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ORIGINAL ARTICLE

Long-term outcomes of living-donor liver transplantation, hepatic resection, and local therapy for hepatocellular carcinoma with three <3-cm nodules in a single institute

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Abstract

Background and Aim: Treatment for small hepatocellular carcinoma (HCC) is determined based on the results of a liver function test and the tumor location and spread. The present study compared the outcomes among local therapy, hepatic resection (HR), and living-donor liver transplantation (LDLT) for small HCC in a single institute.
Methods: We compared the overall survival, recurrence-free survival, and cancer-specific survival rates in patients with three HCC nodules <3 cm in size among local therapy, which included radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transarterial chemoembolization (TACE), and surgical treatment (HR and LDLT).
Results: One hundred and ninety-seven patients with local therapy (109 RFA, 26 PEI, and 78 TACE), 107 with HR, and 66 with LDLT were enrolled in this study. There was no significant difference in OS among these groups. The recurrence-free, cancer-specific survival (CSS) of LDLT was superior to local therapy and HR. The prognostic factors for the survival were Child–Pugh (CP) Grade B and tumor marker for local therapy and multiple tumors and elevated ALT levels for HR.
Conclusions: For CP grade B patients with HCC of three <3-cm nodule, LDLT could be considered because it resulted in better survival and CSS rates than local therapy.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of death worldwide.[1] Treatment for HCC is considered based on the liver function, background cause of liver disease, and tumor size and location in each patient. The Barcelona clinic liver cancer group described the appropriate treatments for small HCC according to various situations. In the preserved liver function group, for example, hepatic resection (HR) for single HCC was recommended, unless the patient had portal hypertension (according to the hepatic venous pressure gradient). Liver transplantation or radiofrequency ablation (RFA) was recommended for patients with three nodules <3 cm in size who had portal hypertension.[2] However, compared with Western countries, HR and local therapy (transarterial chemoembolization

[TACE], RFA, and percutaneous ethanol injection [PEI]) are recommended in Japan for single HCC and HCC with three nodules <3 cm in size in patients with liver damage A and B. Furthermore, liver transplantation (LT) is recommended in patients with liver damage C with one nodule <5 cm in size or <3 nodules <3 cm in size.[3]

LT is a radical treatment typically performed for end-stage liver disease and HCC. In 1996, Mazzafero reported better results after LT in HCC patients with one nodule <5 cm in size or <3 nodules <3 cm in size, criteria now known as the "Milan criteria."[4] As donor organs are scarce around the world, living-donor liver transplantation (LDLT) has been recognized as a viable alternative not only in Western countries but also in Asia, especially Japan. Therefore, treatment for small HCC is now decided by the age, tumor size, location, number, liver function, and presence of portal hypertension.

The present study clarified the outcomes of local therapy (RFA, TACE, PEI), HR, and living-donor LT (LDLT) in patients with small HCC with <3 nodules <3 cm in size.

Patients and methods

A total of 366 patients enrolled in this retrospective cohort study conducted from January 2000 to December 2013 at Nagasaki University Hospital. The treatment procedure and patient selection for each treatment were determined by periodic conferences in our hospital, where a hepatologist, liver surgeon, and radiologist discussed each patient. The diagnosis of HCC was made by multiple modalities, including ultrasound (US), multi-detector computed tomography (MD-CT), and superparamagnetic iron oxide-magnetic resonance imaging (SPIO-MRI) before 2008, with gadoxetic acid-enhanced MRI (Gd-EOB-MRI) being performed after 2008. The imaging and diagnostic methods have previously been described.[5]

Diagnosis of HCC by imaging. Images were diagnosed by an experienced radiologist before LT. HCC was diagnosed if the following two imaging characteristics were identified: (i) clear nodule enhancement during the hepatic arterial phase on MD-CT, SPIO-MRI, and Gd-EOB-MRI; or (ii) washout of the nodule during the portal venous phase on MD-CT, showing a hyperintense signal compared with the surrounding liver that decreased following the uptake of iron to the normal liver parenchyma on SPIO-MRI and was hypointense relative to the surrounding liver during the hepatobiliary phase on EOB-MRI.

