congestion is large (*10, 12*). To overcome this problem, an extended RL graft with the MHV is used in many countries; however, the donor's remnant liver tends to be small (*13, 14*). To maintain the volume of remnant liver volume (RV), Chan et al. (*15*) and Hwang et al. (*16*) demonstrated the feasibility of RL grafts with only the caudal MHV, which might lead to the donor's remnant liver with cranial MHV preserving hepatic vein draining segment 4 (V4) drainage.

On the basis of the strategy by Chan et al. (*15*), we devised a new concept to increase functional GV by improving congested volume (CV) in a procured RL graft with reconstruction of a large caudal MHV trunk draining all V5 tributaries. To select the appropriate liver type for our V5-drainage-preserved RL (VP-RL) graft, donor's livers were classified into three types by V4 anatomy. Furthermore, intraoperative venous reconstruction data and postoperative clinical parameters between VP-RL grafts and M-RL grafts were prospectively evaluated.

RESULTS

Classification of V4 Anatomy in the Retrospective Study

The anatomical patterns of V4 in 49 cases were as follows: type A, n=26; type B, n=15; and type C, n=8 (Fig. 1). Inferior V4 (V4 inf.) drainage territory in type A occupied 48.3%±13.2% of segment 4 of the liver (S4) volume, 19.4%±6.1% of left lobe volume, and 7.0%±2.0 % of whole liver volume (WLV). Superior V4 (V4 sup.) drainage territory in type B occupied 47.2%±12.4% of S4 volume, 19.0%±6.4% of left lobe, and 6.9%±1.8% of WLV. Umbilical vein (UV) from left hepatic vein (LHV) drainage territory in type C occupied 42.6%±12.2% of S4 volume, 17.1%±5.8% of left lobe volume, and 6.2%±1.4% of WLV.

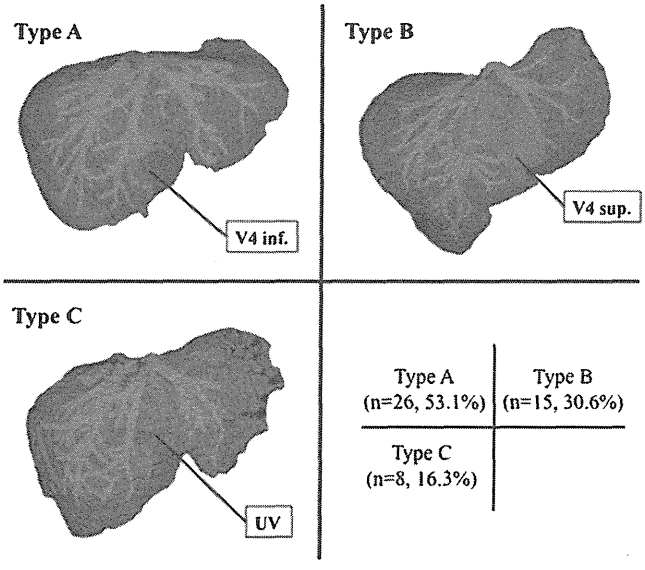

FIGURE 1. 3DR-CT images for classification of V4 anatomy in the retrospective study. The V4 anatomical patterns in 49 cases were classified into three types: A, B, and C, in which V4 inf., V4 sup., and UV from LHV predominantly drain, respectively. 3DR, three-dimensional reconstruction; CT, computed tomography; LHV, left hepatic vein; V4 inf., inferior V4; V4 sup., superior V4; UV, umbilical vein V4; V4, hepatic vein draining segment 4.

TABLE 1. Functional GV and RV with both M-RL and VP-RL grafts in all the V4 anatomical types in the retrospective study (n=49)

V4 classification	Functional GV (mL) (/WLV; %)	Functional RV (mL) (/WLV; %)
Type A (n=26)		
M-RL	593±28	368±16
	(59±2)	(36±2)
VP-RL	614±27	324±23
	(62±3)	(32±2)
P value	<0.05	<0.05
Type B (n=15)		
M-RL	619±34	362±19
	(60±2)	(35±1)
VP-RL	648±34	350±28
	(63±3)	(34±1)
P value	<0.05	NS
Type C (n=8)		
M-RL	642±45	370±25
	(58±3)	(36±2)
VP-RL	683±44	354±38
	(62±3)	(35±3)
P value	<0.05	NS

Values are mean±SD.

SD, standard deviation; M-RL, modified right lobe; GV, graft volume; LV, liver volume; NS, not significant; RL, right lobe; RV, remnant liver volume; VP-RL, V5-drainage-preserved right lobe; WLV, whole liver volume.

Simulation of M-RL and VP-RL Grafts With Three Types of V4 Anatomy in the Retrospective Study

Liver volume, such as GV and RV, was calculated by 3DR-CT volumetry. Functional GV and RV according to the donor's liver type are presented in Table 1. With type A, functional GV in the VP-RL graft was significantly higher than that in the M-RL graft ($P<0.05$); however, functional RV in the VP-RL graft was significantly lower than that in the M-RL graft ($P<0.05$). With types B and C, functional GV in the VP-RL graft was significantly higher than that in the M-RL graft ($P<0.05$), and functional RV in the VP-RL graft was similar to that in the M-RL graft. Considering donor safety, the criteria for graft selection in the prospective study were VP-RL with types B and C, whereas for the M-RL graft, only type A was used.

Outcome of 3DR-CT Volumetry and Venous Reconstruction in the Prospective Study

Baseline characteristics in both donors and recipients were not significantly different between the two groups (data not shown). The data of 3DR-CT volumetry and venous reconstruction are presented in Table 2. For the outcome of donors' side, any parameters, such as WLV and RV, were not significantly different between the groups. Meanwhile, for the outcome of recipients' side, there were no significant

TABLE 2. Outcome of 3DR-CT volumetry, venous reconstruction, and postoperative clinical parameters in the prospective study

Variables	M-RL group (n=7)	VP-RL group (n=8)	P
3DR-CT volumetry			
WLV (mL)	986±41	1015±38	NS
RV (mL)	364±14	359±13	NS
Functional RV (mL)	364±15	330±14	NS
GV (mL)	622±32	656±30	NS
SLV (mL)	1191±47	1284±44	NS
GRWR (%)	1 .00±0.18	0.95±0.33	NS
GV/SLV (%)	52.2±7.2	52.4±14.6	NS
CV (mL)	91±13	47±13	<0.05
CV/GV (%)	9.4±1.4	4.6±1.3	<0.05
Functional GV (mL)	531±37	609±35	<0.05
Venous reconstruction			
Mean size of MHV trunk or V5 (mm)	6.6±0.8	11.4±0.7	<0.01
Proportion of grafts with MHV trunk or V5<10 mm in diameter (%)	6 (85.7)	1 (12.5)	<0.01
Number of MHV trunks or V5	2.9±0.2	1.0±0.2	<0.01
Postoperative parameters of donors			
Operative time (min)	419±16	428±15	NS
Operative blood loss (g)	346±60	420±57	NS
Peak serum T-Bil levels (mg/dL)	2.4±0.3	3.0±0.2	NS
Peak serum ALT levels (U/L)	725±114	531±107	NS
Hospital stay (d)	16±1	13±1	NS
Complications greater than Clavien grade 1 (%)	2 (28.6)	1 (12.5)	NS
Postoperative parameters of recipients			
Operative time (min)	908±34	861±31	NS
Operative blood loss (g)	5349±1402	4524±1312	NS
Hospital stay (d)	36±7	26±7	NS
Complications greater than Clavien grade 3 (%)	2 (28.6)	2 (25.0)	NS
Serum T-Bil levels (mg/dL)			
POD 1	9.4±5.5	4.6±1.2	<0.05
POD 3	4.8±2.4	2.7±0.6	<0.05
POD 5	7.8±4.1	5.4±1.4	NS
POD 7	6.1±4.3	3.2±2.6	NS
Ascites volume on POD 7 (mL)	431±254	59±83	<0.01
Duration of postoperative drainage (d)	16±10	7±2	<0.05

Means are given as±SD or n (%).

3DR-CT, three-dimensional reconstruction-computed tomography; ALT, alanine aminotransferase; CV, congestive volume; GRWR, graft recipient's body weight ratio; GV/SLV, graft volume to recipient standard liver volume ratio; MHV, middle hepatic vein; M-RL, modified right lobe; NS, not significant; POD, postoperative day; RV, remnant liver volume; SLV, standard liver volume; T-Bil, total bilirubin; VP-RL, V5-drainage-preserved right lobe; WLV, whole liver volume.

differences in the graft recipient's body weight ratio and GV versus standard liver volume ratio between the groups. However, CV and CV/GV in the VP-RL graft were significantly lower than those in the M-RL graft ($P<0.05$); therefore, functional GV in the VP-RL graft was significantly higher than that in the M-RL graft ($P<0.05$). With respect to intraoperative venous reconstruction, the mean size of the MHV trunk in the VP-RL graft was significantly larger than that of V5 branches in the M-RL graft ($P<0.01$), and the rate of grafts with MHV less than 10 mm in diameter and the number of MHV trunks in the VP-RL graft were significantly lower than those of V5 branches in the M-RL graft ($P<0.01$).

