Matching two predictors	72.4	38.9
Matching three predictors	24.1	41.2

HCC, hepatocellular carcinoma; MVI, microvascular invasion.

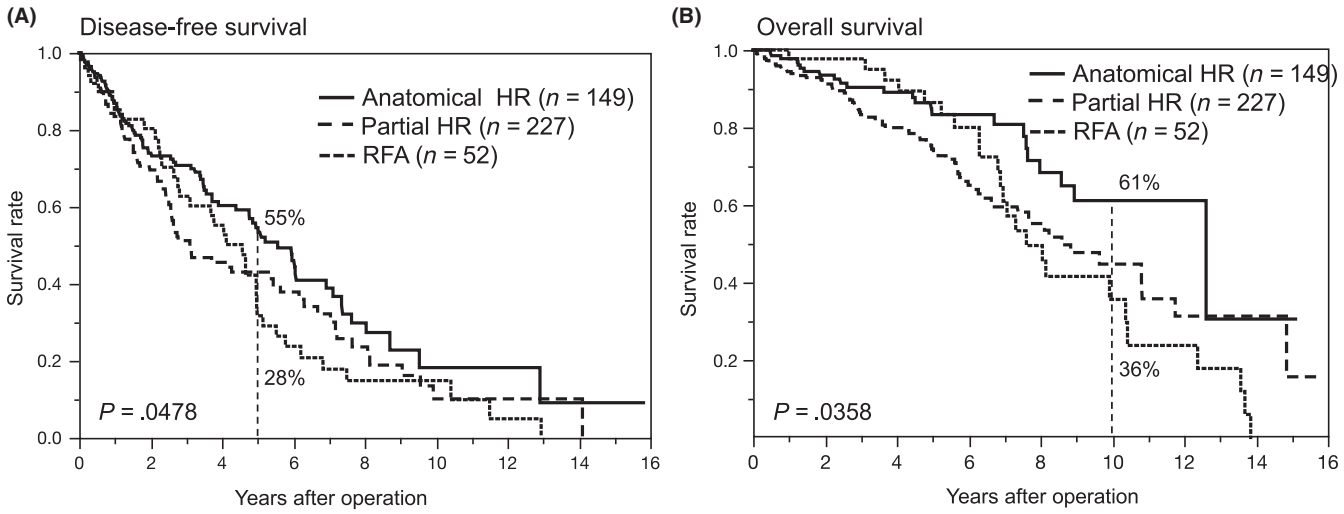

FIGURE 1 (A) Disease-free and (B) overall survival curves after anatomical hepatic resection (HR), partial HR, and radiofrequency ablation (RFA) in patients with hepatocellular carcinoma ≤3 cm matching our criterion for predicting microvascular invasion

(hazard ratio 0.689, $P = .0231$) and overall (hazard ratio 0.589, $P = .0316$) survivals.

4 | DISCUSSION

In the BCLC system, HCC ≤3 cm is considered to be "early stage", which denotes an early clinical entity with a high rate of cure. In both the BCLS system and the JSH-HCC guidelines, HR and RFA are equally recommended for HCC ≤3 cm. This is presumably based on the concept that HCC ≤3 cm is homogeneous and has low malignant potential. In our series, MVI was found in 168 patients (40.6%) among 414 patients with single HCC ≤3 cm, suggesting that the population of HCC ≤3 cm is not homogeneous, and that there may be a subgroup of an advanced biological nature with high-grade malignancy. We previously reported that MVI was also found in HCC ≤2 cm (very early stage in the BCLC system); however, its rate is low at 28.9%.[16] Among 244 patients with 2 cm ≤HCC ≤3 cm in our series, MVI was found in 115 patients (47.1%). This high rate would mean that 2 cm ≤HCC ≤3 cm has high-grade malignancy and, from our data, HR would be preferable to RFA for treating this subgroup.

TABLE 8 Multivariate analysis for better prognostic factors in DFS and OS

Variables	Hazard ratio	95% CI	*P*-value
DFS			
Transfusion (−)	0.422	0.168-0.922	.0294
T-bil ≤1.0 mg/dL	0.615	0.447-0.858	.0046
Age ≤65 y	0.661	0.495-0.858	.0046
ICGR15 ≤20%	0.664	0.471-0.946	.0238
Anatomical resection	0.689	0.501-0.950	.0231
OS			
ICGR15 ≤20%	0.532	0.351-0.812	.0036
Anatomical resection	0.589	0.349-0.956	.0316
Age ≤65 y	0.594	0.405-0.864	.0064

CI, confidence interval; DFS, disease-free survival; ICGR-15, indocyanine green retention rate at 15 min; OS, overall survival; T-bil, total bilirubin.

We have reported that the elevation of DCP is a strong predictor for MVI of HCC.[16–18] DCP may have the ability to enhance cell proliferation by Met receptor and angiogenesis by vascular endothelial growth factor.[19,20] Koike et al[21] carried out a prospective study to clarify the significance of DCP and concluded that DCP positivity was the strongest predictive factor for portal vein invasion. We know that DCP has not been measured worldwide; however, the significance of DCP elevation for predicting MVI in early HCC has been recognized in Western countries.[22] To establish personalized treatment for early HCC, measurement of DCP should be strongly recommended.