Local therapy, HR, and LDLT. The indication of local therapy, HR, and LDLT was determined by HCC treatment algorithm[3] and by the indocyanine green retention rate at 15 min (ICGR15) and liver scintigraphy findings using Tc-99.[6] Before 2010, treatments were decided by a hepatologist and liver surgeon. From 2010 onward, a conference for liver cancers was held in our hospital. The approach to HCC treatment was then discussed in this meeting among hepatologists, radiologists, and liver surgeons. The indication of LDLT was determined by a multidisciplinary committee consisting of a hepatologist, radiologist, infectious control specialist, and hematologist. The HR and LDLT procedures have previously been described.[7–9]

Ethical standards: This study has been approved by the appropriate ethics committee, whose numbers are 19102143 and 20 012 022, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was a retrospective human study that did not need informed consent from each patient. We disclose this retrospective study on the website of our hospital. This study was not registered for any research registration system.

Analyses. To clarify the clinical factors of local therapy, HR, and LDLT, we compared the preoperative clinical data, including age, sex, virus status, Child–Pugh (CP) grade, prothrombin time (PT) (%), serum level of albumin (Alb) (g/dL), serum level of total bilirubin (T.Bil) (mg/dL), platelet count ($\times 10^4$/mm^3), serum level of aspartate aminotransferase(AST)(U/L), serum level of alanine aminotransferase (ALT) (U/L), serum level of alpha-fetoprotein (AFP) (ng/mL), and serum level of des-gamma-carboxy prothrombin (DCP) (PIVKA-II in Japan) (mAU/mL). We also analyzed the clinical factors by the Mann–Whitney *U*-test and chi-square test.

The patient survival was analyzed from the day of treatment to the most recent follow-up. Recurrence was analyzed from the day of treatment to the day on which HCC recurrence was identified by CT or MRI. The cancer-specific survival (CSS) was defined from the day of treatment to the date of death related to cancer, except in cases of liver failure without recurrence of HCC by imaging.

The overall survival (OS), recurrence-free survival (RFS), and CSS rates were assessed with the Kaplan–Meier method and compared using the log-rank test. The multivariate analyses of prognostic factors were performed and included the Cox proportional hazard model for the survival and recurrence after the univariate analyses, with variables identified as significant based on a *P*-value <0.1 in univariate analyses. The findings in the multivariate analyses were considered statistically significant when the *P*-values were <0.05. Statistical analyses were performed using the SPSS Version 24.0 software package (Tokyo, Japan).

Results

Patients' characteristics. The characteristics of each group are described in Table 1. The local therapy group was older than the LDLT group and more frequently had hepatitis C (HCV) and a worse liver function. The median values (range) of each parameter were as follows: platelet count 9.7 $\times$ 10^4/mm^3 (1.9–45), PT 79% (14–122%), AST 55 U/L (15–361), ALT 43 U/L (8–232), T.Bil 1.0 mg/dL (0.3–11.4), and Alb 3.6 g/dL (2–4.9) in the local therapy group; and platelet count 12.49.7 $\times$ 10^4/mm^3 (4.7–28.5), PT 86% (62–115%), AST 35 U/L (15–177), ALT 32 U/L (7–167), T.Bil 0.8 mg/dL (0.4–4.2), Alb 4.1 g/dL (0.6–5.2), ICGR15 17.0% (2.0–45.0), pathological microvascular invasion rate 19.6% (n = 21), and liver fibrosis (f4) rate 36.4% (n = 39) in the HR group. There were no significant differences in the levels of tumor markers (AFP, DCP) among the groups. The proportion of solitary HCC was 72% for local therapy, 75% for HR, and 39% for LDLT, with the LDLT proportion being significantly less than that for local therapy. The median CP score was 6 in the local therapy

