Table 4 Risk factors for adult T-cell leukemia (ATL) development: univariate analysis

Variables	Rate of ATL development	*P*-value
Recipient variables		
Age		0.66
≥60 years (n = 23)	4.3%	
<60 years (n = 58)	6.9%	
Sex		0.47
Male (n = 36)	8.3%	
Female (n = 45)	4.4%	
Etiology		<0.001
FHF (n = 12)	41.7%	
Others (n = 69)	0%	
MELD[a]		0.06
≥15 (n = 56)	8.9%	
<15 (n = 22)	0%	
Splenectomy[a]		0.013
Yes (n = 35)	0%	
No (n = 43)	11.6%	
Calcineurin inhibitor[b]		0.89
TAC (n = 62)	6.5%	
CYA (n = 18)	5.6%	
Donor/graft variables		
Age		0.54
≥40 years (n = 43)	4.7%	
<40 years (n = 38)	7.9%	
Sex		0.47
Male (n = 36)	8.3%	
Female (n = 45)	4.4%	
Graft[c]		0.83
Left lobe (n = 33)	6.1%	
Right lobe (n = 41)	7.3%	
GW-SLW ratio (%)[a]		0.91
<40 (n = 33)	6.7%	
≥40 (n = 45)	6.1%	
Donor HTLV-1[d]		0.16
Positive (n = 12)	16.7%	
Negative (n = 67)	4.5%	
Donor-recipient matching		
ABO identical		0.37
Yes (n = 48)	4.2%	
No (n = 33)	9.1%	
Blood relative donor		0.12
No (n = 17)	0%	
Yes (n = 64)	7.8%	

The ATL development of one case was unknown.
[a] Three cases lacked data on MELD, splenectomy, or GW-SLW ratio
[b] One case was not given calcineurin inhibitor
[c] Seven recipients received a right posterior sector, left lateral segment, or reduced S2 graft
[d] Two cases had an unknown donor HTLV-1 status

Table 5 Risk factors for adult T-cell leukemia (ATL) development: multivariate analysis

Variables	Odds ratio	95% CI	*P*-value
Fulminant hepatic failure: Yes	29.6[a]	3.58 - + INF	0.001
Splenectomy: No	0.7[a]	0.018 - + INF	1.00

[a] Median unbiased estimation

Discussion

Our cohort from the Japanese national registry is the largest cohort to date used to investigate LDLT-associated HTLV-1. Previously, based on data from a single center, we reported that both a primary diagnosis of FHF and a MELD score >15 were risk factors for ATL development [2]. In the previous report, we speculated that a pre-transplant MELD score >15 was mediated by the FHF diagnosis because all of the FHF recipients had a MELD score >15, but a multivariate analysis could not be performed owing to the relatively small number of cases. In this study, a multivariate analysis was performed using more cases than the previous report, and we revealed that only a pre-transplant diagnosis of FHF was an independent risk factor for ATL development after LDLT. Based on the data from both the previous report [2] and this study, we recommend considering the indication for LDLT in HTLV-1-poitive patients with FHF before performing a LDLT because of the very high risk of mortality for these patients. Five of the six HTLV-1-positive patients with FHF in the earlier study died because of ATL development (n = 3) or because of chronic rejection after chemotherapy for ATL (n = 1) or PTLD (n = 1). In this survey, eight of the 12 HTLV-1-positive patients with FHF died; five of these patients were those previously reported. The causes of death for the three newly collected patients were graft failure, graft infarction, or ATL (one patient each).

Fulminant hepatic failure is a life-threatening condition that has a high mortality unless an urgent LT is performed. Although HTLV-1-positive recipients with FHF have a high risk of ATL development, LDLT enables such patients to survive longer than they otherwise would. Based on our findings, transplant surgeons will need to carefully weigh the potential benefits of performing a LDLT on HTLV-1-positive recipients with FHF against the established risks of ATL development or death in these recipients and evaluate each situation on a case-by-case basis.

One possible mechanism for the association between ATL development and FHF is that hepatocyte growth factor (HGF)-c-Met, the receptor of HGF, is present on ATL cells, and signaling through this pathway might augment the proliferation of HTLV-1 infected cells [2]. Furthermore, decreased numbers of natural killer cells in the peripheral

blood of FHF recipients [8] might play a pivotal role for ATL development. In this study, 11 recipients with FHF did not undergo splenectomy during LDLT. Indeed, a lack of splenectomy was a risk factor for ATL development according to the results of a univariate analysis. However, Florins et al. reported that, in sheep, splenectomy accelerated the leukemogenesis induced by bovine leukemia virus, which, like HTLV-1, is a retrovirus [9]. Therefore, they concluded that there is a potential risk for accelerating ATL onset after splenectomy in HTLV-1 carriers. Further study on the impact of the spleen for ATL development is needed. Recently, a nationwide molecular analysis using 426 ATL samples was reported from Japan [10]. The authors identified various somatic alterations in the cellular genome that largely converge on T cell receptor–nuclear factor-κB signaling and other T-cell-related pathways [10]. Further perspective studies should confirm if these alterations are also found in FHF patients.

It is important to consider the ethical aspects of using healthy living donors for transplantation of HTLV-1-poitive recipients that have FHF. Donor safety is of paramount concern in any donor surgery for LDLT. Fortunately, we found that the recipient risks do not increase the surgical risk for the donors. Furthermore, there is no donor coercion at the Japanese institutions that perform LDLT. The risk to the donor must be balanced by the benefit to the donor in terms of the survival of the recipient. Mutual affection generally motivates recipients' family members as donors, as they hoped to see their relatives survive for as long as possible.

The 5-year ATL development rate for the HTLV-1-positive LDLT recipients in this study was 9.2%, which seems to be higher than that for HTLV-1-positive individuals who did not undergo LT (3–5%) [11]. Further study is necessary to make any conclusion about why LDLT is associated with ATL development. Notably, all patients who developed ATL after LDLT died despite treatment. Advances in chemotherapy have contributed to an increase in the overall survival of patients with ATL [12]; however, complete response rates have ranged from 17 to 43% and the median overall survival times have ranged from 5 to 13 months in prospective multicenter studies in Japan [13].

Japanese centers have reported promising results for allogenic hematopoietic stem cell transplantation [14, 15]. Additionally, treatment with mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, combined with traditional chemotherapy has been shown to induce positive responses even in cases with aggressive ATL [16]. Unfortunately, the immunosuppressive status of transplant recipients complicates ATL treatment; therefore, we have to consider whether or not we can prevent ATL development after LDLT. In the non-organ transplant setting, four risk factors have been associated with ATL development in HTLV-1 carriers, including age greater than 40 years, high HTLV-1 proviral loads in peripheral blood, family history of ATL, and any clinical signs or symptoms [17]. There are currently no available means of preventing ATL development in patients with any of these risk factors. Our finding that FHF is the only risk factor in a LDLT setting may contribute to determining the mechanism of how ATL develops in HTLV-1 carriers.

Eighteen partial hepatic grafts from HTLV-1-positive living donors were transplanted to HTLV-1-positive (n = 12) or -negative (n = 6) recipients. Although donor HTLV-1 status was not a risk factor for ATL or HAM development in this study, the 10-year survival rates of these recipients, (48.6% for HTLV-1-positive recipients and 33.3% for HTLV-1-negative recipients), were still quite poor. Transplant teams generally will not select HTLV-1-positive donors unless they have no other choice because of life-threatening recipient conditions. One of the aims of this study was to clarify the risk of ATL or HAM development after LDLT from an HTLV-1-positive donor. Unfortunately, this risk is difficult to analyze because of the poor recipient survival rate and the relatively small number of HTLV-1-positive donors. We believe that LT should be performed in selected recipients who agree to accept these risks to rapidly obtain a life-saving organ. Additionally, it is important to consider the safety of the HTLV-1-positive donor undergoing hepatectomy. Although this study did not reveal any negative impact on the HTLV-1-positive donors after hepatectomy, careful donor follow-up is recommended to confirm that they do not develop any HTLV-1-associated disease.

To prevent or minimize the development of HTLV disease in the recipients of organs from confirmed HTLV-1-positive donors, antiviral prophylaxis therapy with zidovudine (nucleoside analog reverse transcriptase inhibitor) and raltegravir (integrase inhibitor) during a brief period after transplantation has been suggested [18, 19]. Armstrong et al. recommended HTLV-1 prophylaxis/preemptive therapy with these two inhibitors for organ transplantation, but this is still not an established approach [19].

The Japanese Ministry of Health, Labour and Welfare publically announced the following fact in December, 2014: Living donor *renal transplant* recipients who were HTLV-1 negative before the transplant and received a *renal graft* from an HTLV-1- positive donor became infected with HTLV-1. Furthermore, those recipients developed HAM rapidly with a high frequency compared with the usual HAM incident rate [20]. In these recipients, symptoms progressed to serious walking difficulty within several years after the development of HAM. Because HTLV-1 infection is relatively rare in eastern and northern Japan, until this announcement was made, transplant centers in these areas had not been cautious about donor and recipient HTLV-1 status prior to

performing living donor renal transplants. The Japan Society for Transplantation warned that to reduce the risk of unintentional transmission of HTLV-1 through renal transplantation, a serology test should be performed for all donors and recipients who plan to undergo living donor renal transplantation. Furthermore, living donor renal transplantation from an HTLV-1-positive donor or for an HTLV-1-positive recipient should be performed only after fully informed consent that highlights their increased risk of HAM development is obtained both from the recipient and the donor. Lastly, the Japan Society for Transplantation recommends that careful follow-up checks should be performed to identify the development of any HTLV-1-associated disease for any HTLV-1-positive recipient.

