44 patients in the early period group and 21 in the late period group ($p = 0.0017$). Platinum-doublet adjuvant chemotherapy was administered to 3 patients in the early period group and 150 in the late period group ($p < 0.0001$). There was no significant difference between the two groups with regard to sex, smoking history, preoperative $FEV_{1.0}$, pathological stage, and histological types (Table 1).

The 1-year mortality rate was 4.5 % (100/2207) in both the groups; however, it significantly decreased from 6.2 % (66/1070) in the early period group to 3.0 % (34/1137) in the late period group ($p = 0.0003$, Table 2). Furthermore, in those who died from recurrence, it significantly decreased from 5.1 % (55/1070) in the early period group to 1.8 % (20/1137) in the late period group ($p < 0.0003$, Table 2). On the other hand, the 1-year mortality rates of patients' death due to other causes were similar between the two groups (Table 2). The overall 30- and 90-day mortality rates were 0.45 % (10/2207) and 0.77 % (17/2207), respectively (Table 3). The 30- and 90-day mortality rates were 0.56 % (6/1070) and 0.75 % (8/1070) in the early period group and 0.35 % (4/1137) and 0.79 % (9/1137) in the late period group, respectively. There was no statistical difference between the two groups.

Postoperative survival days according to the cause of death are presented in Fig. 1. Bleeding and sudden death were the cause of death in four and three patients, respectively (Table 2). These seven patients died within 30 days after pulmonary resection. Of the four patients with bleeding as the cause of death, two in the early period group died from massive hemoptysis on the 4th and 26th days after pulmonary resection, respectively, and two in the late period group died on the 3rd day after pulmonary resection due to hemorrhage in the pleural cavity and massive hemoptysis due to intraoperative pulmonary artery injury, respectively. Of the three patients who experienced sudden death, one patient from each group was found to have suffered cardiopulmonary arrest on the 30th day after pulmonary resection during therapy at home. Another patient in the late period group was discovered in a hospital bathroom after suffering cardiopulmonary arrest on the 6th day after pulmonary resection. Although an autopsy was performed on this patient, the cause of death could not be determined. In all three cases recorded as sudden death, the cause may have been cardiogenic, but other causes were unknown. In those with respiratory failure as the cause of death, three of eight in the early period group and none in the late period group died within 30 days after pulmonary resection. The median postoperative survival in the early and late period groups was 67 days (20–142 days) and 100 days (47–149 days), respectively. We did not identify

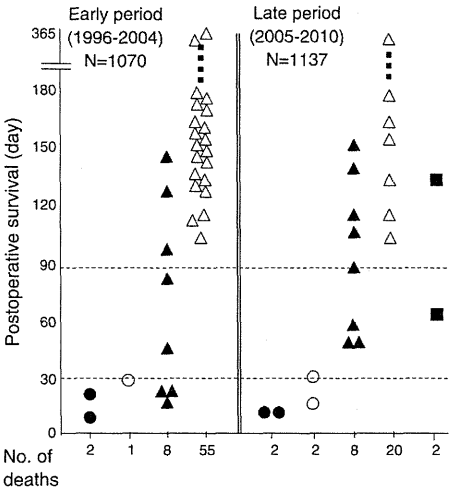

Fig. 1 Among patients who died within 1 year after pulmonary resection, the postoperative survival days are presented according to the cause of death. The causes of death are as follows: *filled circle* bleeding; *unfilled circle* sudden death; *filled triangle* respiratory failure; *unfilled triangle* recurrence; and *filled square* adverse event of chemotherapy

Table 2 One-year mortality rate according to the cause of death

Cause of death	No. of cases (%)		*p*
	Early period (1996–2004) $n = 1070$	Late period (2005–2010) $n = 1137$	
Recurrence	55 (5.1)	20 (1.8)	<0.0001
Respiratory failure	8 (0.7)	8 (0.7)	0.903
Bleeding	2 (0.2)	2 (0.2)	>0.999
Sudden death	1 (0.1)	2 (0.2)	>0.999
Adverse event of chemotherapy	0 (0)	2 (0.2)	0.500
Total	66 (6.2)	34 (3.0)	0.0003

Table 3 The 30- and 90-day mortality rates after pulmonary resection

Mortality	No. of cases (%)			*p*
	Total	Early period (1996–2004) $n = 1070$	Late period (2005–2010) $n = 1137$	
30-day mortality	10 (0.45)	6 (0.56)	4 (0.35)	0.465
90-day mortality	17 (0.77)	8 (0.75)	9 (0.79)	0.467

any significant difference in postoperative survival days between the two groups ($p = 0.345$). Furthermore, the median of days of onset for postoperative pulmonary complications was 5 days (4–18 days) in the early period group and 13 (7–86 days) in the late period group. Patients died from recurrence had a postoperative survival ≥91 days, with 232 days (98–364 days) and 238 days (98–344 days) in the early and late period groups, respectively. There were only two patients who died from adverse event of chemotherapy in the late period group, and the chemotherapy regimens involved cisplatin and vinorelbine. One of these patients was found at home after suffering cardiopulmonary arrest on the 61st day after pulmonary resection on the cessation of the first course of chemotherapy. Another patient had hyponatremia during the 4th course of chemotherapy. Although serum sodium concentration became normal, the patient was found in a state of cardiopulmonary arrest at hospital on the 129th day after pulmonary resection.