Table 1 Clinical characteristics of the local therapy, HR, and LDLT groups

	Local therapy ($n = 197$)	HR ($n = 107$)	LDLT ($n = 66$)	*P*
Age	72.1 (41–92)	68 (34–84)	58.5 (33–72)	<0.01
Gender	M: 122, F: 75	M:85, F: 22	M: 44, F: 22	<0.01
Etiology	HBV 27 (14%)	HBC 33 (31%)	HBV 17 (25%)	<0.01
	HCV 135 (68%)	HCV 40 (37%)	HCV 39 (60%)	
	NBNC 35 (18%)	B+C 1 (1%)	B+C 1(1%)	
		NBNC 33 (31%)	NBNC 5 (8%)	
			PBC 4 (6%)	
AFP (ng/dL)	11(1–2184)	8.7 (0.3–5543)	19 0(0.8–1569)	N.S.
DCP (mAU/mL)	31 (4–7840)	30 (10–5158)	45 (6–4953)	N.S.
Solitary tumor (%)	72	78.5	39	<0.01
Child–Pugh	A 134 (68%)	A 101 (94%)	A 5 (8%)	<0.01
	B 57 (29%)	B 6 (6%)	B 18 (45%)	
	C 6 (3%)		C 23 (47%)	
Child–Pugh score	6 (5–11)	5 (5–7)	9 (6–14)	<0.01

AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HR, hepatic resection; LDLT, living-donor liver transplantation.

group, 5 in the HR group, and 9 in the LDLT group. The procedures for HCC in the local therapy group were RFA in 109, TACE in 78, and PEI in 26, with some duplicates included.

The patient OS, RFS, and CSS rates. The median follow-up in each group was 37.2 months (0.2–219) in the local therapy group, 85.9 months (8.1–183) in the HR group, and 94.7 months (0.5–187) in the LDLT group. The 1-, 3-, 5-, 7-, and 10-year OS rates were 95.4, 81.3, 65.9, 52.9, and 44.5% in patients who received local therapy; 98.1, 85.7, 78.5, 69.2, and 47.6% in those who received HR; and 83.3, 72.7, 66.6, 66.6, and 62.3% in those who received LDLT, respectively (not significant).

The causes of death in the local therapy group were HCC recurrence in 38 (60.3%), liver failure in 12 (19.1%), and other disease in 13 (20.6%). The causes of death in the HR group were HCC recurrence in 30 (63.8%), liver failure in 3 (6.4%), and other disease in 15 (29.8%). The causes of death in the LDLT group were graft failure in 10 (44%), liver dysfunction due to HCV recurrence in 4 (16%), bacterial, fungal infection after LDLT in 3 (12%), HCC recurrence in 2 (6%), secondary cirrhosis due to biliary complications in 2 (6%), post-transplant lymphatic disease (PTLD) in 2 (6%), and other diseases in 2 (6%). There were significant differences in the 1-, 3-, 5-, 7-, and 10-year RFS rates among the groups (local therapy: 79.3, 45.3, 30.1, 22.7, and 11.7%; HR: 83.1, 61.1, 45.8, 42.1, and 32.7%; and LDLT: 98.2, 96.3, 94.2, 94.2, and 94.2%, respectively ($P < 0.01$; Fig. 1b). The 1-, 3-, 5-, 7-, and 10-year CSS rates were 97.3, 86.9, 77.3, 67.8, and 63.2% in patients receiving local therapy; 99.1, 92.0, 87.7, 78.9, and 60.5% in those receiving HR'; and 100, 96.2, 96.2, 96.2, and 96.2% in those receiving LDLT, showing significant differences among the groups (Fig. 1c).