Comparison of Postoperative Clinical Parameters in the Prospective Study

The clinical parameters in donors, such as operative time, operative blood loss, peak values of liver function tests, and incidence of complications are presented in Table 2. There were no significant differences in these parameters between the groups. For the clinical parameters of recipients, with respect to baseline characteristics of graft hemodynamics,

there were no significant differences in portal vein pressure after laparotomy and before abdominal closure, and in the prevalence of refractory ascites, gastrointestinal bleeding, spontaneous splenorenal shunt, transjuglar intrahepatic portosystemic shunt, splenectomy, and ligation of the shunt between M-RL and VP-RL grafts (see **Table, SDC 1,** http://links.lww.com/TP/A641). Data such as operative time, operative blood loss, and hospital stay were not significantly different between the groups (Table 2). The ratio of complications greater than Clavien grade 3 was comparable between the groups: pancreas pseudoaneurysm and intraperitoneal abscess (n = 1) and partial thrombus of the portal vein trunk (n = 1) were found in VP-RL grafts, and thrombus of the portal vein trunk requiring abdominal surgery (n = 1) and bile duct stenosis (n = 1) were found in M-RL grafts (Table 2). Serum total bilirubin (T-Bil) values at postoperative days 1 and 3 in VP-RL grafts were significantly lower than those in M-RL grafts ($P<0.05$) (Table 2). Other function tests such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time were not significantly different between the two groups (data not shown). Ascites volume at postoperative day 7 and the duration of postoperative drainage in VP-RL grafts were significantly lower than those in M-RL grafts (ascites volume, $P<0.01$; duration of postoperative drainage, $P<0.05$) (Table 2). All the grafts and patients survived in the prospective study, including both donors and recipients (the mean follow-up time was 32.7 months).

DISCUSSION

On the basis of the study by Chan et al., tailoring the donation of extended RL (*15*), we classified V4 anatomy in more detail to select an appropriate donor liver type for VP-RL grafts. From our study results, we concluded that VP-RL grafts have a more favorable outcome compared with M-RL grafts. Moreover, types B and C, in which V4 sup. and the UV from LHV predominantly drain S4, were appropriate for VP-RL grafts because of their stable functional RV (Table 1). This could be a strategy against a slow postoperative recovery of liver function or small-for-size syndrome for complications in the recipient. In addition, by using VP-RL grafts with liver types B and C, the size and number of venous reconstructions, and functional GV were significantly improved compared with those using M-RL grafts. Furthermore, postoperative clinical parameters such as ascites volume and serum T-Bil values in VP-RL grafts were significantly improved.

One of the crucial problems for using RL grafts without the MHV is liver dysfunction caused by deficiency of GV or excessive CV (*5, 7*). There are some reports regarding the impact of liver congestion (*7, 10–12, 17–19*). Maetani et al.

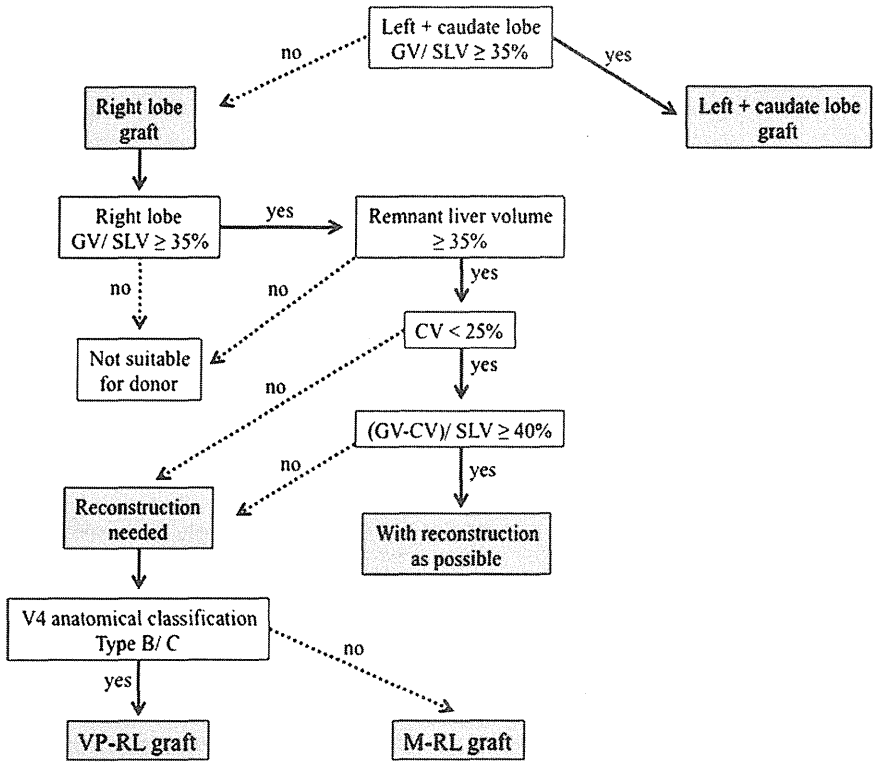

FIGURE 2. Algorithm for the graft selection as used in our institution. The RL graft is chosen if the estimated extended left with caudate lobe volume is less than 35% of the recipient's SLV. If a RV after procurement is less than 35% of WLV, this donor should be rejected. If CV is more than 25% or the deducted CV from the GV is less than 40% of the recipient's SLV, reconstruction of these tributaries is required. If the donor's liver is type B or C by V4 anatomical classification, a VP-RL graft is procured, whereas with type A, a M-RL graft is procured. SLV, standard liver volume; CV, congested volume; GV, graft volume; RV, remnant liver volume; M-RL, modified right lobe, RL, right lobe; VP-RL, V5-drainage-preserved right lobe; WLV, whole liver volume; V4, hepatic vein draining segment 4.

(*17*) demonstrated that for a long-term outcome of 6 postoperative months, the lack of anterior segment regeneration was resolved by a compensatory regeneration of the posterior segment and graft congestion in the anterior segment did not affect overall graft regeneration. On the other hand, for the short-term outcome as postoperative 7 days when postoperative complications sometimes occur, we previously demonstrated that congestion of the anterior segment caused by impaired outflow was severe in several cases, and sometimes the estimated CV exceeded 50% of the RL volume (*7, 10, 12*). This graft congestion could lead to transient liver dysfunction and poor regeneration during the early postoperative period. In addition, Akamatsu et al. (*18*) and Mizuno et al. (*19*) demonstrated that liver regeneration in the congestion area is significantly poorer compared with that in the noncongestion area. Therefore, even in LDLT using RL grafts where the actual GV may be relatively large, the impact of congestion cannot be ignored. Regarding the benefit with reconstruction of MHV tributaries, at least in the short-term, we observed some favorable outcomes such as an improvement in serum T-Bil levels and ascites volume by reducing congestion of the anterior segment in VP-RL grafts.

The advantage of VP-RL grafts was that there was no CV of S5 in the recipient liver, but there was minimal CV of S4 in the donor liver. Considering donor safety, type A could not be used for the VP-RL graft because functional RV in the VP-RL graft was significantly lower than that in the M-RL graft with type A (Table 1). Based on these findings, an algorithm for graft selection was determined (Fig. 2). The left lobe is initially considered as a graft with respect to donor safety. The RL graft is chosen if the estimated extended left with caudate lobe volume is less than 35% of the recipient's standard liver volume (SLV). If a RV after RL procurement is less than 35% of WLV, this donor should be rejected. If CV is more than 25% or the deducted CV from the GV is less than 40% of the recipient's SLV, reconstruction of these tributaries is required. If the donor's liver is type B or C by V4 anatomical classification, a VP-RL graft is procured, whereas with type A, a M-RL graft is procured.

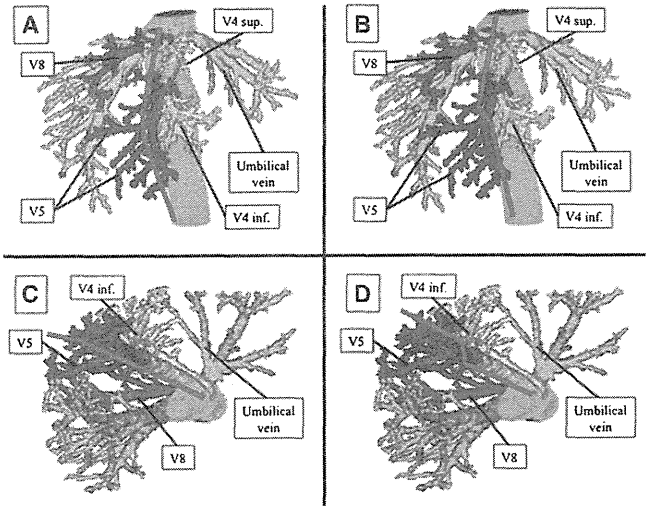

FIGURE 3. Stereoscopic images by 3DR-CT for transection lines in both M-RL and VP-RL grafts. Representative images of a M-RL graft where the transection line is along the right side of the MHV in a coronal plane image (A) and sagittal plane image (C). There is likely to be mild CV of the anterior segment in the recipient liver but no CV of S4 in the donor liver. Representative images of a VP-RL graft where the transection line is along the left side of the caudal MHV and is cut off the caudal MHV trunk and the right side of the cranial MHV in a coronal plane image (B) and sagittal plane image (D). There is not likely to be CV of S5 in the recipient liver with caudal MHV trunk reconstruction, but there might be a little CV of S4 in the donor liver. 3DR, three-dimensional reconstruction; CT, computed tomography; CV, congested volume; MHV, middle hepatic vein; M-RL, modified right lobe, RL, right lobe; S4, segment 4; S5, segment 5; S8, segment 8; VP-RL, V5-drainage-preserved right lobe; V4 inf., inferior V4; V4 sup., superior V4.