As we previously reported, HTLV-1 serology tests were not useful for following up on recipients who were HTLV-1-negative before the LDLT. Checking the proviral load by polymerase chain reaction is necessary to diagnose the transmission of the virus [2, 21]. It was reported that the seroconversion of the recipients receiving blood containing HTLV-1 usually occurred within 50 days after transfusion [22]. Because of their immunosuppressive status, transplant recipients could be HTLV-1 positive and develop ATL without seroconversion or their seroconversion might be delayed [1, 23].

Ramanan et al. recently reported a case of living donor-derived HAM in a renal transplant recipient [18]. Such donor-derived infection could potentially happen in the deceased donor transplant setting in the United States because of the discontinuation in 2009 of universal deceased donor organ screening for HTLV-1. The development rate of HAM in HTLV-1 carriers is 0.25% [11] in a non-transplant setting. In this study, two of the 88 (2.3%) recipients developed HAM after LDLT. Although the HAM development rate seems to be higher in the transplant setting, this result does not provide enough information to make any conclusion about why LDLT might be associated with HAM development.

The present study is subject to limitations. It is a retrospective study and has possible biases because only two institutes had recipients who developed ATL owing to the relatively small number of patients from each institute. Kyushu University Hospital experienced four ATL cases among 32 recipients, which means their ATL development rate was 12.5%, whereas, the ATL development rate at Kyoto University Hospital was 5.2% (one ATL case among 19 recipients). The other 11 institutes did not experience any ATL development, which is probably owing to differences in their recipients' primary diagnoses, and backgrounds, among other factors.

In conclusion, the outcome of HTLV-1-positive recipients who underwent LDLT was acceptable. FHF was the only identified independent risk factor for ATL development in the HTLV-1-positive recipients. A graft from an HTLV-1-positive living donor can be safely transplanted into selected patients, but careful follow-up is recommended for the safety of the HTLV-1-infected living donor.

Conflict of interest None declared.

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References

1. Hoshida Y, Li T, Dong Z, Tomita Y, Yamauchi A, Hanai J, et al. Lymphoproliferative disorders in renal transplant patients in Japan. Int J Cancer. 2001;91:869–75.
2. Yoshizumi T, Shirabe K, Ikegami T, Kayashima H, Yamashita N, Morita K, et al. Impact of human T cell leukemia virus type 1 in living donor liver transplantation. Am J Transplant. 2012;12:1479–85.
3. Kawano N, Shimoda K, Ishikawa F, Taketomi A, Yoshizumi T, Shimoda S, et al. Adult T-cell leukemia development from a human T-cell leukemia virus type I carrier after a living-donor liver transplantation. Transplantation. 2006;82:840–3.
4. Sonoda S, Li HC, Tajima K. Ethnoepidemiology of HTLV-1 related diseases: ethnic determinants of HTLV-1 susceptibility and its worldwide dispersal. Cancer Sci. 2011;102:295–301.
5. Utsunomiya A, Choi I, Chihara D, Seto M. Recent advances in the treatment of adult T-cell leukemia-lymphomas. Cancer Sci. 2015;106:344–51.
6. Marvin MR, Brock GN, Kwarteng K, Nagubandi R, Ravindra KV, Eng M, et al. Increasing utilization of human T-cell lymphotropic virus (+) donors in liver transplantation: is it safe? Transplantation. 2009;87:1180–90.
7. Soyama A, Eguchi S, Takatsuki M, Ichikawa T, Moriuchi M, Moriuchi H, et al. Human T-cell leukemia virus type I-associated myelopathy following living-donor liver transplantation. Liver Transpl. 2008;14:647–50.

8. Zou Y, Chen T, Han M, Wang H, Yan W, Song G, et al. Increased killing of liver NK cells by Fas/Fas ligand and NKG2D/NKG2D ligand contributes to hepatocyte necrosis in virus-induced liver failure. J Immunol. 2010;184:466–75.
9. Florins A, Reichert M, Asquith B, Bouzar AB, Jean G, Francois C, et al. Earlier onset of delta-retrovirus-induced leukemia after splenectomy. PLoS One. 2009;4:e6943.
10. Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet. 2015;47:1304–15.
11. Ishitsuka K, Tamura K. Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. Lancet Oncol. 2014;15:e517–26.
12. Tsukasaki K, Tobinai K. Human T-cell lymphotropic virus type I-associated adult T-cell leukemia-lymphoma: new directions in clinical research. Clin Cancer Res. 2014;20:5217–25.
13. Tsukasaki K, Tobinai K, Hotta T, Shimoyama M. Lymphoma study group of JCOG. Jpn J Clin Oncol. 2012;42:85–95.
14. Okamura J, Utsunomiya A, Tanosaki R, Uike N, Sonoda S, Kannagi M, et al. Allogeneic stem-cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma. Blood. 2005;105:4143–5.
15. Choi I, Tanosaki R, Uike N, Utsunomiya A, Tomonaga M, Harada M, et al. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant. 2011;46:116–8.
16. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol. 2015;169:672–82.
17. Iwanaga M, Watanabe T, Utsunomiya A, Okayama A, Uchimaru K, Koh KR, et al. Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. Blood. 2010;116:1211–9.
18. Ramanan P, Deziel PJ, Norby SM, Yao JD, Garza I, Razonable RR. Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient–case report and literature review. Am J Transplant. 2014;14:2417–21.
19. Armstrong MJ, Corbett C, Rowe IA, Taylor GP, Neuberger JM. HTLV-1 in solid-organ transplantation: current challenges and future management strategies. Transplantation. 2012;94:1075–84.
20. Nagamine Y, Hayashi T, Kato Y, Horiuchi Y, Tanahashi N. Human T lymphotropic virus type-1-associated myelopathy manifesting shortly after living-donor renal transplantation. Intern Med. 2015;54:75–8.
21. Kaul DR. Human T cell lymphotrophic virus 1 after transplantation: what is the risk of recipient disease? Am J Transplant. 2012;12:1365–6.
22. Kubota T, Ikezoe T, Hakoda E, Sawada T, Taguchi H, Miyoshi I. HTLV-I-seronegative, genome-positive adult T-cell leukemia: report of a case. Am J Hematol. 1996;53:133–6.
23. Glowacka I, Korn K, Potthoff SA, Lehmann U, Kreipe HH, Ivens K, et al. Delayed seroconversion and rapid onset of lymphoproliferative disease after transmission of human T-cell lymphotropic virus type 1 from a multiorgan donor. Clin Infect Dis. 2013;57:1417–24.

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ORIGINAL SCIENTIFIC REPORT

Comparison of the Outcomes of Patients with Hepatocellular Carcinoma and Portal Hypertension After Liver Resection Versus Radiofrequency Ablation

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Abstract

Background The aim of this study was to compare the outcome of patients with hepatocellular carcinoma (HCC), Barcelona Clinic Liver Cancer (BCLC) stages 0 and A, and portal hypertension (PHT) who underwent liver resection (LR) or radiofrequency ablation (RFA).

Methods The study population consisted of 121 patients with PHT and HCC of BCLC stage 0 and A who underwent LR ($n = 81$) or RFA ($n = 40$). To reduce bias in patient selection, the different covariate distributions in two groups were adjusted using inverse probability treatment weighting (IPTW). The prognostic outcomes of LR- and RFA-treated patients were then analyzed.

Results Before IPTW adjustment, the 5-year overall survival (OS) of LR and RFA patients was comparable. Five-year recurrence-free survival (RFS) was significantly better in the LR group than in the RFA group ($P < 0.0001$). Multivariate analysis showed that RFA was an independent predictor of worse RFS ($P = 0.0004$). The local recurrence rate was higher in the RFA than in the LR group, with recurrences in each group tending to be treated with the same modality as initially. After IPTW adjustment, the OS of patients in the LR and RFA groups did not significantly differ, whereas the RFS of the LR group remained significantly better than that of the RFA group ($P = 0.00014$). However, the RFA group had fewer postoperative complication rates and a shortened length of hospital stay.

Conclusions By reducing postoperative complications, LR may be a treatment option for patients with BCLC stage 0 or A HCC and PHT.

Introduction

According to the guidelines of the Barcelona Clinic Liver Cancer (BCLC) Group [1] and the American Association for the Study of Liver Disease (AASLD) [2], patients with HCC and clinically significant portal hypertension (PHT) are candidates for radiofrequency ablation (RFA) or liver transplantation, whereas hepatectomy is contraindicated.

Clinically significant PHT, defined as a hepatic venous pressure gradient (HVPG) $\geq$10 mmHg, is the most powerful predictor of postoperative liver failure or poor long-term survival in patients with Child–Pugh A liver function [3]. However, this conclusion was based on a small retrospective cohort study of only 77 patients who underwent

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liver resection (LR). Preoperative HVPG measurement is invasive and is not performed routinely in most liver centers; instead, indirect clinical parameters, including esophageal varices (EVs) and/or splenomegaly associated with thrombocytopenia, are considered clinical signs of PHT [4]. Conversely, there are many reports that LR improves survival in patients with PHT and that PHT should not be considered as an absolute contraindication for hepatectomy in patients with cirrhosis [5–7]. Given the serious shortage of available liver transplant donor organs [8], surgical resection may be a better treatment option for some HCC patients with clinical PHT [9].

In this study, we compared the long-term outcome of patients with BCLC stages 0 and A HCC and PHT who underwent LR or RFA. Inverse probability treatment weighting (IPTW) was applied to reduce the bias in patient selection. IPTW weighs the samples using the propensity score to reduce the confounding that frequently occurs in cohort studies of the effects of treatment on outcome. In addition, IPTW enables the estimation of marginal or population-average treatment effects [10].