The comparison of the OS, RFS, and CSS rates in patients with CP grades B and C. With respect to the liver function, the 1-, 3-, and 5-year OS rates were 92.2, 72.5, and 47.4% in patients receiving local therapy and 90.0, 80.0, and 73.3% in patients receiving LDLT, respectively, showing significant differences between these groups in patients with CP grade B (Fig. 2a). The 1-, 3-, and 5-year RFS rates were 72.1, 42.7, and 34.0% in patients receiving local therapy and 100, 100, and 95.7% in patients receiving LDLT, respectively, also showing significant differences between these groups (Fig. 2b). The 1-, 3-, and 5-year CSS rates were 97.9, 83.3, and 61.7% in patients receiving local therapy and 100, 100, and 100% in patients receiving LDLT, again showing significant differences between these groups (Fig. 2c).

The 1-, 3-, and 5-year OS rates were 25.0, 25.0, and 0% in patients receiving local therapy ($n = 6$) and 74.2, 64.5, and 61.3% in patients receiving LDLT ($n = 31$), respectively, showing significant differences between these groups in patients with CP grade C.

Uni- and multivariate analyses for the survival and recurrence in patients receiving local therapy. Table 2 shows the prognostic factors for the OS identified in the multivariate analysis. The univariate analysis identified CP grade B, AFP ≥10 ng/mL, and DCP ≥40 mAU/mL as significant prognostic factors for the OS in patients receiving local therapy. A multivariate analysis based on the variables with significance in the univariate analysis revealed that CP grade B (hazard ratio [HR]: 2.27), DCP ≥40 mAU/mL (HR: 2.393), and AFP ≥10 ng/mL (HR: 1.765) after local therapy were independent prognostic factors for the OS.

Table 3 shows the prognostic factors for recurrence identified in the multivariate analysis. A multivariate analysis based on the variables with significance in the univariate analysis revealed that male gender (HR: 1.754), AFP ≥10 ng/mL (HR: 1.716), and multiple tumors (2 or 3) (HR: 1.615) after local therapy were independent prognostic factors for recurrence.

Uni- and multivariate analyses for the survival and recurrence in patients receiving HR. Tables 4 and 5 show the prognostic factors for the survival and recurrence identified in the uni- and multivariate analyses. The univariate analysis identified multiple tumors (2 or 3) and ALT ≥40 U/L as significant prognostic factors for the OS in patients receiving