Since the M-RL graft was first demonstrated by Lee et al. (*11*), there have been some reports demonstrating the reconstruction method of V5 and hepatic vein draining segment 8 to prevent congestion of the anterior segment. We previously demonstrated the feasibility of autogenous interposition vein grafts, such as the portal vein, saphenous vein, inferior vena cava, inferior mesenteric vein, and internal jugular vein (*8, 9*). Another method to improve CV is to use an extended RL graft with the whole MHV (*13, 14*). To overcome CV of S4 in the donor's remnant liver, Chan et al. (*15*) procured an extended RL with only the caudal MHV. With this particular graft, the donors' postoperative clinical parameters were significantly improved compared with normal extended RL; however, their strategy has a major limitation. It was not clear how the V4 anatomical classification by which the donor's liver type their tailoring extended RL should be procured. They also classified V4 anatomy into three types based on S4 drainage into the MHV, UV, and equally into MHV and UV. However, in our retrospective analysis, functional RV was significantly decreased in LDLT using the VP-RL graft with type A in which V4 inf. predominantly drains S4. Furthermore, the cutoff level of the MHV trunk needed be clear, immediately above the MHV where all V5 drains into, to preserve the thick caudal MHV trunk to reconstruct for complete drainage of S5.

In conclusion, VP-RL graft procurement is a safe and reliable RL graft for improving functional LV and the postoperative clinical course in the recipients, without impairment of functional RV and the postoperative clinical course in the donors by venous reconstruction with a large-sized caudal MHV. Using preoperative V4 anatomical graft classification, a suitable liver type of the donor for the VP-RL graft should be selected to ensure a good outcome for both recipients and donors. However, these data should be interpreted carefully because of the small numbers of cases, and step-by-step analysis is essential to strengthen the interpretation.

MATERIALS AND METHODS

Donors in the Retrospective Study and Patients in the Prospective Study

From July 2004 to May 2008, measurements of GV from preoperative 3DR-CT volumetry for LDLT using RL grafts at Kyushu University Hospital were retrospectively evaluated for 49 donors. The characteristics and 3DR-CT volumetry of the 49 donors were as follows: age, 35 years; proportion of males, 65.3%; height, 167 cm; weight, 61 kg; body mass index,

22.3 mg/dL; serum T-Bil, 0.6 mg/dL; serum AST, 17 U/L; ALT, 17 U/L; WLV, 913 mL; GV, 520 mL; and RV, 393 mL.

Patients in the Prospective Study

For the prospective study, 15 donors were evaluated from June 2008 to February 2009. The characteristics and 3DR-CT volumetry of the 15 donors were as follows: age, 37 years; proportion of males, 40.0%; height, 162 cm; weight, 56 kg; body mass index, 21.6 mg/dL; serum T-Bil, 0.6 mg/dL; serum AST, 20 U/L; ALT, 19 U/L; WLV, 1002 mL; GV, 640 mL; and RV, 361 mL. None of these parameters in the 15 donors in the prospective study were significantly different from those in the 49 donors in the retrospective study (data not shown).

The indications for LDLT in the prospective study were liver cirrhosis resulting from unknown cause (n = 3), hepatitis C (n = 7), hepatitis B (n = 2), alcohol abuse (n = 1), Wilson disease (n = 1), and chronic rejection (n = 1). Eight patients had liver cirrhosis with hepatocellular carcinoma. All LDLTs were performed after obtaining full informed consents from all patients and approval by the Liver Transplantation Committee of Kyushu University. The study protocol confirmed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board.

Graft Selection and Criteria for Venous Reconstruction

Graft selection, including reconstruction of the MHV tributaries, was performed according to a previously described algorithm (*10*). The SLV of recipients was calculated according to the formula described by Urata et al. (*20*). The explanted portal vein grafts were used for the reconstruction of MHV tributaries in 10 cases, and other interposition grafts included the saphenous vein (n = 4), inferior mesenteric vein (n = 3), and internal jugular vein (n = 3).

Classification of V4 Anatomy and Evaluation of Functional GV and RV

LV, CV, and drainage volume of each small vein were calculated by specialized computer software (Resion Growing Software Version 0.5a; Hitachi Medical Corporation, Chiba, Japan). By using this software, the stereoscopic patterns of V4 were visualized through 3DR of preoperative dynamic CT images. Additionally, based on their diameter and length, WLV and the volume of each hepatic venous branch territory were automatically calculated (*10, 12, 21*). To identify the predominant V4 branch for S4, we calculated a drainage liver volume for each of the V4 branches. The CV/WLV ratio for each of the V4 branches was also calculated. Based on these evaluated data, V4 anatomical patterns were then classified into three groups as types A, B, and C, which predominantly drain S4 as the V4 inf., the V4 sup., or the UV to LHV, respectively (Fig. 1). Both M-RL and VP-RL grafts were retrospectively simulated with all three types to calculate the functional GV and the functional RV by deducting CV, which was computed by the sum of the venous branches that were not reconstructed (*10, 12*).

Surgical Procedure With M-RL graft and VP-RL Graft Donation

Figure 3 shows stereoscopic images through 3DR-CT images with simulated different patterns for the two types of transection lines, for the M-RL graft (Fig. 3A) and VP-RL graft (Fig. 3B) in the donated liver. The operative procedures with M-RL grafts have been described elsewhere (*3, 4, 22, 23*). Significant drainage veins from the anterior segment and inferior right hepatic veins more than 5 mm in diameter were clipped and procured with grafts for reconstruction at the back table. There was mild CV of the anterior segment in the recipient liver but no CV of S4 in the donor liver because the numbers of V5 were not always simple and the interposition grafts to be anastomosed with the RHV were limited in number.

The VP-RL graft was procured by transecting along the left side of the caudal MHV, it was cut off the caudal MHV trunk, and then transected along the right side of the following cranial MHV, as described previously (*15*) (Fig. 3B). To preserve the thick caudal MHV trunk with the graft and to reconstruct for complete drainage of S5, the MHV trunk was transected immediately above the MHV where all V5 drained into. There was no CV of S5 in the recipient liver, but there was a little CV of S4 in the donor liver. The size and number of V5 branches in the M-RL graft were measured and those of the MHV trunk in the VP-RL graft.

Evaluation of Postoperative Clinical Parameters in the Prospective Study

After preoperative V4 classification through 3DR-CT images, M-RL grafts were procured in donors with type A of the V4 anatomical classification, and VP-RL grafts were procured in those with types B and C. The clinical follow-up of patients after LDLTs followed a strict protocol, which did not change during the study period (*3, 4*). The operative time and intraoperative blood loss were measured, and postoperative complications including ascites volume and hospital stay were compared between the two types of grafts. Complications were classified according to Clavien's classification (*24*). The indication to remove drains was when the postoperative drainage volume was less than 500 mL/day and the general condition of the patients including other laboratory data were improved. When the patients' condition was not improved or clinically stable, drains were not removed.

Statistical Analysis

All statistical analyses were performed using JMP statistical software version 7.01 (SAS Institute Inc., Cary, NC). All variables are expressed as the mean±standard deviation. The continuous variables were compared with independent samples using the nonparametric Wilcoxon test or with dependent samples using the parametric paired *t* test. The categorical data were compared using the Fisher's test and χ^2-squared test. *P* values less than 0.05 were considered significant.

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RESEARCH Open Access

Analysis of the risk factors for early death due to disease recurrence or progression within 1 year after hepatectomy in patients with hepatocellular carcinoma

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Abstract

Background: Liver resection for hepatocellular carcinoma (HCC) has the highest local controllability among all local treatments and results in a good survival rate. However, the recurrence rates of HCC continue to remain high even after curative hepatectomy Moreover, it has been reported that some patients with HCC have an early death due to recurrence. We analyzed the preoperative risk factors for early cancer death.

Methods: Between 1997 and 2009, 521 consecutive patients who underwent hepatectomy for HCC at our center were assigned to group ED (death due to HCC recurrence or progression within 1 year after hepatectomy) and group NED (alive over 1 year after hepatectomy). Risk factors for early cancer death were analyzed.

Results: Group ED included 48 patients, and group NED included 473 patients. The cause of death included cancer progression (150; 78.1%), operation-related (1; 0.5%), hepatic failure (15; 7.8%), and other (26; 13.5%). Between the ED and NED groups, there were significant differences in albumin levels, Child-Pugh classifications, anatomical resections, curability, tumor numbers, tumor sizes, macroscopic vascular invasion (portal vein and hepatic vein), alpha-fetoprotein (AFP) levels, AFP-L3 levels, protein induced by vitamin K absence or antagonism factor II (PIVKA-II) levels, differentiation, microscopic portal vein invasion, microscopic hepatic vein invasion, and distant metastasis by univariate analysis. Multivariate analysis identified specific risk factors, such as AFP level > 1,000 ng/ml, tumor number ≥ 4, tumor size ≥ 5 cm, poor differentiation, and portal vein invasion. With respect to the preoperative risk factors such as AFP level, tumor number, and tumor size, 3 (1.1%) of 280 patients with no risk factors, 12 (7.8%) of 153 patients with 1 risk factor, 24 (32.9%) of 73 patients with 2 factors, and 9 (60.0%) of 15 patients with 3 risk factors died within 1 year of hepatectomy ($p < 0.0001$).