Materials and methods

Patients and inclusion criteria

The study population consisted of 121 consecutively enrolled patients with HCC who underwent LR or RFA at the Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital between January 2008 and December 2013. All patients had tumors measuring <3 cm, each with a maximum of three tumors or a solitary tumor <5 cm, and had been diagnosed with PHT, defined as the presence of EVs and/or a platelet count of <100,000/μL in association with splenomegaly. EV was determined preoperatively based on upper gastrointestinal endoscopic findings. Splenomegaly was defined as spleen length exceeding 10 cm on preoperative computed tomography [5, 11]. Patients with ascites who did not respond to diuretic drugs were excluded.

Surgical procedure, RFA procedure, and treatment decision

The surgical indications were based on the patient's daily living activities, age, and fitness, the degree of tumor invasion, extent of resection, and remnant liver function [12, 13]. The type of hepatectomy was selected based on liver function and tumor extension [14–16]. Treatment modalities were mainly determined by Child-Pugh class and the results of indocyanine green retention tests at 15 min ($ICGR_{15}$). Patients with Child-Pugh class A or B and $ICGR_{15} \leq 45$ % tended to be treated with LR. Surgical procedures included hemihepatectomy or segmentectomy for patients with $ICGR_{15} < 20$ %, subsegmentectomy for patients with $ICGR_{15} < 30$ %, and partial resection for patients with $ICGR_{15} \leq 45$ %. If $ICGR_{15}$ was >45 %, 99mTc-GSA scintigraphy was performed, followed by partial resection to ensure that $ICGR_{15}$ was <45 % by scintigraphy [17]. The presence of ascites was considered an absolute contraindication for resection. The hepatectomy procedures have been described elsewhere [13, 14].

All patients scheduled for RFA underwent outpatient abdominal ultrasonography (US) to assess the feasibility of US-guided percutaneous RFA [18]. The method and therapeutic strategy of RFA were the same as described in previous studies [19]. RFA was selected for patients with Child-Pugh class A or B, $ICGR_{15} > 45$ %, and contraindications for general anesthesia, and for those requesting RFA. RFA was not performed in patients with segment 1 tumors; tumors overhanging the liver margin or near adjacent organs, including the gallbladder, stomach, or colon; or tumors located near major intrahepatic vessels.

Written informed consent was obtained from all patients for surgical treatment and RFA therapy according to the guidelines of our hospital. Decisions regarding treatment modalities were made at a meeting attended by all participating surgeons and gastroenterologists. The HCC patients were then divided accordingly into those to be treated with LR (LR group) and those to be treated with RFA (RFA group).

The selection criteria for the treatment of recurrent HCC were identical to those for primary tumors. TACE, microwave coagulation therapy, radiation, or best supportive therapy was chosen based on liver function, number of tumors, and patient choice. The study protocol conformed with the updated ethical guidelines of the 2013 Declaration of Helsinki and was approved by our Institutional Review Board.

Definitions

HCCs were diagnosed in the LR group by pathological methods and in the RFA group by pretreatment imaging modalities, including abdominal contrast-enhanced dynamic CT and Gd-EOB-DTPA enhanced MRI. On contrast-enhanced dynamic CT, HCCs appeared as early enhancement during the arterial phase and hypoattenuation during the portal venous or equilibrium phase. On Gd-EOB-DTPA enhanced MRI, HCC was defined as a nodular lesion with enhancement in the arterial phase and washout in the late phase or decreased uptake in the hepatobiliary phase. If a nodule did not completely fulfill the above criteria, a pretreatment biopsy was performed.

Table 1 Characteristics of the patients with BCLC stage 0 and A HCC and portal hypertension who underwent LR or RFA

Variables	LR group ($n = 81$)	RFA group ($n = 40$)	P value
Age (years) at enrollment	70.4 (53–85)	71.9 (58–87)	0.357
Sex			
Male	45 (55.6 %)	23 (57.5 %)	0.839
Female	36 (44.4 %)	17 (42.5 %)	
Etiology of hepatopathy			
HBsAg positive	8 (9.9 %)	2 (5.0 %)	0.340
Anti-HCVAb positive	61 (75.3 %)	29 (72.5 %)	0.740
Alcohol	9 (11.2 %)	4 (10.0 %)	0.852
NASH 1	(1.2 %)	2 (5 %)	0.229
Others	2 (2.4 %)	3 (7.5 %)	0.208
Esophageal varices	68 (84.0 %)	30 (75.0 %)	0.245
ASA status <3	73 (90.1 %)	36 (90.0 %)	0.983
Serum biochemistry			
Albumin (g/dL)	3.8 (2.7–4.7)	3.7 (2.7–4.7)	0.090
Total bilirubin (mg/dL)	0.8 (0.2–2.3)	1.1 (0.4–2.4)	0.027
AST (U/L)	47 (16–150)	45 (19–80)	0.956
ALT (U/L)	43 (14–245)	39 (14–105)	0.733
Creatinine (mg/dL)	0.8 (0.34–2.0)	0.9 (0.35–4.3)	0.735
Prothrombin activity (%)	85.9 (61–117)	82.5 (60–118)	0.126
Platelet count ($\times 10^4/\mu L$)	10.3 (4.6–24)	9.7 (3.8–33)	0.229
$ICGR_{15}$ (range %)	25.6 (5.6–68.7)	32.2 (9.5–83.4)	0.021
Splenomegaly with platelet count			
<10,0000/μL	34 (42.0 %)	21 (52.5 %)	0.275
Child-pugh score (points)	5.5 (5–8)	5.7 (5–9)	0.737
AFP (ng/mL)	132 (2.8–2340)	61 (3.3–283)	0.493
Maximum tumor diameter (cm)	2.1 (0.7–5)	1.4 (0.7–2.4)	<0.0001
Number of tumors	1.3 (1–3)	1.2 (1–3)	0.659
Intrahepatic tumor location			
S1/2/3/4/5/6/7/8 (n)	4/4/13/15/13/17/13/17	0/3/1/3/13/4/8/12	–
BCLC stage			
Stage 0	35 (43.2 %)	28 (70.0 %)	0.005
Stage A	46 (56.8 %)	12 (30.0 %)	

Values are expressed as percent, mean (range), or number

BCLC Barcelona clinic liver cancer, *HCC* hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation, *HBsAg* hepatitis B surface antigen *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

Major hepatectomy was defined as the resection of at least one subsegment. Minor resection, including partial resection, involved less than one subsegment. EVs were preoperatively classified according to the general rules based on endoscopic findings [20]. Serious postoperative complications were defined as Clavien–Dindo grade III or higher [21, 22].

Survival and recurrence

Patients underwent blood tests and CT every 3 months after LR or RFA. Recurrence was diagnosed based on imaging findings. Patients with intrahepatic distant recurrence or local recurrence were managed with ablative therapy, transcatheter arterial chemoembolization (TACE), surgery, microwave coagulation therapy under laparotomy, radiation, or best supportive care. In case of death, survival time after surgery and cause of death were recorded.

Statistical analysis

For continuous variables, the Wilcoxon rank-sum test was used for nonparametric analyses. Categorical variables were compared using the χ^2 test. The Kaplan–Meier

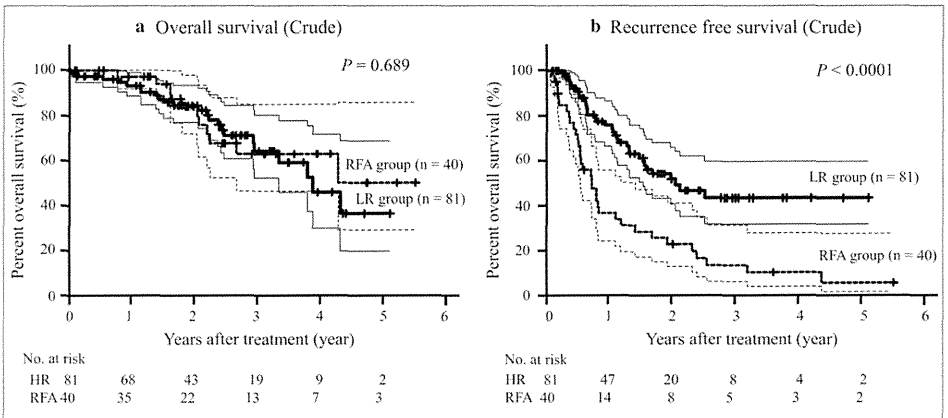

Fig. 1 Prognosis of 121 patients with BCLC stage 0 and A HCC and portal hypertension who underwent liver resection (LR group; $n = 81$) or radiofrequency ablation (RFA group; $n = 40$) therapy. **a** Unweighted (crude) Kaplan–Meier curve showing the percent overall survival (OS) after treatment. The OS of the LR group (*bold black line*) was comparable to that of the RFA group (*bold dotted line*, $P = 0.689$). **b** Unweighted (crude) Kaplan–Meier curve of recurrence-free survival (RFS) after treatment. The RFS of the LR group (*bold black line*) was significantly better than that of the RFA group (*bold dotted line* $P < 0.0001$). Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

method was used to construct overall survival (OS) and recurrence-free survival (RFS) curves. All survival curves were compared using log-rank tests. To identify independent factors of OS and RFS, the factors resulting in P values <0.2 on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model.

IPTW analysis was used to overcome possible bias in the different distributions of the covariates among the LR and RFA groups. Propensity scores from the IPTW analysis were calculated using a logistic regression model to predict the probability of each patient receiving LR or RFA on the basis of clinicopathological variables. After IPTW balancing of the two groups, the differences in the OS and RFS rates were tested by Cox regression analyses. Statistical significance was defined as a P value <0.05. Statistical analyses were performed using the R statistical programming environment and JMP 9.0 software (SAS Institute, Cary, NC, USA) [10].