Although many reports refer to the superiority of DCP to AFP in predicting MVI in HCC, AFP is nevertheless another tool for evaluating the malignant potential of HCC.[23] In our series, the value of AFP itself had no correlation with MVI in HCC ≤3 cm; however, AFP ≥200 ng/mL had a significant correlation with MVI (+). The cut-off value of 200 ng/mL was from the appropriate value of 196 ng/mL identified by the ROC curve for predicting MVI in our first cohort. Mild to moderate elevation of AFP is sometimes found in patients with hepatitis or cirrhosis, but severe elevation of AFP to levels of 200 ng/mL or more is likely to be caused by HCC with high malignant potential.

We previously reported that invasive gross type was the strongest predictor for MVI in HCC ≤2 cm.[16] In the present study, invasive gross type was also the strongest predictor for MVI in HCC ≤3 cm (odds ratio 13.68). Therefore, the preoperative diagnosis for HCC gross type should be another potent tool. We previously found that preoperative diagnosis for gross type of HCC ≤2 cm is highly challenging, because distinguishing between single nodular type with

extranodular growth from single nodular type and confluent multinodular type from vaguely nodular type is difficult.[16] Hui et al[24] tried to classify the gross type of HCC by reviewing CT images, but the rate of correct diagnosis was only 46%. Nakayama et al[25] also reported an objective morphological classification system using multiphase CT. These systems should be useful for diagnosis for multinodular type, but are unlikely to be effective for single nodular type with extranodular growth type, especially for small HCC. Diffusion-weighted imaging of MRI[26,27] or standardized uptake value $(SUV)_{max}$ in positron emission tomography (PET)[26,27] are other possible tools for predicting MVI in HCC ≤3 cm; for these tools, however, the small tumor size itself presents an obstacle for accurate evaluation.

To eradicate the MVI of HCC, anatomical HR[28] or partial HR with a wide tumor margin[15] should be recommended. Anatomical HR, in theory, can ideally eradicate MVI confined to tumor-bearing portal tributaries. In our series involving 428 patients with HCC ≤3 cm matching our criterion of predicting MVI, a positive survival impact of anatomical HR was found. The 5-year DFS of the anatomical HR group was 55%, compared to 46% for the partial HR group and 28% for the RFA group. This result meant high curability for HCC ≤3 cm with MVI by anatomical HR, and anatomical HR would therefore be recommended for HCC ≤3 cm, matching our criterion for predicting MVI. In contrast, liver function reserve may be one of the most important factors for patients' survival after treatment for HCC.[9] Actually, in our own study, there were significant differences in the ICGR15 values among anatomical HR (15.6 ± 6.8%), partial HR (21.3 ± 8.6%), and RFA groups (27.9 ± 7.9%). Recent meta-regression analysis concerning patients' survival after anatomical HR versus partial HR for HCC showed this critical concern.[29]

Limitations of the present study are its retrospective design; in addition, our results may be biased as a result of the physicians' varying therapeutic policies. Furthermore, patients' backgrounds, such as liver function reserves, differ among the anatomical HR, partial HR, and RFA groups. These differences may substantially affect survival after treatment. Propensity score matching is one of the potent methods to compare treatment modalities under homogeneous conditions; however, in our series, matching was very difficult because of the definite difference of liver functional reserve among the three groups. Therefore, randomized control study with the same therapeutic policies and the same patients' backgrounds will be necessary to confirm our results. Second, the specificity of our criterion for predicting MVI in HCC ≤3 cm was relatively low. Actual positive rate of MVI in this cohort was 35% (198 in 563 patients); therefore, there is a possibility of carrying out unnecessary anatomical HR in patients without MVI. We consider that "sensitivity" has more priority than "specificity" in this situation; however, a better criterion with high specificity should be discussed. Finally, in this study, the positive rates of MVI in HCC ≤3 cm considerably differed between the two institutions (40.6% vs 20.1%). This difference may be related to the characteristics of patients; however, there is no significant difference in the positive rates of poorly differentiated HCC (21.3 vs 20.8%, $P = .9079$). The same pathologist or pathological team did not examine MVI; however, pathologists of these two institutions are skilled experts because both institutions are high-volume centers of HR for HCC of over 100 cases per year. In addition, pathologists examined MVI according to the same published general rules.[13] We cannot show the reason there was a big difference in the positive rate of MVI in HCC ≤3 cm between the two institutions, but this difference itself would be a problem to be resolved by additional concerns of the pathological definitions of MVI for small-sized HCC.

In conclusion, matching at least one factor among three factors (tumor diameter ≥2 cm, AFP ≥200 ng/mL, or DCP ≥40 mAU/mL) can predict MVI in HCC ≤3 cm. In such patients, we recommend anatomical HR for better survival.

DISCLOSURE

Conflicts of Interest: Authors declare no conflicts of interest for this article.

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