Conclusions: Hepatectomy should be judiciously selected for patients with AFP level > 1,000 ng/ml, tumor number ≥ 4, and tumor size ≥ 5 cm, because patients with these preoperative risk factors tend to die within 1 year after hepatectomy; these patients might be better treated with other therapy.

Keywords: Hepatocellular carcinoma, Hepatectomy, Early death

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Background

Liver resection for the treatment of hepatocellular carcinoma (HCC) has the highest controllability among all local treatments and results in a good survival rate [1,2]. However, recurrence rates remain high and are the main cause of early death even after curative hepatectomy [3]. Moreover, it has been reported that some patients with HCC have an early death due to recurrence [4]. In the remnant liver after hepatectomy, tumor recurrence is recognized as intrahepatic metastasis caused by dissemination of cells in the portal vein or metachronous multicentric hepatocarcinogenesis [5]. The risk factors for early recurrence are reported to be related to tumor cell dissemination due to tumor characteristics such as vascular invasion [6,7] and intrahepatic metastasis [8]. Though the two algorithms that were proposed from the Barcelona Clinic Liver Cancer (BCLC) classification [9] and Japanese guideline [10] recommend that multiple HCCs be treated by transcatheter arterial chemoembolization with lipiodol (TACE) or sorafenib, hepatectomy beyond these algorithms was actually performed in the clinical scene. However, the risk factors for early death due to HCC recurrence or progression within 1 year after hepatectomy have not been clearly evaluated [11].

On the other hand, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial [12] recently reported the effectiveness of sorafenib in the treatment of advanced HCC. In this report, median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group. If patients have an early death within 1 year due to recurrence after hepatectomy, there might be no benefit of hepatectomy compared to sorafenib. Therefore, the risk factors for early death within 1 year after hepatectomy due to HCC recurrence or progression should be evaluated, and the appropriateness of hepatectomy for patients with advanced HCC should be investigated.

To identify the risk factors related to early death after hepatectomy, we analyzed the outcomes of 521 consecutive patients who underwent primary hepatectomy for HCC at our center.

Methods

Patients

Between January 1997 and May 2009, 521 consecutive patients underwent hepatectomy for HCC at our center. These patients were followed for at least 1 year, and then assigned to group ED (death due to HCC recurrence or progression within 1 year after hepatectomy) or group NED (alive over 1 year after hepatectomy). The resulting ED group included 48 (9.2%) patients, and the resulting NED group included 465 (89.3%) patients. Of all 521 patients, 8 (1.5%) patients who died of liver failure, other causes, and postoperative complications within 1 year after hepatectomy were excluded from group ED and NED. The mean age of 513 patients of group ED and NED was 61.3 years, with a range of 18–87 years. Of the 513 patients, 427 (83.2%) were male and 86 (16.8%) were female, 221 (43.1%) were hepatitis B virus surface antigen-positive, 189 (36.8%) were hepatitis C virus antibody-positive, and 175 (34.1%) had cirrhosis. At least 2 weeks before hepatectomy, imaging studies were performed and preoperative serum alpha-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and protein induced by vitamin K absence or antagonism factor II (PIVKA-II) levels were simultaneously measured using standard methods. Among the 513 patients, 499 (97.3%) were categorized as Child-Pugh class A (Table 1). The patients were followed up for a median of 84.2 months (range, 12.5–165.0 months). This study was approved by the Institutional Review Board of the Hokkaido University, School of Advanced Medicine.

Hepatectomy

Anatomical resection is defined as a resection in which lesion(s) are completely removed anatomically on the basis of Couinaud's classification (segmentectomy, sectionectomy, and hemihepatectomy or extended hemihepatectomy) in patients with sufficient functional reserve. Non-anatomical partial resection was performed as a limited resection or tumor enucleation. When R0 resections were performed, the resection surface was found to be histologically free of HCC. Indocyanine green retention rates at 15 min (ICGR15) were measured to evaluate liver function reserve, regardless of the presence or absence of cirrhosis.

HCC recurrence

Every 3 months for the first 2 years after hepatectomy, the patients underwent follow-up evaluations comprising liver function tests, measurements of tumor markers AFP and PIVKA-II, ultrasonography (US), and dynamic computed tomography (CT). After 2 years, routine CT was performed only once every 4 months. If recurrence was suspected, CT and magnetic resonance imaging (MRI) were performed; if necessary, CT during angiography and bone scintigraphy were also performed. This enabled precise diagnoses of the site, number, size, and invasiveness of the recurrent lesions.

Statistical analysis

Patient survival (PS) rates were determined via the Kaplan-Meier method. Univariate analysis was performed; then multivariate analysis and logistic regression were performed only on significant variables. Statistical analyses (StatView 5.0 for Windows: SAS Institute Inc., Cary, NC) were performed using standard tests (X^2, t-test) where appropriate. Significance was defined as $p < 0.05$.

Table 1 Univariate analysis of the risk factors of death from cancer progression within 1 year after hepatectomy

		Group ED ($n=48$)	Group NED ($n=465$)	*p*-value
Sex	Male	40	387	
	Female	8	78	0.9849
Age	<60	24	211	
	60 ≤	24	254	0.5405
HBV	+	26	195	
	-	22	270	0.1033
HCV	+	14	175	
	-	34	290	0.2469
Albumin	<4	33	214	
(g/dl)	4 ≤	15	251	0.0027
Total bilirubin	<0.8	32	283	
(mg/dl)	0.8 ≤	16	182	0.4314
ICGR15 (%)	<15	27	250	
	15 ≤	21	215	0.7421
Child-Pugh	A	42	457	
	B	6	8	<0.0001
AFP (ng/ml)	≤200	15	355	
	200<, ≤1,000	5	37	
	1,000<	28	73	<0.0001
AFP-L3 (%)	≤15	23	334	
	15% < 40<	5	49	
	40<	20	83	0.0002
PIVKA-II (mAU/ml)	≤100	10	258	
	100<, ≤1,000	8	93	
	1,000<	30	114	<0.0001
Liver cirrhosis	Present	17	158	
	Absent	31	307	0.8414
Curability	R0 R1	40	443	
	R2	8	22	0.0008
Anatomical resection	Yes	42	326	
	No	6	139	0.0108
Tumor number	1	16	321	
	2, 3	11	113	
	4 ≤	21	31	<0.0001
Tumor size	≤2 cm	4	64	
	2-5 cm	6	254	
	5 cm ≤	38	147	<0.0001
Macroscopic vascular invasion	Absent	28	440	
(portal vein, hepatic vein)	Present	20	25	<0.0001
Differentiation	Well	0	50	
	Moderate	19	308	
	Poor	29	92	
	Necrosis	0	15	<0.0001
Microscopic portal vein invasion	vp0	10	369	
	vp1	13	60	
	vp2	7	15	
	vp3	12	15	
	vp4	6	6	<0.0001
Microscopic hepatic vein invasion	vv0	28	439	
	vv1	8	12	
	vv2	9	10	
	vv3	3	4	<0.0001
Distant metastasis	Absent	43	459	
	Present	5	6	<0.0001

HCC: hepatocellular carcinoma.
NED: alive 1 year after hepatectomy.
ED: death due to HCC recurrence or progression within 1 year after hepatectomy.
HBV: hepatitis B virus s antigen.
HCV: anti-hepatitis C virus antibody.
ICGR15: indocyanin green retention rate at 15 min.
AFP: alpha-fetoprotein.
AFP-L3: *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein.
PIVKA-II: protein induced by vitamin K absence or antagonism factor II.
vp0: no tumor thrombus in the portal vein.
vp1: tumor thrombus distal to the second branches of the portal vein.
vp2: tumor thrombus in the second branches of the portal vein.
vp3: tumor thrombus in the first branch of the portal vein.
vp4: tumor thrombus extension to the trunk or the opposite side branch of the portal vein.
vv0: no tumor thrombus in the hepatic vein.
vv1: tumor thrombus in a branch of the hepatic vein.
vv2: tumor thrombus in the right, middle, or left hepatic vein trunk or the short hepatic vein.
vv3: tumor thrombus to the inferior vena cava.

Results

Causes of death

PS rates ($n=521$) at 1, 2, 5, and 10 years were 90.5%, 84.6%, 69.0%, and 54.2%, respectively (Figure 1), with 192 deaths (36.9%). The causes of death, whether within 1 year post-hepatectomy or later, included HCC recurrence or progression ($n=150$; 78.1%), liver failure ($n=15$; 7.8%), other causes ($n=26$; 13.5%), and postoperative complications ($n=1$; 0.5%). Of the 150 patients who died of HCC recurrence or progression, 48 (32.0%) died within 1 year after hepatectomy (Figure 2). The patients who died of liver failure ($n=4$), other causes ($n=3$), and postoperative complications ($n=1$) within 1 year after hepatectomy were excluded from group ED and NED.