Results

HCC diagnosis

All 104 nodules in the LR group (80 patients) were diagnosed as HCC by pathological methods. In the RFA group, 44 nodules in 36 patients were diagnosed as HCC based on contrast-enhanced dynamic CT and/or Gd-EOB-DTPA enhanced MRI, and eight nodules in five patients were diagnosed as HCC by pathological examination of pretreatment biopsy specimens.

Clinicopathological characteristics of patients with BCLC stage 0 and A HCC and PHT who underwent LR or RFA.

The preoperative background characteristics of the patients with HCC and PHT who underwent LR or RFA are summarized in Table 1. Compared with the RFA group, the LR group had a lower mean serum total bilirubin (0.8 vs. 1.1 mg/dL, $P = 0.027$), lower mean $ICGR_{15}$ (25.6 vs. 32.2 %, $P = 0.021$), and greater maximum tumor diameter (2.1 vs. 1.4 %, $P < 0.0001$). In the RFA group, in addition to the absence of tumors in S1, the proportion of right lobe tumors (S5, 6, 7, and 8; 84.1 %) was significantly higher than in the LR group (63.5 %; $P = 0.023$). Sixty-two patients underwent partial resection, 11 underwent subsegmentectomy, and four each underwent segmentectomy and lobectomy. Thus, 23.5 % of patients underwent major resection and 76.5 % underwent minor resection.

Crude OS and RFS (before IPTW adjustment)

The median follow-up after surgery was 24.6 months (range 0.8–65.7 months). There were no significant differences in the OS of LR and RFA patients ($P = 0.689$). The percentages at 1, 3, and 5 years were 93.4, 84.5, and 37.1 %, respectively, for the LR group and 97.2, 84.1, and

Table 2 Univariate and multivariate analyses of overall survival in all HCC patients with portal hypertension

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age (per 1 year)	1.03 (0.99–1.08)	0.174	1.05 (1.00–1.10)	0.053
Sex: male/female	2.12 (1.02–4.82)	0.042	3.27 (1.48–7.84)	0.003
Treatment (RFA/LR)	0.86 (0.58–1.74)	0.687		
HBsAg positive	0.59 (0.10–1.97)	0.444		
Anti-HCVAb positive	1.76 (0.81–4.41)	0.219		
Esophageal varices (yes/no)	1.52 (0.64–4.50)	0.368		
ASA status <3 (yes/no)	1.33 (0.40–8.25)	0.679		
Serum biochemistry				
Albumin (g/dL)	0.45 (0.23–0.87)	0.017	4.97 (1.79–14.3)	0.003
Total bilirubin (mg/dL)	1.26 (0.62–2.37)	0.498		
AST (U/L)	1.00 (0.98–1.01)	0.806		
ALT (U/L)	0.99 (0.97–1.00)	0.124	0.99 (0.97–1.01)	0.314
Creatinine (mg/dL)	1.35 (0.39–2.74)	0.572		
Prothrombin activity (%)	0.99 (0.97–1.02)	0.654		
Platelet count ($\times 10^4/\mu L$)	0.94 (0.86–1.03)	0.205		
$ICGR_{15}$	1.01 (0.99–1.03)	0.250		
Child-Pugh score (points)	1.35 (0.91–1.94)	0.133	0.74 (0.40–1.32)	0.311
AFP (ng/mL)	1.00 (1.00–1.00)	0.067	1.00 (1.00–1.00)	0.066
Maximum tumor diameter (cm)	1.16 (0.78–1.64)	0.441		
Number of tumors	1.64 (0.82–2.92)	0.149	2.33 (1.15–4.26)	0.022
Postoperative serious complications (Clavien–Dindo ≥ III) yes/no	1.46 (0.43–3.76)	0.501		

HCC hepatocellular carcinoma, *HR* hazard ratio, *CI* confidence interval, *RFA* radiofrequency ablation, *LR* liver resection, *HBsAg* hepatitis B surface antigen *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

50.6 %, respectively, for the RFA group (Fig. 1a). By contrast, RFS at 1, 3, and 5 years was significantly better in the LR group than in the RFA group ($P < 0.0001$): 74.1, 48.8, and 42.9 % versus 36.1, 22.2, and 4.8 %, respectively (Fig. 1b).

The clinicopathological factors were evaluated to identify those associated with worse OS (Table 2). In univariate analyses, the *P* values for age, sex, serum albumin, serum ALT, Child–Pugh score, AFP, and number of tumors were <0.20. The inclusion of these seven variables in a multivariate Cox proportional hazards analysis showed that male sex [$P = 0.003$; hazard ratio (HR) 3.27; 95 % confidence interval (CI) 1.48–7.84], serum albumin value ($P = 0.003$; HR 24.7; 95 % CI 1.72–15.2), and number of tumors ($P = 0.022$; HR 2.33; 95 % CI 1.15–4.26) were independent predictors of worse OS.

The clinicopathological factors were also evaluated to identify those associated with worse RFS (Table 3). In univariate analyses, the P values for male sex, LR, anti-HCV antibody positivity, serum total bilirubin, serum ALT, $ICGR_{15}$, and number of tumors were <0.20. The inclusion of these seven variables in a multivariate Cox proportional hazards analysis showed that RFA ($P = 0.0004$; HR 2.56; 95 % CI 1.53–4.29) and number of tumors ($P = 0.019$; HR 1.93; 95 % CI 1.12–3.17) were independent predictors of worse RFS.

Postoperative complications and hospital stay

The 30-day postoperative complication rates in the LR and RFA groups were 46.9 and 12.5 % ($P < 0.0001$), respectively. In the LR group, one in-hospital death occurred secondary to sepsis. This group had a significantly higher rate of postoperative complications than the RFA group (46.9 vs. 12.5 %; $P < 0.0001$, Table 4) as well as a significantly higher rate of serious postoperative complications (Clavien–Dindo grade III or higher; 16.1 vs. 2.5 %; $P = 0.025$). Patients in the LR also had a significantly longer postoperative hospital stay (median 15 days; range 7–80 days) than the RFA group (median 8 days; range 2–29 days, $P < 0.0001$).

Table 3 Univariate and multivariate analyses of recurrence-free survival in all HCC patients with portal hypertension

Variables	Univariate analysis		Multivariate analysis	*P* value
	HR (95 % CI)	*P* value	HR (95 % CI)	
Age (per 1 year)	0.99 (0.96–1.02)	0.547		
Sex: male/female	1.39 (0.85–2.29)	0.188	1.46 (0.86–2.51)	0.161
Treatment (RFA/LR)	2.74 (1.70–4.43)	<0.0001	2.56 (1.53–4.29)	0.0004
HBsAg positive	0.88 (0.31–1.99)	0.780		
Anti-HCVAb positive	0.69 (0.42–1.19)	0.179	0.71 (0.41–1.27)	0.240
Esophageal varices (yes/no)	1.11 (0.62–2.13)	0.732		
ASA status <3 (yes/no)	1.17 (0.55–3.05)	0.699		
Serum biochemistry				
Albumin (g/dL)	1.07 (0.65–1.77)	0.791		
Total bilirubin (mg/dL)	1.44 (0.84–2.35)	0.177	0.76 (0.40–1.40)	0.378
AST (U/L)	0.99 (0.98–1.00)	0.223		
ALT (U/L)	0.99 (0.98–1.00)	0.062	0.99 (0.98–1.00)	0.080
Creatinine (mg/dL)	1.09 (0.62–1.61)	0.713		
Prothrombin activity (%)	1.01 (0.99–1.03)	0.498		
Platelet count ($\times 10^4/\mu L$)	1.01 (0.94–1.06)	0.821		
$ICGR_{15}$	1.01 (1.00–1.03)	0.113	1.01 (0.99–1.04)	0.209
Child-Pugh score (points)	0.96 (0.69–1.29)	0.791		
AFP (ng/mL)	1.00 (1.00–1.00)	0.222		
Maximum tumor diameter (cm)	0.93 (0.69–1.21)	0.613		
Number of tumors	1.65 (0.99–2.60)	0.054	1.93 (1.12–3.17)	0.019
Postoperative serious complications (Clavien–Dindo ≥ III) yes/no	0.93 (0.36–1.99)	0.869		

HCC hepatocellular carcinoma, *HR* hazard ratio, *CI* confidence interval, *LR* liver resection, *RFA* radiofrequency ablation, *HBsAg* hepatitis B surface antigen, *HCVAb* hepatitis C virus antibody, *ASA* American Society of Anesthesiologists physical status score, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention test at 15 min, *AFP* alpha-fetoprotein

Recurrence pattern and treatment modalities after recurrence

At the time of data collection, tumor recurrence had developed in 34 of the 81 patients in the LR group: 33 (40.7 %) intrahepatic distant recurrences and 1 (1.2 %) local recurrence. In the RFA group, tumor recurrence had developed in 34 of the 40 patients: 27 (67.5 %) intrahepatic distant recurrences and 7 (17.5 %) local recurrences. The differences in intrahepatic distant recurrence and local recurrence were significant ($P = 0.0056$ and $P = 0.0007$, respectively).

Table 5 shows the treatment modalities after tumor recurrence in both groups of HCC patients with PHT. The most frequent treatment modality for patients in the LR and RFA groups with recurrent disease was TACE. Within the recurrence cohort, hepatic resection was significantly more frequent in the LR group than in the RFA group ($P = 0.031$), while the RFA group had a significantly higher frequency of repeat RFA (including RFA plus TACE) ($P = 0.0006$).