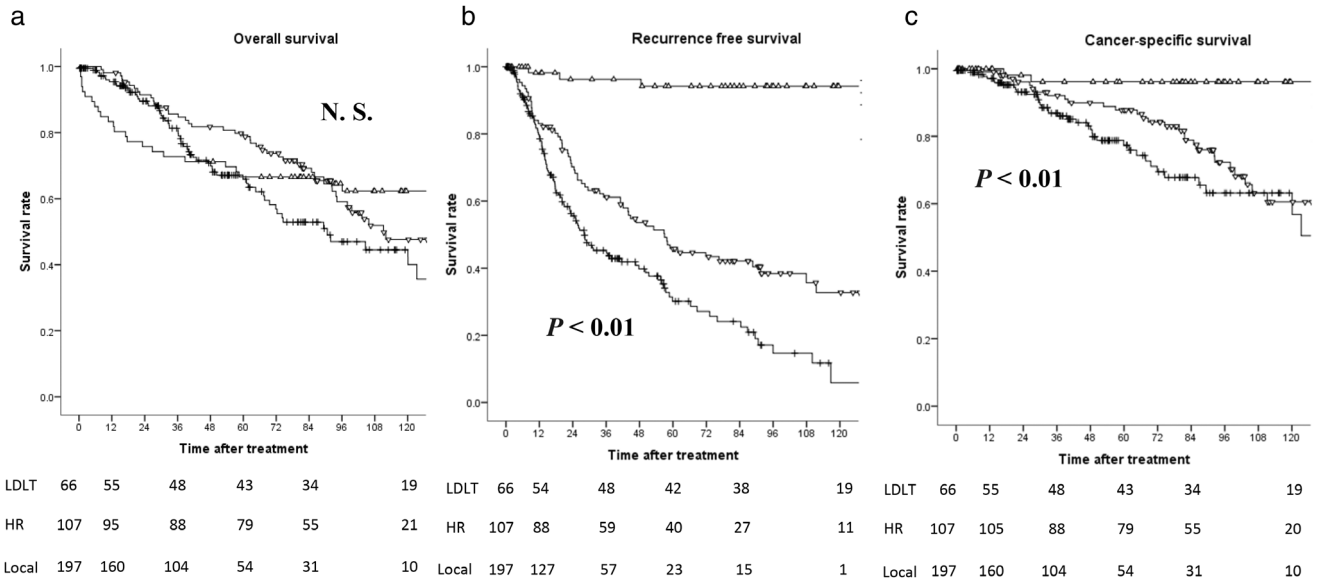

Figure 1 (a) Comparison of the overall survival rate (N.S.). △, LDLT; ▽, HR; +, local. (b) Comparison of the recurrence-free survival rate ($P < 0.01$). △, LDLT; ▽, HR; +, local. (c) Comparison of the cancer-specific survival rate ($P < 0.01$) of hepatocellular carcinoma patients with three <3-cm nodules among local therapy, hepatic resection (HR), and living-donor liver transplantation (LDLT). △, LDLT; ▽, HR; +, local.

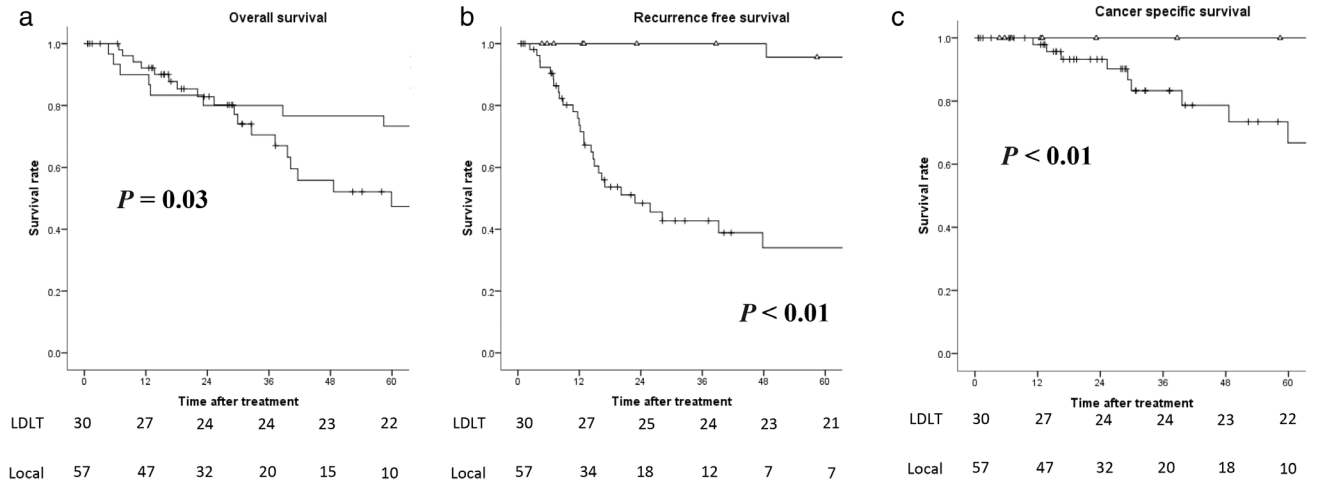

Figure 2 (a) Comparison of the overall survival rate ($P = 0.03$). △, LDLT; +, local. (b) comparison of the recurrence-free survival rate ($P < 0.01$). △, LDLT; +, local. (c) comparison of the cancer-specific survival rate ($P < 0.01$) of hepatocellular carcinoma patients with three <3-cm nodules between local therapy and living-donor liver transplantation (LDLT) in Child–Pugh grade B. △, LDLT; +, local.