Clinicopathological characteristics and operative variables

Patient characteristics and perioperative outcomes are shown in Table 1. Between the ED and NED groups,

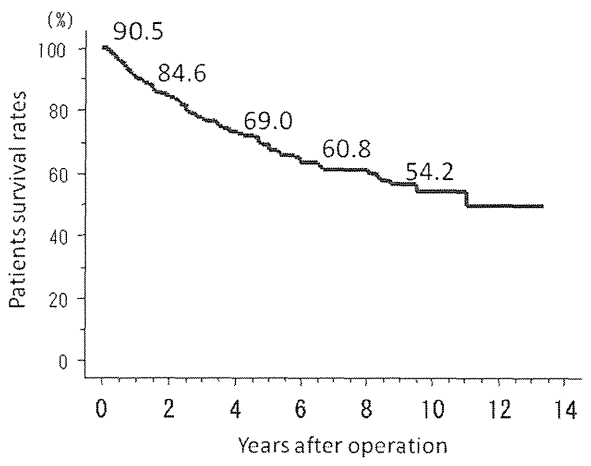

Figure 1 Survivals of all 521 patients at 1, 2, 5, 7, and 10 years were 90.5%, 84.6%, 69.0%, 60.8%, and 54.2%, respectively.

there were significant differences in albumin levels, Child-Pugh classifications, anatomical resections, curability, tumor numbers, tumor sizes, macroscopic vascular invasion (portal vein and hepatic vein), AFP levels, AFP-L3 levels, PIVKA-II levels, differentiation, microscopic portal vein invasion, microscopic hepatic vein invasion, and distant metastasis. Tumor-related factors are also shown in Table 1. When the risk factors that were identified as significant by univariate analysis were included in a multivariate analysis via logistic regression, it was found that AFP level, tumor number, tumor size, differentiation, and microscopic portal vein invasion were independent risk factors for early death due to HCC recurrence or progression within 1 year after hepatectomy (Table 2).

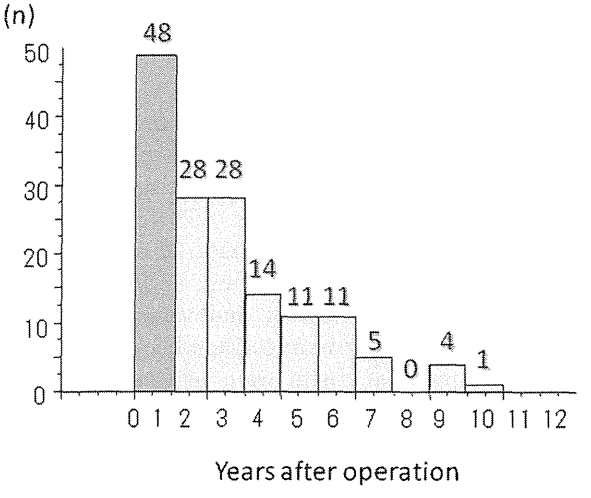

Figure 2 The number of patients who died of HCC recurrence or progression after hepatectomy. Of the 150 patients who died of HCC recurrence or progression, 48 patients (32.0%) died within 1 year after hepatectomy.

Table 2 Logistic regression analysis based on univariate analysis of the risk factors of death from cancer progression within 1 year after hepatectomy

Risk factor	*p*	Risk ratio	95% CI
AFP(ng/ml):>1,000(vs. ≤ 200)	0.0079	4.098	1.447-11.628
Tumor number 4 ≤ (vs. 1)	0.0208	3.535	1.206-10.361
Tumor size (cm) 5 ≤ (vs. 2–5)	0.0295	3.687	1.139-11.936
Differentiation poor (vs. moderately)	0.0179	2.8	1.194-6.565
vp1(vs. vp0)	0.0037	5.02	1.691-14.909
vp2(vs. vp0)	0.0034	8.507	2.029-35.667

AFP: alpha-fetoprotein.
vp0: no tumor thrombus in the portal vein.
vp1: tumor thrombus distal to the second branches of the portal vein.
vp2: tumor thrombus in the second branches of the portal vein.

Risk factors for early death

Independent, preoperatively evaluable risk factors for early death were identified by multivariate analysis as AFP > 1,000 ng/ml, tumor number ≥ 4, and tumor size ≥ 5 cm. The patients of group ED and NED ($n = 513$) were categorized into three levels of risk: risk 0 if they had no risk factors ($n = 276$), risk 1 if they had any one risk factor ($n = 151$), risk 2 if they had any two risk factors ($n = 71$), and risk 3 if they had all three risk factors ($n = 15$). In risk 0, 3 patients (1.1%), in risk 1, 12 patients (7.9%), in risk 2, and 24 patients (33.8%); in risk 3, 9 patients (60.0%) died within 1 year after hepatectomy ($p < 0.0001$) (Table 3). PS rates for risk 0, risk 1, risk 2, and risk 3 at 1 year were 98.9%, 91.7%, 66.1%, and 40.0%, respectively (Figure 3). Multivariate analysis showed that the risk ratio of risk 1 vs. risk 0 was 7.856, that of risk 2 vs. risk 0 was 46.468, and that of risk 3 vs. risk 0 was 136.5 (Table 3).

Discussion

When the patients were categorized by the number of independent, preoperatively evaluable risk factors, the

Table 3 Logistic regression analysis of three risk levels of death from cancer progression within 1 year after hepatectomy

	No. of patients	No. of ED (%)	Risk ratio	95% CI
Risk 0	276	3 (1.1)	1	
Risk 1	151	12 (7.9)	7.856	2.181-28.302
Risk 2	71	24 (33.8)	46.468	13.452-160.514
Risk 3	15	9 (60.0)	136.5	29.354-634.752

HCC: hepatocellular carcinoma.
ED: death due to HCC recurrence or progression within 1 year after hepatectomy.
Risk 0: they had no risk factors.
Risk 1: they had any 1 risk factor.
Risk 2: they had any 2 risk factors.
Risk 3: they had all 3 risk factors.
Risk factors: AFP > 1,000 ng/ml, tumor number ≥ 4, and tumor size ≥ 5 cm.

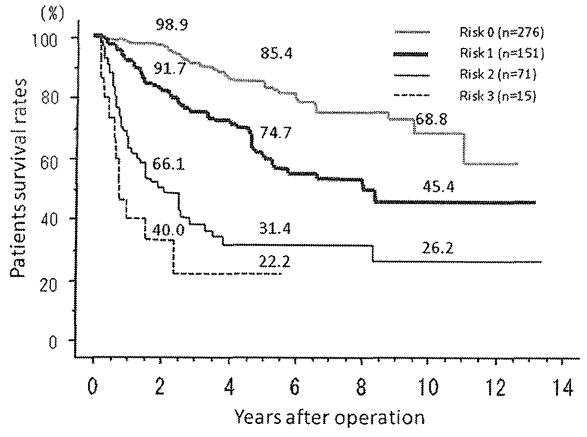

Figure 3 PS rates for risk 0, risk 1, risk 2, and risk 3 at 1 year were 98.9%, 91.7%, 66.1%, and 40.0%, respectively. PS rates for risk 0, risk 1, risk 2, and risk 3 at 1 year were 85.4%, 61.5%, 31.4%, and 22.2%, respectively.

early death rate within 1 year was 60.0% for patients with three risk factors: AFP > 1,000 ng/ml, tumor number ≥ 4, and tumor size ≥ 5 cm, while the early death rate was 1.1% for patients with no risk factors. Therefore, the appropriateness of hepatectomy for HCC should be carefully examined for patients who have large and multiple HCC with high AFP levels; these patients might be better treated with other therapeutic options, such as TACE or sorafenib.

Early recurrence is the main cause of early death within 1 year after hepatectomy. The risk factors for early recurrence are reported to be related to tumor cell dissemination due to tumor characteristics such as vascular invasion [6,7] and intrahepatic metastasis [8]. Because these factors are diagnosed only by postoperative pathological examination, preoperatively evaluable factors are necessary to decide the appropriateness of hepatectomy in advanced HCC. Among preoperative risk factors, an HCC tumor larger than 5 cm is reported to be an important indicator of a high risk of recurrence after resection [13] and has a higher incidence of intrahepatic metastasis and portal venous invasion [14,15]. Therefore, it is believed that an HCC tumor larger than 5 cm has high malignant potential. In this study and another report [11], tumor size ≥ 5 cm reflected this high malignant potential and was selected as an independent risk factor for early death due to HCC recurrence or progression within 1 year after hepatectomy.

Multivariate analysis also shows that tumor number is an important predictor of recurrence. Lai et al. [16] reported that the presence of multiple nodules was the most powerful predictor of both long-term survival and tumor recurrence. Because multiple HCC originates from disseminated cancer cells and not from multicentric carcinogenesis, multiple HCC is a more aggressive phenotype than solitary HCC. Yang reported that, after resection of solitary large HCC, the clinical and pathological characteristics and outcome are similar to those of small HCC, but are significantly better than those of nodular HCC (node number ≥ 2) [17]. It has also been reported that the expression levels of some human genes closely related to invasion and metastasis were significantly lower in solitary large HCC than in nodular HCC [17,18]. They proposed solitary large HCC as a specific subtype, less malignant than nodular HCC. Moreover, in multiple HCC, it was speculated that latent tumors, intrahepatic micrometastases that might be subsequently found to produce early recurrent tumors, could already be present in the remnant liver at the time of surgery. Therefore, tumor number ≥ 4 was selected in the current study as a significant factor predicting early death after hepatectomy.

In our study, multivariate analysis showed that an AFP level over 1,000 ng/ml was an independent factor related to early death. Previous reports have shown that AFP is an independent predictor of prognosis [19], even in patients who had undergone hepatectomy [20]. High levels of AFP in fully developed HCC or in the serum of the host are associated with more aggressive behavior and increased anaplasis [21]. On the other hand, it is well known that AFP levels may increase in some patients with acute and chronic hepatitis without HCC [22,23] and that elevation of AFP levels correlates with inflammation caused by background diseases and hepatocyte regeneration [24]. However, because the elevation of AFP levels by hepatitis or regeneration is usually not so high, only 200 ng/ml [25], AFP levels over 1,000 ng/ml might specifically indicate tumor malignancy. Yamanaka et al. [26] also reported that the serum AFP value per tumor diameter was the most significant risk factor for early death within 1 year after resection in patients with stage II–III HCC by multivariate analysis.