OS and RFS after IPTW adjustment

Among the 18 clinicopathological variables (age, sex, HBsAg, anti-HCV antibody, EVs, ASA status, albumin, total bilirubin, AST, ALT, creatinine, prothrombin activity, platelet count, $ICGR_{15}$, Child-Pugh score, AFP levels, maximum tumor diameter, and number of tumors), the distributive covariates that differed between the LR and RFA groups were total bilirubin, $ICGR_{15}$, and maximum tumor diameter (Table 1). After IPTW adjustment of these covariates, the weighted OS of the LR group was not significantly lower than that of the RFA group ($P = 0.485$, adjusted HR 1.35; 95 % CI 0.57–3.21; Fig. 2a). By contrast, the weighted RFS of the LR group remained significantly lower than that of the RFA group ($P = 0.00014$, adjusted HR 0.37; 95 % CI 0.22–0.61; Fig. 2b).

Subgroup analyses

As >70 % of patients in the original cohort were anti-HCV positive, subgroup analysis was performed. The 5-year OS

Table 4 Complications and mortality of early HCC patients with portal hypertension receiving LR or RFA

Variables	LR group (n = 81)	RFA group (n = 40)	*P* value
Complications	38 (46.9 %)	5 (12.5 %)	<0.0001
Clavien–Dindo classification			
Grade I			
Shoulder pain	0 (0.0 %)	1 (2.5 %)	
Ascites (treated with diuretics)	6 (7.4 %)	0 (0.0 %)	
Grade II			
Superficial surgical site infection	6 (7.4 %)	0 (0.0 %)	
Colitis	3 (3.7 %)	0 (0.0 %)	
Cholangitis	1 (1.2 %)	3 (7.5 %)	
Delirium	2 (2.5 %)	0 (0.0 %)	
Bile leakage (treated with antibiotics)	2 (2.5 %)	0 (0.0 %)	
Pneumonia 2	(2.5 %)	0 (0.0 %)	
Atrial fibrillation	1 (1.2 %)	0 (0.0 %)	
Deep vein thrombosis	1 (1.2 %)	0 (0.0 %)	
Urinary tract infection	1 (1.2 %)	0 (0.0 %)	
Grade IIIa			
Pleural effusion (requiring drainage)	1 (1.2 %)	1 (2.5 %)	
Deep surgical site infection	5 (6.0 %)	0 (0.0 %)	
Bile leakage (requiring drainage)	3 (3.7 %)	0 (0.0 %)	
Grade IVa			
Liver failure	2 (2.5 %)	0 (0.0 %)	
Grade V			
Sepsis	1 (1.2 %)	0 (0.0 %)	
Postoperative serious complications			
(Clavien–Dindo grade III or higher)	13 (16.1 %)	1 (2.5 %)	0.025
Mortality	1 (1.2 %)	0 (0.0 %)	

HCC hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation

rates in anti-HCV patients who underwent LR (29.6 %) and RFA (56.1 %) were comparable, whereas the 5-year RFS rate was significantly higher in the LR than in the RFA group (46.2 vs. 0 %, $P < 0.0001$). IPTW analysis showed that OS did not differ significantly in the LR and RFA groups ($P = 0.7258$, adjusted hazard ratio [aHR] 1.182; 95 % confidence interval [CI] 0.45–3.1), whereas RFS was significantly higher in the LR than in the RFA group ($P < 0.0001$, aHR 0.32; 95 % CI 0.18–0.56).

The LR and RFA groups also differed significantly in the percentages with BCLC stages 0 and A (Table 1). Crude analyses showed that 5-year RFS was significantly higher in BCLC 0 ($P = 0.0002$, Fig. 3a) and A ($P = 0.036$, Fig. 3b) patients who underwent LR than RFA. IPTW analyses of the BCLC 0 and A groups also showed that 5-year RFS was significantly higher with LR than with RFA in BCLC stage 0 ($P = 0.0017$, aHR 0.25; 95 % CI 0.12–0.51; Fig. 4a). RFS was also significantly better in the LR than in the RFA group in BCLC stage A ($P = 0.040$, aHR 0.45; 95 % CI 0.22–0.93; Fig. 4b).

Discussion

Neither the BCLC nor the AASLD Group guidelines recommend LR for patients with BCLC stage 0 or A HCC and PHT; however, for these patients the guidelines do recommend RFA or liver transplantation. In patients with cirrhosis and/or PHT and disease extent within the Milan criteria, liver transplantation is clearly the best option [23]. But given the serious shortage of available liver transplant donor organs [8], surgical resection may be the next best option for the treatment of some HCC patients with clinical PHT [9]. The major drawback in these recommendations is that they were formulated in the absence of a control, nonsurgical treatment group that could be compared with the group of HCC patients with PHT who underwent surgical resection.

To date, there have been only a few studies comparing the outcome of patients with BCLC stage 0 and A HCC and PHT who underwent LR vs. RFA. In a recent report, LR was shown to be a safe procedure for patients with HBV-

Table 5 Recurrence pattern and treatment modalities of HCC patients with portal hypertension who underwent LR or RFA

Variables	LR group ($n = 81$)	RFA group ($n = 40$)	P value
Recurrence	34	34	<0.001
Intrahepatic distant recurrence	33 (40.7 %)	27 (67.5 %)	0.0056
TACE	19 (23.4 %)	10 (25.0 %)	
TACE and RFA	0	2 (5.0 %)	
TACE and liver resection	0	0	
RFA	2 (2.5 %)	9 (22.5 %)	
Liver resection	10 (12.3 %)	2 (5.0 %)	
MCT under laparotomy	2 (2.5 %)	1 (2.5 %)	
Radiation	0	1	(2.5 %)
Best supportive care	0	2 (5.0 %)	
Local recurrence	1 (1.2 %)	7 (17.5 %)	0.0007
TACE	0	2 (5.0 %)	
TACE and RFA	0	0	
TACE and liver resection	0	1 (2.5 %)	
RFA	0	3(7.5 %)	
Liver resection	0	0	
MCT under laparotomy	0	0	
Radiation	0	0	
Best supportive care	1 (1.2 %)	1 (2.5 %)	

HCC hepatocellular carcinoma, *LR* liver resection, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *MCT* microwave coagulation therapy

related PHT and it conferred a survival advantage over ablation. Thus, LR may be recommended as an optimal form of treatment for these patients [24].

In the present study, LR resulted in a significantly better RFS than achieved with RFA for patients with BCLC stage 0 or A HCC and PHT. However, in clinical studies, bias often arises in the selection of patients with BCLC stage 0 and A HCC, because those with PHT may prefer minimally invasive treatment, and thus RFA rather than LR. To reduce the potential for bias in patient selection, an IPTW analysis was conducted. A comparison of the background characteristics of the two group showed that the RFA group had significantly higher serum total bilirubin level and $ICGR_{15}$ and a smaller maximum tumor diameter than the LR group. These results implied that our BCLC stage 0 or A HCC patients with PHT who underwent RFA had more severe liver dysfunction than the patients in the LR group. Patients in the latter had a greater maximum tumor diameter than those in the RFA group. Thus, some patients with slightly better liver function [25] and a greater maximum tumor diameter [19, 26] may be candidates for LR. Using data from the BRIDGE study, Roayaie et al. clearly demonstrated that safe hepatic resection with excellent outcomes is possible for patients with moderate PHT or for those with slightly elevated bilirubin, but not both [27].

The reason for the better RFS of the LR group than the RFA group is unclear; however, at least in theory, LR has the advantage of offering better local control of HCC, whereas RFA carries with it the potential risk of local recurrence associated with insufficient ablation [26]. Moreover, about one-fourth of the patients in the LR group underwent anatomical resection to remove minute tumor satellites [28], which might have decreased the intrahepatic recurrence rate compared with the RFA group. Based on the tumor location data, no patients with S1 tumors underwent RFA, which suggests that LR, but not RFA, can be performed regardless of tumor location.

Despite significant differences in recurrence rates, survival rates were similar in the LR and RFA groups. Patients were followed-up every 3 months after RFA treatment, enabling the early detection of recurrence and more rapid and appropriate treatment with surgical or interventional methods. As a result, the high HCC recurrence rate in the RFA group did not markedly increase the death rate.

In addition, there are several limitations to the use of RFA based on the location of the tumor(s). Specifically, in patients with tumors overhanging the liver margin and approaching adjacent organs such as the gallbladder, stomach, or colon, or tumors located near major intrahepatic vessels, RFA may be technically unfeasible owing to the risk of thermal injuries to these structures [29]. In our study, all ablation procedures were performed in our hospital by one of the two experienced hepatologists, each

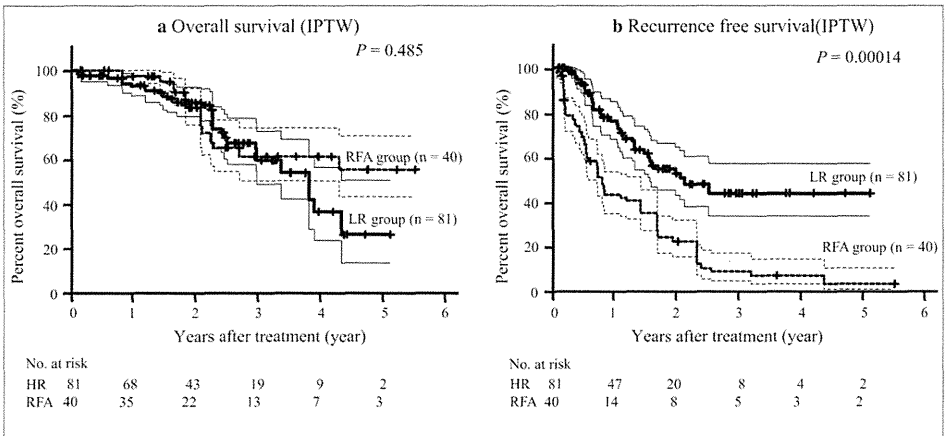

Fig. 2 **a** Kaplan–Meier curve after inverse probability treatment weighting (IPTW) showing OS after treatment. The percent OS of the LR group (*bold black line*) was comparable to that of the RFA group (*bold dotted line*, $P = 0.485$). **b** Kaplan–Meier curve after IPTW showing RFS after treatment. The RFS of the LR group (*bold black line*) was significantly better than that of the RFA group (*bold dotted line*, $P = 0.00014$). Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