Table 2 Results of multivariate Cox proportional hazard analyses of the prognostic factors for overall survival after local therapy

Variable	Category	Hazard ratio	*P*
Child–Pugh Class	B	2.27 (1.340–3.868)	0.002
DCP (mAU/mL)	≥40	2.393 (1.398–4.096)	0.001
AFP (ng/dL)	≥10	1.765 (1.030–3.023)	0.039

AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

HR. A multivariable analysis based on the variables with significance in the univariate analysis revealed that multiple tumors (HR: 3.454) and ALT ≥40 U/L (HR: 1.777) were independent prognostic factors for the OS after HR (Table 4).

The univariate analysis identified HBV, HCV, ALT >40 U/L, ICGR15 >15%, and multiple tumors (2 or 3) as significant prognostic factors for recurrence in patients receiving HR. A multivariable analysis based on the variables with significance in the univariate analysis revealed that HBV (HR: 0.435) and

multiple tumors (HR: 5.214) were independent prognostic factors for recurrence after HR (Table 5).

Discussion

As the guidelines for HCC treatment differ between Western and Eastern countries, the treatment strategy for HCC and guidelines are reported by each region.[3,10–13] Small HCC with portal hypertension (PHT) is included as an indication for cadaveric LT in Western countries. However, Ishizawa *et al*. reported that multiple HCC and PHT were not a contraindication for HR in Japan.[14]

We previously reported on the influence of the portal venous pressure (PVP) measured directly during surgery on the long-term outcome of HCC patients after HR. We found that the outcome was significantly worse in cases with a PVP ≥20 cmH_2O by direct measurement than in cases with a PVP <20 cmH_2O.[9] In a systematic review and meta-analysis, Liu *et al*. revealed that the incidence of severe postoperative complications, surgical mortality, and 5-year survival rate was significantly worse in patients with PHT than in those without PHT. However, PHT had no influence on the short- or long-term survival of European HCC patients with PHT diagnosed by the standard surrogate criteria.[15]

Kim reported that the rate of severe complications, including hepatic failure, and the long-term outcomes were worse after TACE in patients with PHT than in those without it under propensity score matching.[16] In the present study, the average platelet count was around $10 \times 10^4/mm^3$ in each group, except for the LDLT group; patients with severe PHT might therefore not have been included in the local therapy or HR groups in our study.

In our study, long-term follow-up for treated patients in the local therapy group by a hepatologist. Actually, there was a significant difference in the follow-up period among the three groups, meaning censored patients in local therapy were the most. Since there were significant differences observed in RFS and CCS, not in OS, the influence of the difference in follow-up duration on long-term RFS and CSS might be slight.

Omata *et al*. described the treatment algorithm in the Asian Pacific Association for the Study of the Liver (APASL) in 2017. In this guideline, liver resection is a first-line curative treatment for HCC in patients with CP grade A, provided the resectability is approved by a multidisciplinary evaluation. In CP grade B and C patients, LT is recommended as the best curative treatment for HCC from an oncological perspective as a first-line treatment, provided a liver graft is available.[11] Although Japanese guideline for HCC 2019 recommended that the LT was suitable in patients with CP grade C in the algorithm, APASL guideline recommended that CP grade B and C was an indication for LT, which corresponded to our results.[17]

Chu reviewed the update concerning the management of HCC in Eastern countries, with major treatment modalities including liver resection, liver transplantation, local ablation therapy, transarterial therapy, locoregional treatment, and systemic treatment. Each treatment is chosen according to the liver function, number of tumors, and tumor location.[18]

There have been six randomized control trials (RCTs) comparing RFA and HR for small HCC.[19–24] Four of the studies found no marked difference in the OS and RFS,[19,21,22,24] whereas the other two found that HR was superior to RFA in terms of the OS and RFS.[20,23] Ng *et al*. compared the long-term outcomes (10-year OS and RFS) of RFA *versus* HR for early-stage HCC, with inclusion criteria of HCC with a maximum diameter <5 cm, ≤3 tumor nodules, and no vascular invasion. There was no significant difference in the RFS between the groups, although the recurrence rate (81.7%) in the RFA group tended to be higher than that (71.3%) in the HR group ($P = 0.092$).[24] In the present study, there was a significant difference in the RFS between the local therapy and HR groups, probably because the disease population was different from that in Ng's study. In our study, most