Given these preoperatively evaluable risk factors, the probability of early death after hepatectomy can be estimated by the number of risk factors. In risk 0, 3 patients (1.1%), in risk 1, 12 patients (7.9%), in risk 2, 24 patients (33.8%), and in risk 3, 9 patients (60.0%) died within 1 year after hepatectomy. The risk ratio of risk 1 vs. risk 0 was 7.856, that of risk 2 vs. risk 0 was 46.468, and that of risk 3 vs. risk 0 was 136.5 by multivariate analysis. PS rates for risk 3 at 1 year were 40.0%, while in the SHARP trial, survival rates at 1 year were 44% in the sorafenib group [12]. Moreover, Takayasu et al. reported that the survival rate at 1 year of patients with ≥ 4 tumors, ≥5.1 cm in diameter was 74% [27]. In this way, because the surgical outcome of patients with all three risk factors was worse than that of the patients treated with sorafenib or TACE, these patients might be better treated with other therapeutic options than hepatectomy for the first

line treatment. However, selected patients with risk 1 and 2 who might be beyond BCLC and Japanese algorithms should not be excluded from hepatectomy because of their good outcome: 91.7%, 66.1% at 1 year of PS.

On the other hand, in this study, macroscopic vascular invasion (portal and hepatic veins) was not indicated by multivariate analysis as an independent risk factor related to early death. It has been reported that the prognosis of patients with portal vein tumor thrombus (PVTT) in the main trunk or first branch is very poor; the median survival period of patients with portal thrombosis is only 2.7 months without appropriate treatment [28]. However, recently reported patients showed long-term survival rates when hepatectomy was combined with pre- or postoperative treatment. We reported the efficacy of a combination of hepatectomy and preoperative radiotherapy for PVTT in the main trunk or first branch. The 1-, 3-, and 5-year survival rates in hepatectomized patients with preoperative radiotherapy for PVTT were 100%, 53.3%, and 40.0%, respectively [29]. Minagawa [30] reported that the survival rate of patients with PVTT, including those who underwent hepatic resection with preoperative transcatheter arterial chemoembolization, was 42% at 5 years. Nagano [31] reported that 15 patients with HCC with PVTT were treated with FU arterial infusion and interferon therapy (FAIT) and surgery, and that all the patients (100%) survived over 1 year; without FAIT and surgery, 10 patients (67%) died within 1 year. Therefore, even if patients have HCC with macroscopic vascular invasion, particularly PVTT in the main trunk or first branch, hepatectomy is not contraindicated in these patients when combined with pre- or postoperative treatment. In the patients with risk 0, 1, of 45 patients 19 had macroscopic vascular invasion. Of these 19 patients, only 5 (26.3%) died within 1 year after hepatectomy. In the 26 patients with risk 2, 3, 15 patients (57.7%) died within 1 year after hepatectomy. Concerning Child-Pugh B cirrhosis, the high-risk patients could be also indentified. From these data, though macroscopic vascular invasion and Child-Pugh B cirrhosis were poor prognostic factors, the patients who had these factors did not always die in 1 year after hepatectomy. Using our risk levels, the patients with extremely poor prognosis could be identified from the patients who had poor prognostic factors such as macroscopic vascular invasion or Child-Pugh B. Therefore, concerning risk levels, risk 0 to 3 was very important and useful for predicting the prognosis of patients with HCC who underwent hepatectomy.

Conclusions

In conclusion, the appropriateness of hepatectomy in the treatment of HCC should be carefully considered when patients have the following preoperative risk factors: AFP > 1,000 ng/ml, tumor number ≥ 4, and/or tumor size ≥ 5 cm; these patients might be better treated with other therapeutic options, i.e., sorafenib and TACE. However, even if patients have HCC with PVTT in the main trunk or first branch, hepatectomy is not contraindicated when combined with pre- or postoperative treatment.

Abbreviations

HCC: Hepatocellular carcinoma; PS: Patient survival; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; AFP-L3: *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein-L3 fraction; PIVKA-II: Protein induced by vitamin K absence or antagonism factor II; US: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; TACE: Transcatheter arterial chemoembolization.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TK designed the research; TK, KN, and HY acquired of the data; TK, KN, HY, HK, TK, YT, ST, and AT analyzed the data; TK wrote the paper. All authors read and approved the final manuscript.

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Original Article

Clinical usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for patients with primary liver cancer with special reference to rare histological types, hepatocellular carcinoma with sarcomatous change and combined hepatocellular and cholangiocarcinoma

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Aim: The role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis and staging of primary liver cancer has been demonstrated in several reports. However, no preoperative evaluations of sarcomatous hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (cHCC-CC) with FDG-PET have been reported so far.

Methods: Fifty-three HCC patients and three cHCC-CC patients who received liver resection or living-donor liver transplantation were enrolled in this study. All 56 patients had undergone preoperative FDG-PET, and a total of 67 HCC and three cHCC-CC were analyzed histologically. The relationship between clinicopathological features and the maximum standardized uptake value (SUVmax) of tumors were evaluated.

Results: The detection rate of HCC by FDG-PET was 43.3 %, and the sensitivity of FDG-PET for the detection of HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion. All three cHCC-CC were detected by FDG-PET. The SUVmax values of the three sarcomatous HCC (SUVmax 14.1, 18.6 and 25.0) and the three cHCC-CC (SUVmax 9.9, 12.0 and 13.0) were higher than that of the poorly differentiated HCC (mean SUVmax 5.7 ± 2.3).

Conclusion: SUVmax may be a useful diagnostic tool for the preoperative evaluation of the aggressiveness of primary liver cancers such as sarcomatous HCC and cHCC-CC.

Key words: ^{18}F-fluorodeoxyglucose positron emission tomography, combined hepatocellular and cholangiocarcinoma, hepatocellular carcinoma, sarcomatous hepatocellular carcinoma

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) using ^{18}F-fluorodeoxyglucose (FDG) has become standard procedure for the detection of a variety of malignant tumors.[1] It is considered a useful diagnostic tool for tumor characterization and assessing therapy response.[2] For hepatocellular carcinoma (HCC), however, several reports suggest that the sensitivity of FDG-PET (50–55%) is insufficient.[3,4] Because the enzymatic activity of well-differentiated HCC cells is similar to that of the surrounding normal liver, the accumulation of FDG in these tumors is low, and the role of FDG-PET imaging in the early detection of HCC is limited.[5] On the other hand, previous studies have demonstrated that FDG accumulation is increased in undifferentiated HCC, and recently, preoperative FDG-PET has been shown to be closely associated with tumor differentiation and prognosis in HCC patients.[6,7]

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The histological differentiation grade is an important prognostic factor for HCC.[8] Once cancer is established, HCC dedifferentiates to a more malignant histology in a multistep fashion, from well- and moderately to poorly differentiated tumors.[9] Although the prognosis of well-differentiated HCC is good following resection, poorly differentiated HCC have a poor prognosis due to a high rate of vascular invasion and metastasis.[10,11] The basic histological pattern of HCC is trabecular; however, a sarcomatous appearance has been sporadically reported as one of the histological features of HCC.[12] Approximately 1.8% of all resected HCC have a sarcomatous feature, usually associated with a very poor prognosis because of its rapid growth, low resectability and frequent recurrence after resection.[13,14]

Combined hepatocellular and cholangiocarcinoma (cHCC-CC) is a rare primary liver cancer that contains the histological features of both HCC and CC.[15] cHCC-CC has been reported to show frequent vascular invasion and lymph nodes metastasis, and has a poorer prognosis than HCC.[16,17] It is difficult for patients with cHCC-CC to get a correct preoperative diagnosis because of the lack of a sensitive diagnosis procedure.[18]

Although previous studies have shown that FDG-PET is useful for evaluating various liver tumors, there have been no reports regarding preoperative FDG uptake in resectable sarcomatous HCC and cHCC-CC. In the present study, we retrospectively investigated the feasibility of FDG-PET for the detection of different types of primary liver cancer including sarcomatous HCC and cHCC-CC.

METHODS

Patients

IN THIS STUDY, we retrospectively reviewed 53 HCC patients and three cHCC-CC patients who received liver resection (LR) or living-donor liver transplantation (LDLT) at Kyushu University Hospital between April 2010 and August 2011. There were 35 male and 21 female patients, and the mean age (± standard deviation [SD]) of the patients was 65 ± 12 years (range, 36–87). All 56 patients were diagnosed as having HCC or cHCC-CC by conventional radiologic imaging and FDG PET/computed tomography (CT). Thirteen patients with HCC in cirrhosis underwent LDLT, and the other 43 patients with HCC or cHCC-CC underwent LR. Among the HCC patients, 29 had a single lesion, and the other 24 had multiple lesions. Among the cHCC-CC patients, one had a single lesion and the other two had multiple lesions.

Patient follow up

After discharge, all patients were examined for recurrence by ultrasound and by tumor markers every 1–3 months. Dynamic CT was performed every 6 months. Patients with any sign of recurrence and/or inconclusive imaging studies underwent additional FDG PET/CT. All of the patients were followed up while they were alive.