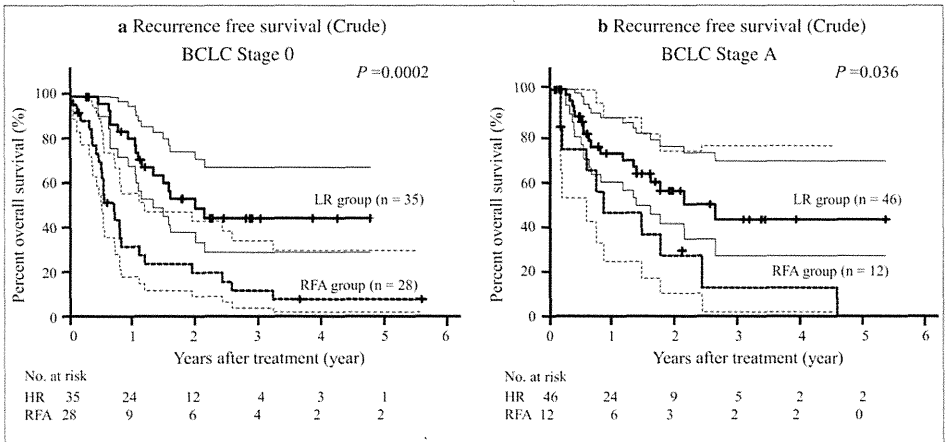

Fig. 3 Prognosis of patients with BCLC stage 0 ($n = 63$) and A ($n = 58$) HCC and portal hypertension who underwent liver resection or radiofrequency ablation therapy. **a** Unweighted (crude) Kaplan–Meier curve showing the percent RFS after treatment. The RFS of the LR group ($n = 35$; *bolded black line*) was significantly better than that of the RFA group ($n = 28$, *bold dotted line*, $P = 0.0002$) in BCLC stage 0. **b** Unweighted (crude) Kaplan–Meier curve of RFS after treatment. The RFS of the LR group ($n = 46$; *bold black line*) was significantly better than that of the RFA group ($n = 12$; *bold dotted line*, $P = 0.036$) in BCLC stage A. Each confidence interval of the RFS were displayed using normal *black* and *dotted line*

with at least 10 years of experience in RFA. Nonetheless, the local recurrence rate was 17.5 %. In a previous study, local recurrence rates ranged from 0.9 to 33.3 %; in cirrhotic patients, they were as high as 46.2 % [30]. Thus, local recurrence remains a challenging issue in cirrhotic patients with PHT who have been treated with RFA.

Our study showed that RFA was associated with fewer postoperative complications and shorter hospital stays

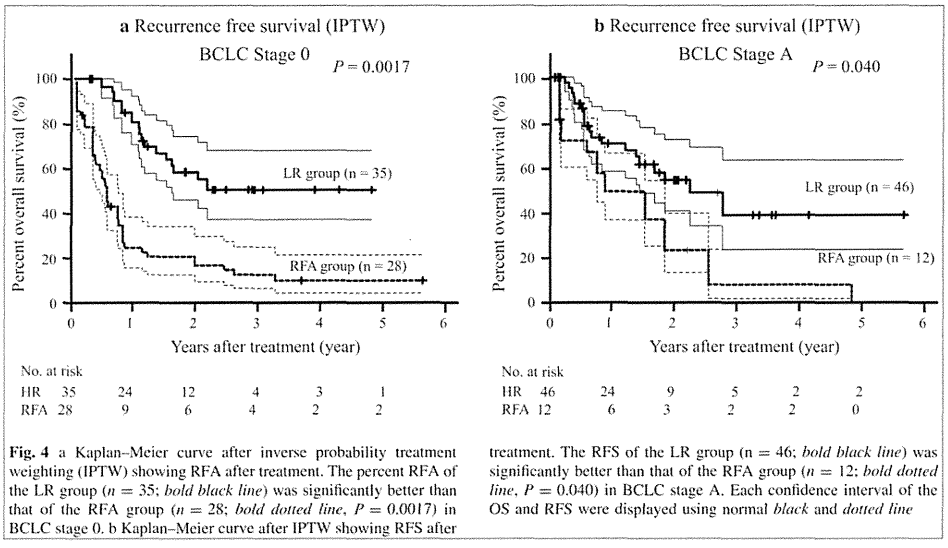

Fig. 4 a Kaplan–Meier curve after inverse probability treatment weighting (IPTW) showing RFA after treatment. The percent RFA of the LR group ($n = 35$; *bold black line*) was significantly better than that of the RFA group ($n = 28$; *bold dotted line*, $P = 0.0017$) in BCLC stage 0. b Kaplan–Meier curve after IPTW showing RFS after treatment. The RFS of the LR group (n = 46; *bold black line*) was significantly better than that of the RFA group ($n = 12$; *bold dotted line*, $P = 0.040$) in BCLC stage A. Each confidence interval of the OS and RFS were displayed using normal *black* and *dotted line*

after treatment. These results are in agreement with those of a previous meta-analysis comparing RFA and LR [31]. LR is a more invasive treatment than RFA and requires careful intraoperative management of hemostasis and the endoscopic treatment of EVs [9]. Similarly, HCC patients with PHT require meticulous postoperative management and treatment should be carried out only in specialized high-volume centers [5].

There were several limitations to our study. First, the sample size was relatively small, which made it difficult to evaluate the outcome of HCC patients with BCLC stage 0 and A disease and PHT who underwent LR or RFA. However, unlike in other studies, tumor location, surgical procedure, postoperative complications, and treatment after recurrence were evaluated in detail. Second, our study results might not be applicable in other centers because ours was a single-center study and our study was not an randomized controlled trial.

Despite these limitations, our findings contribute to validating the current BCLC and AASLD criteria by providing additional clinical evidence subjected to IPTW analysis to compare LR and RFA. In the study by Roayaie et al. [27], only one-third of the 2342 patients undergoing LR fulfilled the criteria for this procedure.

In conclusions, our results suggest that, by caring for postoperative complications, LR is an appropriate treatment option for patients with BCLC stage 0 or A HCC and PHT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Forner A, Reig ME, Bruix J et al (2010) Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30(1):61–74
2. Bruix J, Sherman M, American Association for the Study of Liver Diseases (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022
3. Bruix J, Castells A, Rodés J et al (1996) Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 111(4):1018–1022
4. Llovet JM, Brú C, Bruix J (1996) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19(3):329–338
5. Ishizawa T, Kokudo N, Makuuchi M et al (2008) Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 134(7):1908–1916
6. Cucchetti A, Ercolani G, Pinna AD et al (2009) Is portal hypertension a contraindication to hepatic resection? Ann Surg 250(6):922–928
7. Capussotti L, Ferrero A, Bouzari H et al (2006) Portal hypertension: contraindication to liver surgery? World J Surg 30(6):992–999. doi:10.1007/s00268-005-0524-9

8. Dutkowski P, Müllhaupt B, Clavien PA et al (2014) Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 148:307–323
9. Harada N, Shirabe K, Maehara Y et al (2015) Surgical resection for hepatocellular carcinoma with concomitant esophageal varices. World J Surg 39:2510–2518. doi:10.1007/s00268-015-3110-9
10. Austin PC (2012) The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 32:2837–2849
11. Bezerra AS, D'Ippolito G, Ahmed M et al (2005) Determination of splenomegaly by CT: is there a place for a single measurement? AJR Am J Roentgenol 184(5):1510–1513
12. Shirabe K, Takeishi K, Maehara Y et al (2011) Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. World J Surg 35:1072–1084. doi:10.1007/s00268-011-1013-y
13. Yamashita YI, Shirabe K, Maehara Y et al (2014) Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution. Am J Surg 13:522–529
14. Takeishi K, Shirabe K, Maehara Y et al (2011) Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. World J Surg 35(5):1063–1071. doi:10.1007/s00268-011-1017-7
15. Pugh RN, Pietroni MC, Williams R et al (1973) Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60(8):646–649
16. Chau GY, King KL, Wu CW et al (2005) Evaluation of effect of hemihepatic vascular occlusion and the Pringle maneuver during hepatic resection for patients with hepatocellular carcinoma and impaired liver function. World J Surg 29(11):1374–1383. doi:10.1007/s00268-005-7766-4
17. Kawamura H, Kamiyama T, Todo S et al (2008) Preoperative evaluation of hepatic functional reserve by converted ICGR15 calculated from Tc-GSA scintigraphy. J Gastroenterol Hepatol 23(8 Pt 1):1235–1241
18. Rhim H, Lim HK, Choe BK et al (2010) Ultrasonography-guided percutaneous radiofrequency ablation of hepatocellular carcinomas: a feasibility scoring system for planning sonography. Eur J Radiol 75(2):253–258
19. Waki K, Aikata H, Chayama K et al (2010) Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. J Gastroenterol Hepatol 25(3):597–604
20. Tajiri T, Yoshida H, Idezuki Y et al (2010) General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc 22(1):1–9
21. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213
22. Rahbari NN, Garden OJ, Weitz J et al (2011) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 149(5):713–724
23. Jarnagin WR (2010) Management of small hepatocellular carcinoma: a review of transplantation, resection, and ablation. Ann Surg Oncol 17(5):1226–1233
24. Qiu J, Zheng Y, Yuan Y et al (2015) Resection versus ablation in hepatitis B virus-related hepatocellular carcinoma patients with portal hypertension: A propensity score matching study. Surgery 158:1235–1243
25. Kokudo N (2015) Is it a time to modify the BCLC guidelines in terms of the role of surgery? World J Surg 39(2):469–470. doi:10.1007/s00268-014-2915-2
26. Cammà C, Di Marco V, Craxì A et al (2005) Unità Interdipartimentale Neoplasie Epatiche (U.I.N.E) Group. Treatment of hepatocellular carcinoma in compensated cirrhosis with radiofrequency thermal ablation (RFTA): a prospective study. J Hepatol 42(4):535–540
27. Roayaie S, Jibara G, Sherman M et al (2015) The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 62:440–451
28. Makuuchi M, Hasegawa H, Yamazaki S (1985) Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet 161(4):346–350
29. Fonseca AZ, Santin S, Ribeiro MA Jr et al (2014) Complications of radiofrequency ablation of hepatic tumors: Frequency and risk factors. World J Hepatol 6(3):107–113
30. Bertrand J, Caillol F, Giovannini M et al (2015) Percutaneous hepatic radiofrequency for hepatocellular carcinoma: results and outcome of 46 patients. Hepat Med 7:21–27
31. Duan C, Ma K, Bie P (2013) Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis. World J Surg Oncol 11(1):190