Table 3 Results of multivariate Cox proportional hazard analysis of the prognostic factors for recurrence after local therapy

Variable	Category	Hazard ratio	*P*
Male	(+)	1.754 (1.173–2.623)	0.006
AFP (ng/dL)	≥10	1.716 (1.170–2.517)	0.006
Multiple tumor	(+)	1.615 (1.089–2.396)	0.017

AFP, alpha-fetoprotein.

Table 4 Results of multivariate Cox proportional hazard analysis of the prognostic factors for overall survival after hepatic resection

Variable	Category	Hazard ratio	*P*
Multiple tumors	(+)	3.454 (1.881–6.343)	0.001
Alanine aminotransferase (U/L)	≥40	1.777 (1.006–3.139)	0.048

Table 5 Results of multivariate Cox proportional hazard analysis of the prognostic factors for recurrence after hepatic resection

Variable	Category	Hazard ratio	*P*
HBV	(+)	0.435 (0.206–0.916)	0.028
HCV	(+)	0.71 (0.393–1.281)	0.255
Alanine aminotransferase (U/L)	≥40	1.62 (0.901–2.913)	0.107
ICGR15 (%)	≥15	1726 (0.956–3.115)	0.07
Multiple tumors	(+)	5.214 (1.881–6.343)	0.001

cases in the local therapy group had an HCV-infected liver, whereas in Ng's study, most cases of HCC were HBV-related.

Wang analyzed the outcome of RFA *versus* HR for small HCC by a meta-analysis of randomized and nonrandomized control trials in 2014. This meta-analysis showed no marked difference between the two groups with regard to the OS, RFS, and disease-free survival, with the 5-year OS and RFS rates being significantly worse in the RFA group than in the HR group. Furthermore, the 3- and 5-year recurrence rates were higher in the RFA group than in the HR group.[26] In the present study, the RFS and CSS in the LDLT group were superior to those in the local therapy and HR groups, although there was no significant difference in the OS among the groups.

There have been a few studies comparing RFA, TACE, and HR for small HCC, as TACE is recommended as the first-line treatment of HCC for patients with unresectable, multifocal HCC. In addition, selective TACE is recommended in patient with small HCC for which ablation is difficult to perform because of the tumor location. Cucchetti compared the treatment effect between HR and locoregional therapies for HCC. Their retrospective analysis of 1585 patients included 815 with HR, 337 with RFA, and 433 TACE. The outcome of TACE was worse than that of RFA and HR because the rate of multifocal HCC exceeding the Milan criteria was higher in the TACE group than in the other groups.[25]

LT seems to be the best treatment for achieving a complete cure for both HCC and the underlying liver cirrhosis (LC); however, the shortage of liver grafts and the risk of tumor recurrence remain issues to be resolved. To reduce the rate of HCC recurrence, the Milan criteria have been accepted as the standard selection criteria around the world. However, the indication and allocation of LT are based on the model for end-stage liver disease (MELD) score, with additional points given to HCC patients in Western countries. LT is provided to patients with CP grade A. Besides, in Asian countries, based on the extremely scarce donor, LT is recommended in patients with decompensated LC. In Japan, medical insurance approved an extended indication of LT for HCC, which was indicated for tumor diameter less than 5 cm, tumor number less than five nodules, and tumor marker AFP level within 500 ng/mL.[27]

Regarding the influence of the liver function on the indication for LT, the 5-year survival rate after HR for HCC with CP grade B is around 60% at best.[28] The indication of LT for HCC with CP grade A liver dysfunction is controversial. Bigourdan reported that LT resulted in better survival and disease-free survival than HR in CP grade A patients.[29] In addition, Adam reported that the outcomes of HR among patients with a solitary HCC nodule <5 cm in size were worse than that of LT. Furthermore, the RFS of HR was also significantly worse in cases of a solitary nodule HCC <3 cm in size.[30]