FDG PET/CT

^{18}F-Fluorodeoxyglucose positron emission tomography studies were performed with Discovery ST Elite (GE Healthcare, Milwaukee, WI, USA) and Biograph mCT (Siemens AG, Erlangen, Germany) PET/CT scanners. All patients fasted for at least 4 h before FDG administration, and 185 MBq of FDG was i.v. administrated to each patient. Approximately 60 min after the FDG injection, whole-body PET images were acquired from thigh to head with 7–10 bed positions. The Discovery ST Elite scanner consists of a 16-slice multidetector CT and bismuth germanium oxide crystal. The unenhanced CT was performed first with the following parameters: 5-mm slice thickness, 120 kV, 30–250 mAs with auto mode (Smart mA). Then, PET images were obtained in 3-D mode for 3 min per bed position with a 3.27-mm slice thickness, at 70 cm field of view (FOV) in a 128 × 128 matrix. Based on the CT data, transmission maps were created and used for the attenuation correction of the PET images. The PET data were reconstructed using a 3-D ordered subset expectation maximization (3D-OSEM) algorithm (VUE Point Plus) with two iterations and 28 ordered subsets. A 6-mm post-filter of full-width at half maximum (FWHM) was applied. The Biograph mCT scanner is equipped with a 128-slice multidetector CT and lutetium crystal. The unenhanced CT was performed at 120 kV with automatic mAs adjustment (Care Dose 4D) and the slice thickness was 3 mm. The PET emission time was 2 min per bed position. The PET images were acquired with a 2-mm slice thickness, at 70 cm FOV in a 256 × 256 matrix. The concomitant CT data were used for attenuation correction. The PET data were reconstructed using a 3D-OSEM algorithm with two iterations and 21 subsets. Time of flight and point spread function techniques were also used for the image reconstruction (ultra-HD-PET). A 3-D Gaussian filter of 6-mm FWHM was applied. The PET images were qualitatively evaluated to assess whether the FDG uptake in the tumor was (PET positive status) or was not

(PET negative status) significantly higher than in the surrounding non-cancerous hepatic parenchyma.

Histopathological study

A total of 67 HCC and three cHCC-CC were evaluated histologically. Formalin-fixed specimens were embedded in paraffin. Deparaffinized 4-μm sections were stained with hematoxylin–eosin for microscopic evaluation. The histopathological definition of HCC and the criteria for cHCC-CC were based on the classification proposed by the World Health Organization. The cHCC-CC contain unequivocal hepatocellular and cholangiocellular components that are intimately admixed. The HCC displayed a trabecular pattern with little stroma, a pseudoglandular pattern with or without bile production, abundant eosinophilic cytoplasm, and immunoreactivity for Hep par 1. The CC was defined by a definite glandular pattern with fibrous stroma, low columnar cells with round vesicular nuclei, mucin production confirmed by Alcian blue, and immunoreactivity for cytokeratin 19 but not Hep par 1.

Statistical analysis

All statistical analyses were performed using the StatView ver. 5.0 software package. Continuous variables were compared using the Mann–Whitney *U*-test or Student's *t*-test. The χ^2-test was used for categorical variables. The differences were considered to be significant if $P < 0.05$.

RESULTS

Patients with HCC

PATIENT CHARACTERISTICS ARE summarized in Table 1(a). The mean age (± SD) was 66 ± 12 years (range, 36–87), and the sex ratio (M : F) was 32:21. Thirty-two patients (60.4%) were seropositive for hepatitis C virus, 11 for hepatitis B surface antigen (20.8%) and 10 (18.8%) had non-B/non-C etiologies. Twelve of the 53 patients had a serum α-fetoprotein (AFP) level of more than 100 ng/mL (median, 11.8; range, 1.6–994 600) and 24 patients had a serum des-γ-carboxy prothrombin (DCP) level above 100 mAU/mL (median, 81; range, 10–109 730). Twenty-nine patients with solitary tumors were divided into two groups: PET positive ($n = 16$) and PET negative ($n = 13$). Although there was no significant difference in serum AFP levels between the PET positive and negative groups (110.2 ± 196.9 and 132.9 ± 372.7 ng/mL, respectively), the PET positive group had higher serum

Table 1 Characteristics of patients with HCC and clinicopathological data of HCC

a. Characteristics of patients with HCC

Characteristic	No. of patients (%)
Total number of patients	53
Age (years)	
Mean (range)	66 (36–87)
Sex	
Male : female	32 (60.4):21 (39.6)
Etiology of liver disease	
Hepatitis B	11 (20.8)
Hepatitis C	32 (60.4)
Other	10 (18.8)
Child–Pugh classification	
A	40 (75.5)
B	6 (11.3)
C	7 (13.2)
Tumor stage (UICC)	
I	21 (39.6)
II	25 (47.2)
III	5 (9.4)
IV	2 (3.8)
Type of hepatic surgery	
Resection	40 (75.5)
Liver transplantation	13 (24.5)
Tumor number	
Solitary	29 (54.7)
Multiple	24 (45.3)
Preoperative serum AFP (ng/mL)	
Median (range)	11.8 (1.6–99 4600)
Preoperative serum DCP (mAU/mL)	
Median (range)	81 (10–109 730)

b. Clinicopathological data of HCC

Characteristic	No. of HCC (%)
Total number of nodules	67
Tumor differentiation	
Well	7 (10.4)
Moderately	47 (70.1)
Poorly	9 (13.4)
Undifferentiated	1 (1.5)
Moderately with sarcomatous change	1 (1.5)
Poorly with sarcomatous change	2 (3.0)
Tumor size (cm)	
Mean ± SD	3.4 ± 3.4
Microvascular invasion	16 (23.9)

AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HCC, hepatocellular carcinoma; SD, standard deviation; UICC, Union for International Cancer Control.

Table 2 Association between PET status and clinicopathological data of HCC

Characteristic	PET negative ($n = 38$)	PET positive ($n = 29$)	*P*-value
Tumor differentiation (%)			<0.05
Well	7 (100)	0 (0)	
Moderately	31 (66)	16 (34)	
Poorly	0 (0)	9 (100)	
Undifferentiated	0 (0)	1 (100)	
Moderately with sarcomatous change	0 (0)	1 (100)	
Poorly with sarcomatous change	0 (0)	2 (100)	
Tumor size (cm)			
Mean ± SD	2.1 ± 1.5	5.1 ± 4.3	<0.05
Microvascular invasion (%)	4 (11)	12 (41)	<0.05

HCC, hepatocellular carcinoma; PET, positron emission tomography; SD, standard deviation; UICC, Union for International Cancer Control.

DCP levels than the PET negative group (529.6 ± 748.3 and 54.2 ± 50.7 mAU/mL, respectively; $P < 0.05$) (± SD). Using the modified Union for International Cancer Control staging system, we enrolled 21 (39.6%) stage I patients, 25 (47.2%) stage II patients, five (9.4%) stage III patients and two (3.8%) stage IV patients.

The characteristics of HCC are summarized in Table 1(b). The histological grades were well differentiated in seven HCC (10.4%), moderately differentiated in 47 (70.1%), poorly differentiated in nine (13.4%), undifferentiated in one (1.5%), moderately differentiated with sarcomatous change in one (1.5%) and poorly differentiated with sarcomatous change in two (3.0%). Mean tumor size (± SD) was 3.4 ± 3.4 cm, and microvascular invasion was observed in 16 HCC (23.9%). The detection rate of HCC by PET was 43.3%. The sensitivity of PET for the detection of HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion (Table 2). None of the seven well-differentiated HCC were detected by PET. The mean maximum standardized uptake value (SUVmax) (± SD) was 4.7 ± 1.3 in moderately differentiated HCC with positive PET findings, 5.7 ± 2.3 in poorly differentiated HCC and 26.2 in undifferentiated HCC. One poorly differentiated HCC with a maximum diameter of 17.0 cm, direct invasion to the stomach, and lymph node and pulmonary metastases, had a high SUVmax of 11.3. Moderately differentiated HCC with sarcomatous change had a high SUVmax of 18.6, and poorly differentiated HCC with sarcomatous change also showed high FDG uptake (SUVmax 14.1 and 25.0) (Fig. 1). One poorly differentiated HCC with sarcomatous change had a high SUVmax of 14.1 despite the small size of the tumor (1.6 cm) and absence of microvascular invasion (Fig. 2). The patients with poorly differentiated HCC with sarcomatous change developed recurrences soon after surgery. One patient with an SUVmax of 14.1 had metastasis to the mediastinal lymph nodes 9 months after surgery, and another with an SUVmax of 25.0 developed intrahepatic metastasis 44 days after surgery.

Patients with cHCC-CC

Patient characteristics are summarized in Table 3. All three cHCC-CC were detected by PET and the SUVmax

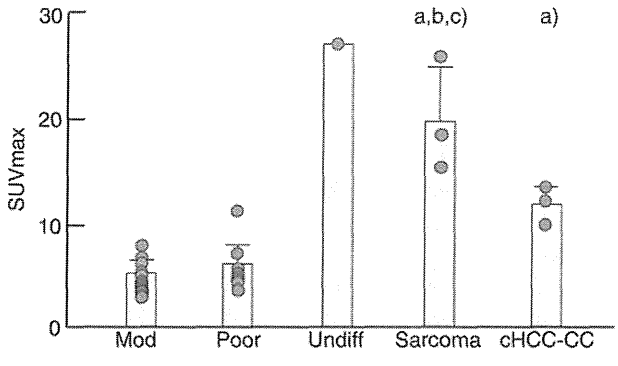

Figure 1 Maximum standardized uptake value (SUVmax) values of hepatocellular carcinoma (HCC) and combined hepatocellular and cholangiocarcinoma (cHCC-CC) with positive positron emission tomography (PET) findings. Undifferentiated HCC, moderately or poorly differentiated HCC with sarcomatous change, and cHCC-CC have high SUVmax values (>9.9), respectively. Data are expressed as mean ± standard deviation. (a) $P < 0.05$ vs mod; (b) $P < 0.05$ vs poor; (c) $P < 0.05$ vs cHCC-CC. Mod, moderately differentiated HCC; poor, poorly differentiated HCC; undiff, undifferentiated HCC; sarcoma, moderately or poorly differentiated HCC with sarcomatous change.