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Original Article

Simeprevir or telaprevir with peginterferon and ribavirin for recurrent hepatitis C after living-donor liver transplantation: A Japanese multicenter experience

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Aim: This study aimed to clarify the efficacy and safety of simeprevir, a second-generation NS3/4A inhibitor, with peginterferon and ribavirin for recurrent hepatitis C after liver transplantation.

Methods: A retrospective cohort study of living-donor liver transplant recipients with recurrent hepatitis C with the hepatitis C virus genotype 1 treated with either simeprevir- or telaprevir-based triple therapy was carried out at eight Japanese liver transplant centers.

Results: Simeprevir- and telaprevir-based triple therapies were given to 79 and 36 patients, respectively. Of the 79 patients treated with simeprevir-based triple therapy, 44 (56%) achieved sustained virological response 12 weeks (SVR12) after treatment ended, and there was no significant difference in the SVR12 between the simeprevir- and telaprevir-based triple therapy groups (69%). The rates of adverse events were not significantly different between the simeprevir- and telaprevir-based triple therapy groups, although the rate of patients who received blood cell transfusion and erythropoietin due to anemia and had renal insufficiency were significantly higher in the telaprevir group than in the simeprevir group. Three baseline factors, the presence of prior dual therapy with peginterferon and ribavirin ($P = 0.001$), a non-responder to the prior dual therapy ($P < 0.001$), and male sex ($P = 0.040$), were identified as significant predictive factors for non-SVR with simeprevir-based triple therapy.

Conclusion: Simeprevir-based triple therapy for recurrent hepatitis C after living-donor liver transplantation resulted in a high SVR rate and good tolerability, especially in treatment-naive patients.

Key words: hepatitis C, liver transplantation, living donor, simeprevir, telaprevir

INTRODUCTION

LIVER CIRRHOSIS AND hepatocellular carcinoma caused by hepatitis C virus (HCV) infection are the leading indications for liver transplantation in many countries, including Japan. However, almost all HCV-positive recipients develop recurrent hepatitis C.[1–3] After hepatitis C recurrence, the progression of fibrosis in the transplanted liver is often accelerated, and 10–30% of transplant recipients with an HCV infection develop cirrhosis within 5 years,[4–8] resulting in a poorer prognosis for HCV-positive recipients than HCV-negative recipients.[2,9]

To prevent the progression of hepatitis C after liver transplantation, dual therapy with peginterferon and ribavirin

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has been administered as standard therapy for a long time.[10,11] However, the efficacy of dual therapy for liver transplant recipients is limited, with a mean sustained virological response (SVR) rate of only 30% (range, 8–50%).[12] In addition, many adverse events due to dual therapy, including immune-mediated graft dysfunction (IGD), have been reported.[13]

The first direct acting antivirals (DAA), telaprevir and boceprevir in combination with peginterferon and ribavirin, became available for clinical use in 2011. However, using these first-generation NS3/4A inhibitors in liver transplant recipients is challenging because of the drug–drug interaction with calcineurin inhibitors, tacrolimus, and cyclosporine.[14] Triple therapy with telaprevir or boceprevir in addition to peginterferon and ribavirin reportedly increases the SVR rate to 50–63%, according to findings from large multicenter studies.[15–18] Severe anemia, renal dysfunction, and infection, in addition to the adverse events observed with dual therapy, were frequently observed during triple therapy, and patients died while receiving triple therapy.

Since 2013, the second-generation NS3/4A inhibitor simeprevir along with peginterferon and ribavirin has been used in patients with recurrent hepatitis C after liver transplantation. Simeprevir has two major benefits for use in liver transplant recipients compared with the first-generation NS3/4A inhibitors telaprevir and boceprevir. First, no clinically significant interactions were observed between simeprevir and calcineurin inhibitors in transplant recipients.[19–21] Second, there are fewer adverse events associated with simeprevir-based triple therapy. In non-transplant settings, the incidence of severe adverse events and treatment discontinuation due to adverse events did not increase with simeprevir-based triple therapy compared to dual therapy with peginterferon and ribavirin.[22–25] However, telaprevir-based triple therapy showed more frequent adverse events, including anemia and skin rush, compared to dual therapy.[26–28] Therefore, simeprevir-based triple therapy may be safe and effective therapy for liver transplant recipients, although the efficacy and safety of this therapy is largely unknown.

More recently, the high efficacy and safety of interferon-free therapy for recurrent hepatitis C after liver transplantation have been reported.[29–32] Sofosbuvir-based regimens, in particular, have shown no clinically significant drug–drug interactions with immunosuppressive agents, and they achieve a high SVR rate in transplant recipients.[29,30,32] Therefore, first-line therapy for recurrent hepatitis C after liver transplantation has been changed to interferon-free therapy.[33] However, several obstacles must be overcome to use interferon-free therapy in liver transplant recipients, including DAA-resistant HCV, the high cost, and treatment for decompensated cirrhosis. For these reasons, interferon-containing therapy would be one of the treatment options, even in this interferon-free therapy era. Interferon-containing therapy will need to be used for some populations of patients, for example, those with multiple DAA-resistant HCV, and patients who cannot afford to use interferon-free therapy. Therefore, the efficacy and safety of DAA-containing triple therapy, especially second-generation NS3/4A inhibitors with peginterferon and ribavirin, should be clarified.

We evaluated the efficacy and safety of the second-generation NS3/4A inhibitor simeprevir-based triple therapy by comparing it with the first-generation NS3/4A inhibitor telaprevir-based triple therapy in patients with recurrent hepatitis C after living-donor liver transplantation (LDLT) in a Japanese multicenter study.

METHODS

Study design and patients

THIS WAS A retrospective cohort study of LDLT recipients with recurrent hepatitis C and the HCV genotype 1 treated with either simeprevir- or telaprevir-based triple therapy at eight Japanese liver transplant centers. Data were collected until July 2015.

The study protocol was approved by the ethics committee of each liver transplant center, and written informed consent was obtained from patients for participation.

Treatment protocol

Triple therapy with simeprevir or telaprevir, peginterferon, and ribavirin was administered for the first 12 weeks, followed by dual therapy with peginterferon and ribavirin for at least another 12 weeks. Telaprevir- and simeprevir-based triple therapies were administered when patients were diagnosed with recurrent hepatitis C between November 2011 and November 2013, and between December 2013 and August 2014, respectively. Telaprevir was administered at a dose of 1500 mg/day (750 mg twice daily) or 2250 mg/day (750 mg three times daily). Simeprevir was administered at a dose of 100 mg once daily. The standard dose of peginterferon was 180 μg for peginterferon α-2a or 1.5 μg/kg of peginterferon α-2b per week. The standard ribavirin dose was determined based on the patient's body weight (BW): 600 mg/day for BW <60 kg, 800 mg/day for BW of 60–80 kg, and 1000 mg/day for BW >80 kg. These doses were reduced according to renal function, the baseline hemoglobin level, and anemia during the previous treatment, at the investigator's discretion. The management of anemia, including the

use of erythropoietin and blood transfusion, was not standardized across centers and was determined at the investigator's discretion. The selection of immunosuppressive drugs and conversion from tacrolimus to cyclosporine before treatment was decided by the investigators at each center. The blood concentration of cyclosporine or tacrolimus was adjusted using therapeutic drug monitoring. The reduction and discontinuation of treatment were also left to the investigator's discretion.

Study definitions

The HCV genotype was determined using a genotyping system based on polymerase chain reaction (PCR) of the core region using genotype-specific primers.[34] The serum HCV RNA load was evaluated using a real-time PCR-based quantification method for HCV (COBAS AmpliPrep/COBAS TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, USA). The host interleukin (IL)-28B genotype for single nucleotide polymorphism at rs8099917 and inosine triphosphatase genotype for single nucleotide polymorphism at rs1127354 were analyzed with the InvaderPlus assay, which combines PCR and the invader reaction using methods previously reported.[35]

The rapid virological response (RVR), complete early virological response (cEVR), and end-of-treatment response (ETR) were defined as HCV RNA undetectable at 4 weeks, 12 weeks, and end of treatment, respectively. The absence of HCV RNA in the serum for >12 weeks after completing treatment was defined as SVR12. Breakthrough and relapse were defined as the reappearance of HCV RNA in the serum after being undetectable during treatment and after discontinuing therapy, respectively.