Kutlu compared each of these treatments in patients with HCC measuring ≤20, 21–30, and 31–50 mm in size using the Surveillance, Epidemiology, and End Results (SEER) database. LT resulted in better survival than RFA or HR. Regarding tumors <3 cm in size, RFA had similar disease-specific survival and OS rates to those for HR; however, HCC ≥3 cm was associated with a worse outcome. In such cases, LT or HR should be recommended as the first-line therapy.[31] Beumer *et al*. reviewed the treatment effect of LT *versus* HR. In the review, LT provided longer disease-free survival after LT compared with HR in all studies. They stated that patients receiving LT often have different characteristics in terms of their cancer stage and liver function compared with those being resected. This makes a comparison of the two treatment modalities difficult. They recommended that future studies were needed on whether LT offers a survival benefit over liver resection in patients who are eligible for both treatments.[32] From the Japanese institute, three studies compared HR and LDLT, especially focusing on patients with CP grade B.[33–35] Harada *et al*. compared the patients with HR plus microwave coagulation therapy (MCT) and LDLT in patients with CP grade B. LDLT had a longer disease-free survival and OS than HR with MCT; however, they recommended the LDLT was not indicated in patients with higher tumor marker (DCP).[33] Harimoto *et al*. indicated that LDLT had better survival in patients with CP grade B, especially with a low level of tumor parker (DCP).[34] Besides, Kaido *et al*. indicated that the outcome between HR and LDLT after propensity matching was no significant difference. Their study included the same number of CP grade B patients after propensity matching. They concluded that HR should be considered a valid alternative to LDLT.[35] In our study, we could not perform the comparison of HR and LDLT in patients with CP grade B because of fewer HR patients in CP grade B. The surgical benefit between HR and LDLT was still controversial.

In the present study, the comparison of the OS between local therapy and LDLT in HCC patients with CP grade B disease revealed a better outcome in the LDLT group. In addition, a multivariate analysis showed that CP grade B and elevated tumor marker levels (DCP, AFP) were independent prognostic factors for the survival following local therapy, while those for recurrence were male gender, elevated AFP levels, and multiple tumors. These results indicate that patients with an impaired liver function and worse malignancy (represented by elevated tumor marker levels) were associated with repeated recurrence and difficulty receiving repeat treatment after recurrence. An investigation of the explanted liver by a whole-liver histological examination revealed many more small HCCs in cases of severe cirrhotic liver than were found on imaging.[36]

The main issue and item of note in the treatment and management of HCC patients is recurrence after treatment. The present study indicated that LDLT resulted in the best outcome among these therapies with respect to the CSS; however, there was no marked difference in the OS among local therapy, HR, and LDLT. The main causes of death after LDLT were liver graft failure, graft dysfunction due to HCV recurrence, and bacterial or fungal infection. Treatment for HCV has improved dramatically in the past 10 years with the advent of direct-acting antiviral (DAA) therapy. The outcome of LDLT depends on the graft liver function, infection status, and immunotolerance of the recipient.

Several limitations associated with the present study warrant mention, including the marked differences in patient characteristics among the three groups and selection bias due to the retrospective nature of the study and single-center setting. Most of the elderly patients in the local therapy group could not indicate LDLT. Patients less than 65–70 years old might get a benefit from successful LDLT. However, we feel that the findings of this retrospective analysis comparing the outcome among local

therapies, HR, and LDLT are important for real-world practice in Asian countries.

Conclusion

The CSS and recurrence rates of LDLT were superior to those of local therapy and HR. Among the CP grade B patients, LDLT achieved better survival and CSS rates than local therapy. Multiple tumors were associated with recurrence after local therapy and HR. The liver function (CP grade B) was associated with survival after local therapy, so LDLT should be considered based on the liver function.

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