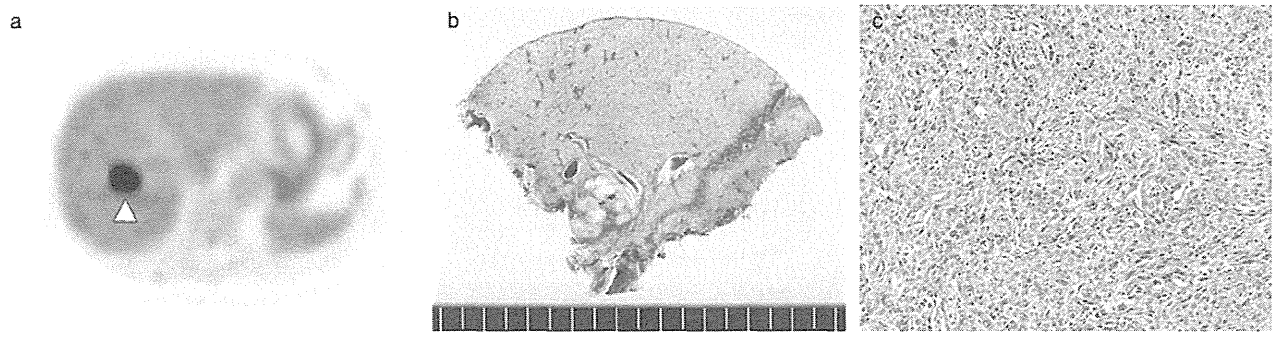

Figure 2 A 74-year-old female patient with poorly differentiated hepatocellular carcinoma (HCC) with sarcomatous change. (a) ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 14.1 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of poorly differentiated HCC with sarcomatous change (hematoxylin–eosin, original magnification ×100).

of cHCC-CC was 9.9, 12.0 and 13.0 (Fig. 1). One cHCC-CC had a high FDG uptake (SUVmax 12.0) despite the small size of the tumor (2.2 cm) and low levels of tumor markers (patient no. 1) (Fig. 3).

DISCUSSION

THE ROLE OF FDG PET/CT in the diagnosis and staging of HCC and other forms of liver cancer has been demonstrated in several reports.[6,7,19] However, preoperative evaluation of sarcomatous HCC and cHCC-CC with FDG PET/CT has not been reported so far. In the present study, we showed that sarcomatous HCC and cHCC-CC could be detected by PET/CT with high FDG uptake, and positive preoperative FDG uptake in HCC was significantly associated with tumor differentiation, tumor size and microvascular invasion.

Recently, several studies have shown that FDG-PET is useful for predicting tumor characterization, clinical outcome and prognosis in patients with HCC. Well-differentiated HCC regions were reported to show a tendency toward negativity by PET, whereas poorly differentiated types show increased FDG accumulation.[6,7] Our data also demonstrate that well-differentiated and some moderately differentiated HCC do not show FDG uptake exceeding that of the surrounding normal liver, whereas poorly differentiated and undifferentiated HCC have positive PET findings. There was no significant difference between the mean SUVmax of poorly differentiated HCC and that of moderately differentiated HCC with positive PET findings. On the other hand, the SUVmax of sarcomatous HCC were 18.6, 14.1 and 25.0, much higher than that of poorly differentiated HCC.

Table 3 Characteristics of patients with cHCC-CC

Characteristic	Patient no. 1	Patient no. 2	Patient no. 3
Age (years)/sex	78/M	54/M	47/M
Viral infection	HBsAg positive	Negative	HCVAb positive
Maximal tumor size (cm)	2.2	12.3	4.0
Microvascular invasion	Positive	Positive	Positive
Tumor stage (UICC)	II	IV	III
AFP (ng/mL)	4.3	16.4	18 286
DCP (mAU/mL)	20	45	231
CEA (ng/mL)	1.7	0.5	2.8
CA19-9 (U/mL)	7.4	76.6	31.9
Maximum SUV	12.0	9.9	13.0

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCVAb, anti-hepatitis C virus antibody; SUV, standardized uptake value; UICC, Union for International Cancer Control.

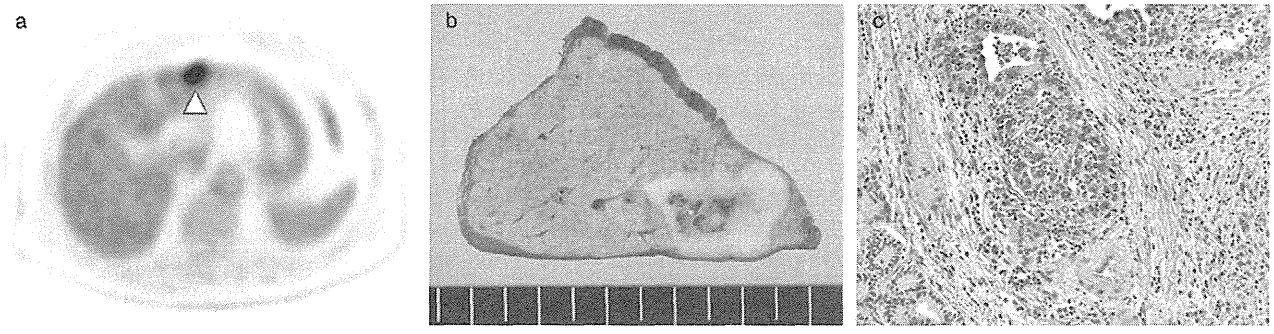

Figure 3 A 78-year-old male patient with combined hepatocellular and cholangiocarcinoma (cHCC-CC). (a) ^{8}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) image shows a liver mass with a maximum standardized uptake value (SUVmax) of 12.0 (arrow head). (b) Macroscopic image of the liver mass. (c) The liver tumor demonstrates histological features of cHCC-CC with microvascular invasion (hematoxylin–eosin, original magnification ×100).

Sarcomatous HCC is a rare histological variant of HCC.[13] Although the pathogenesis of sarcomatous HCC has not been clarified, the sarcomatous components are thought to be derived from a dedifferentiation or anaplasia, rather than from a combination of HCC and sarcoma.[13,20] Previous reports have suggested that anticancer therapy has an influence on the development of sarcomatous features in HCC, and the prognosis of patients with sarcomatous HCC is very poor due to frequent widespread metastases.[13,14,21] Although we performed curative resection for primary sarcomatous HCC, two of the three patients developed recurrences soon after surgery. Honda *et al.* reported that sarcomatous HCC appears as an irregularly demarcated intrahepatic mass with delayed or prolonged peripheral enhancement on CT.[22] However, it seemed to be difficult to make a correct preoperative diagnosis of sarcomatous changes by imaging or serological tumor markers. Our results show that FDG-PET may be a useful diagnostic tool for sarcomatous changes of HCC because the high FDG uptake of sarcomatous HCC seems to be related to its progression or aggressiveness.

In the present study, the SUVmax values of three cHCC-CC were higher than those of the poorly differentiated HCC. cHCC-CC is an uncommon subtype of primary liver cancer that contains elements of both HCC and CC.[15] Several studies have reported that the prognosis of patients with cHCC-CC was worse than that of patients with HCC because of frequent portal venous invasion and metastasis to lymph nodes and other organs.[16,17] Vascular invasion, tumor size and tumor stage were found to be prognostic factors for poor outcome in patients with cHCC-CC.[16,23] Moreover, recent studies have demonstrated that a large CC component in cHCC-CC and a high serum carbohydrate antigen 19-9 (CA19-9) level were also associated with poorer survival rates.[24,25] We demonstrated that one cHCC-CC showed high FDG uptake (SUVmax 12.0) despite the low CA19-9 level (7.4 U/mL) and small size of the tumor (2.2 cm) (patient no. 1). In addition, another cHCC-CC showed high FDG uptake (SUVmax 13.0) despite the small CC component in the tumor (1%) (patient no. 3) (data not shown). If the degree of FDG uptake in cHCC-CC also reflects the aggressiveness of the tumor like other malignant tumors, FDG-PET may become a useful diagnostic tool for the preoperative evaluation of cHCC-CC.

Our data show that the SUVmax of sarcomatous HCC and cHCC-CC are much higher than those of liver cancers reported to be associated with poor prognosis in previous studies. Seo *et al.* have demonstrated that high FDG uptake (SUVmax ≥5.0) was a predictive factor of postoperative early recurrence and poor survival in patients with HCC.[7] Riedl *et al.* have also reported that an SUVmax of 5.0 or greater was correlated with worse long-term prognosis after liver resection for colorectal metastases.[26]

In summary, our studies demonstrate that FDG-PET shows high FDG uptake in sarcomatous HCC and cHCC-CC that have been reported to be associated with poor prognosis after surgery. Therefore, FDG-PET may be an effective diagnostic tool for the non-invasive evaluation of the aggressiveness of primary liver cancer before surgical resection and liver transplantation. Further clinical studies are warranted.

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