Safety assessments

Patients were hospitalized before the initiation of treatment and received strict clinical monitoring until they were stabilized. Clinical and biological data were collected during treatment. All adverse events were recorded during the

Table 1 Characteristics of patients treated with protease inhibitor with peginterferon and ribavirin after living-donor liver transplantation (LDLT)

	Simeprevir $n = 79$	Telaprevir $n = 36$	*P*-value
Age, years	62 (42–73)	60 (42–70)	0.049†
Males / females	35/44	24/12	0.026‡
Weight, kg	56.5 (35.4–84.9)	62.0 (36.0–120.2)	0.052†
Body mass index	21.8(13.8–33.1)	22.0 (16.2–41.4)	0.816†
Graft type left / right / dual	40/39/0	15/20/1	0.443‡
Splenectomy	66	33	0.243‡
Months from LDLT to therapy	29 (2–147)	26 (2–92)	0.524†
Recipient IL28B genotype (rs8099917)			
TT / TG / GG / not examined	48/19/3/9	23/13/0/0	0.079‡
Donor IL28B genotype (rs8099917)			
TT / TG / GG / not examined	28/8/1/42	22/6/0/8	0.015‡
Recipient ITPA genotype (rs1127354)			
CC / CA / AA / not examined	38/1/1/39	20/3/0/13	0.155‡
HCV RNA, log copies/mL	6.8 (4.9–7.8)	6.45 (2.7–7.8)	0.004†
HCV genotype 1a /1b / unspecified	2/71/6	1/35/0	0.236‡
Hemoglobin, g/dL	11.6 (8.1–16.0)	12.35 (6.8–16.0)	0.372†
eGFR, mL/min/1.73 m^2	61.0 (29.9–138.8)	64.5 (32.1–114.0)	0.171†
Calcineurin inhibitor tacrolimus / cyclosporine / none	48/28/3	5/31/0	<0.001‡
MMF	36	19	0.473‡
Peginterferon α-2a/α-2b	20/59	0/36	0.001‡
Prior dual therapy post-transplant			
NR / relapse / withdrawal / none / uncertain	41/19/3/16/0	19/6/3/7/1	0.658‡

Qualitative variables are shown in number; quantitative variables are expressed as median (range) for non-normally distributed variables.
†Wilcoxon test.
‡χ^2-test.
eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IL28B, interleukin-28B; ITPA, inosine triphosphatase; MMF, mycophenolate mofetil; NR, no response.

treatment period and until 12 weeks after the last dose was given. Blood transfusion, the use of growth factors, and reductions and discontinuations of simeprevir, telaprevir, peginterferon, and ribavirin were also recorded.

Statistical analysis

The characteristics of patients, adverse events, and virological response to treatment were described and compared between simeprevir-based triple therapy and telaprevir-based triple therapy (Tables 1, 2; Figs. 1, 2). Predictive factors associated with SVR were described and compared between the SVR and non-SVR groups (Table 3, Fig. 3). For continuous variables that were nearly symmetrically distributed, means and standard deviations are given, and these data were analyzed by the *t*-test. For non-normally distributed variables, medians and ranges are presented, and the data were analyzed by Wilcoxon tests. For categorical variables, counts are given, and the data were analyzed by the χ^2-test. $P < 0.05$ was considered significant.

RESULTS

Patients' characteristics

BETWEEN SEPTEMBER 2012 and July 2015, 115 patients with recurrent hepatitis C with the HCV genotype 1 after LDLT completed treatment with NS3/4A inhibitor-based triple therapy and were followed for at least 12 weeks at eight transplant centers in Japan after treatment was terminated. In the 115 patients, simeprevir was used in 79 (69%, simeprevir group) and telaprevir was used in 36 (31%, telaprevir group) (Fig. 1).

A comparison of the patients' baseline characteristics in the simeprevir group and telaprevir group is presented in Table 1. Six characteristics were significantly different between the two groups, including age, sex, the donor IL28B genotype, the HCV RNA load, type of calcineurin inhibitors, and type of peginterferon. Patients in the telaprevir group were significantly younger than those in the simeprevir group. More women were treated with simeprevir. The donor IL28B genotype was not examined in 42 patients (53%) in the simeprevir group compared to 8 patients (22%) in the telaprevir group because a Japanese phase III trial for patients in non-transplant settings showed that there are no clinically relevant differences in the efficacy of simeprevir-based triple therapy according to the IL28B genotype.[23,36] The serum HCV RNA levels before treatment were significantly lower in the telaprevir group than in the simeprevir group. Cyclosporine was preferentially used with telaprevir because the drug–drug interaction of cyclosporine with telaprevir has been reported to be much less than that of tacrolimus.[14] Peginterferon α-2b was

Table 2 Adverse events during triple therapy after living-donor liver transplantation

Adverse events	Simeprevir ($n = 79$) *n* (%)	Telaprevir ($n = 36$) *n* (%)	*P*-value
Any adverse event	49 (62)	26 (72)	0.287
Any adverse event leading to discontinuation of treatment	10 (13)	7 (19)	0.342
Serious adverse event	9 (11)	9 (25)	0.063
Death	2 (3)	1 (3)	0.939
Anemia			
Lowest hemoglobin <10 g/dL	61 (77)	31 (86)	0.269
Lowest hemoglobin <8 g/dL	35 (44)	17 (47)	0.771
Lowest hemoglobin <6 g/dL	4 (5)	5 (14)	0.102
Received blood cell transfusion	14 (18)	16 (44)	0.002
Use of erythropoietin	4 (5)	6 (17)	0.041
Renal insufficiency			
eGFR >30 decrease from baseline	8 (10)	14 (39)	<0.001
Symptomatic skin rash	5 (6)	2 (6)	0.872
Immune-mediated graft dysfunction	6 (8)	4 (11)	0.535
Acute cellular rejection	3	0	
Chronic rejection	1	0	
Plasma cell hepatitis	0	4	
Veno-occlusive disease	2	0	
Infection	1 (1)	3 (8)	0.055

eGFR, estimated glomerular filtration rate; *n*, number of patients.

Table 3 Predictive factors associated with sustained virological response 12 weeks after treatment ended (SVR12) in patients with simeprevir triple therapy

		SVR $n = 44$	Non-SVR $n = 35$	*P*-value
Age, years		62.9 (5.2)	59.7 (8.4)	0.052†
Gender	Male	15 (43%)	20 (57%)	0.040‡
	Female	29 (66%)	15 (34%)	
Weight, kg		56.2 (10.5)	58.8 (11.1)	0.280†
Body mass index		22.7 (4.0)	22.5 (3.9)	0.860†
Graft type	Left	25 (62.5%)	15 (37.5%)	0.218‡
	Right	19 (49%)	20 (51%)	
Splenectomy	Yes	36 (55%)	30 (45%)	0.643‡
	No	8 (62%)	5 (38%)	
Months from LDLT to therapy		28 (2–118)	41 (5–147)	0.194§
Recipient IL28B genotype	TT	30 (62.5%)	18 (37.5%)	0.181‡
(rs8099917)	TG or GG	10 (45%)	12 (55%)	
	Not examined	4	5	
HCV RNA, log copies/mL		6.7 (0.6)	6.9 (0.5)	0.087†
Hemoglobin, g/dL		11.25 (8.1–15.8)	12.5 (8.5–16.0)	0.636§
eGFR, mL/min/1.73 m^2		57.5 (32.9–138.8)	62.8 (29.9–101.0)	0.459§
Calcineurin inhibitor	Tacrolimus	25 (52%)	23 (48%)	0.179‡
	Cyclosporine	19 (68%)	9 (32%)	
	None	0	3	
MMF	Yes	19 (53%)	17 (47%)	0.633‡
	No	25 (58%)	18 (42%)	
Prior dual therapy	Yes	29 (46%)	34 (54%)	0.001‡
	No	15 (94%)	1 (6%)	
Prior dual therapy	No response	14 (34%)	27 (66%)	<0.001‡
	Relapse or withdrawal or none	30 (79%)	8 (21%)	
Peginterferon	α-2a	12 (60%)	8 (40%)	0.654‡
	α-2b	32 (54%)	27 (46%)	

Qualitative variables are shown in number (%); quantitative variables are expressed as mean (standard deviation) for continuous variables that were nearly symmetrically distributed, or as median (range) for non-normally distributed variables.
†*t*-test.
‡χ^2-test.
§Wilcoxon test.
eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IL28B, interleukin-28B; LDLT, living donor liver transplantation; MMF, mycophenolate mofetil.

given to all patients treated with telaprevir, whereas 20 patients (25%) in the simeprevir group received peginterferon α-2a.

Efficacy

Of the 79 patients treated with simeprevir-based triple therapy, 58 completed the treatment protocol, whereas 21 discontinued treatment due to adverse events ($n = 10$), no virological response ($n = 7$), or viral breakthrough during treatment ($n = 4$) (Fig. 1). Forty-four (56%) of 79 patients achieved SVR12. Of the 36 patients who received telaprevir-based triple therapy, 28 completed the treatment protocol, whereas 8 discontinued treatment because of adverse events ($n = 7$) or no virological response to the treatment ($n = 1$). SVR12 was achieved in 25 patients (69%) who received telaprevir-based triple therapy.

Figure 2 shows the virological outcomes of simeprevir-based triple therapy and telaprevir-based triple therapy. The serum level of HCV RNA became undetectable within 4 weeks (i.e., RVR) in 48% and 53% of patients in the simeprevir and telaprevir groups, respectively, and >80% of the patients achieved cEVR in both groups. End-of-treatment response was achieved in 78% and 83% of the patients in the simeprevir and telaprevir groups, respectively. Finally, the SVR12 rates were 56% and 69% for simeprevir-based triple therapy and telaprevir-based triple therapy, respectively. Simeprevir-based triple therapy tended to have lower rates of RVR, cEVR, ETR, and SVR12