The detailed causes of death in 16 patients with respiratory failure are presented in Table 4. Twelve patients (75 %) died from pneumonia/ARDS and four (25 %) from empyema with/without bronchopleural fistula. Of the 12 pneumonia/ARDS deaths, seven occurred in the early period group and five in the late period group. Of the empyema deaths, one occurred in the early period group and three in the late period group. Ten (83.3 %) of the 12 deaths due to pneumonia/ARDS were caused by acute exacerbation of interstitial pneumonia.

Discussion

In this study, we examined the 30- and 90-day mortality rates of 2207 patients who underwent pulmonary resection for primary lung cancer, and divided these patients into the early period group (1070 patients, 1996–2004) and the late period group (1137 patients, 2005–2010). The 30-day mortality rates decreased from 0.56 % in the early period group to 0.35 % in the late period group without a statistically significant difference. Similarly, there was no statistically significant difference in the 90-day mortality rates between the two groups. When examining every cause of death, three patients in the early period group were found to have died from respiratory failure within 30 days after pulmonary resection, but no patients in the late period group died from this cause within 30 days. Furthermore, the postoperative survival days of all patients who died from recurrence were ≥91 days. For both the periods, the 90-day mortality rate was 0.77 %, and this was approximately double to that of the 30-day mortality rate with 0.45 %. Therefore, it was suggested that risk assessment of only the 30-day mortality rate after pulmonary resection is becoming difficult.

It has been precisely reported that the 90-day mortality rate was approximately double to that of the 30-day mortality rate [4, 5], and our results were also similar. Recent reports for the 30- and 90-day mortality rates after pulmonary resection, including this report, are summarized in Table 5. Watanabe et al. [9] reported that the 30-day mortality rates decreased from 0.8 % in the early period to

Table 4 Cause of death in patients with pulmonary complication

Cause of death	No. of cases (%)		
	Total	Early period (1996–2004)	Late period (2005–2010)
Pneumonia/ ARDS	12 (75)	7 (87)	5 (62)
Empyema with BPF	1 (6)	0 (0)	1 (13)
Empyema without BPF	3 (19)	1 (13)	2 (25)
Total	16 (100)	8 (100)	8 (100)

ARDS acute respiratory distress syndrome, *BPF* bronchopleural fistula

Table 5 Literature describing postoperative mortality after pulmonary resection for primary lung cancer

Report	Year	No. of resections	No. of cases (%)	
			30-day mortality (%)	90-day mortality (%)
Watanabe et al. [9]	1987–1996	1615	13 (0.8)	–
	1997–2002	1655	8 (0.5)	–
Annual report by JATS	1996–2004	163951	1198 (0.7)	–
1996–2010 [10]	2005–2010	168956	729 (0.4)	–
Watanabe et al. [11][a]	1994–2006	56	2 (3.6)	4 (7.1)
Saito et al. [12][a]	1994–2007	28	0	1 (3.6)
Yano et al. [13][a]	2004–2009	62	1 (1.6)	3 (4.8)
This study	1996–2004	1070	6 (0.6)	8 (0.8)
	2005–2010	1137	4 (0.4)	9 (0.8)
Damhuis et al. [3]	1997–2002	1365	65 (4.8)	114 (8.4)
	2003–2008	1307	49 (3.7)	85 (6.5)
Bryant et al. [4]	2002–2008	1845	55 (3.0)	99 (5.4)
Kim et al. [5][b]	1990–2010	1039	72 (6.9)	122 (11.7)

JATS Japanese Association for Thoracic Surgery

[a] Analysis of patients with lung cancer in addition to idiopathic pulmonary fibrosis

[b] Meta-analysis of pneumonectomy

0.5 % in the late period. They suggested the following reasons for this decrease: an increase in identification of early primary lung cancer by popularization of chest computed tomography scans; improvement in perioperative management; and reduction of pneumonectomy. Moreover, according to the national aggregation by the Japanese Association for Thoracic Surgery, the 30-day mortality rate in 33112 patients undergoing pulmonary resection for primary lung cancer in Japan was 0.4 % in 2010 [10]. When we considered the results of the national aggregation by the Association in accordance with the target period in our report, the 30-day mortality rate decreased from 0.7 % in the early period to 0.4 % in the late period. Damhuis et al. [3] and Bryant et al. [4] reported that the 30-/90-day mortality rates after pulmonary resection for primary lung cancer were 3.7/6.5 and 3.0/5.4 %, respectively. Kim et al. [5] reported that the 30- and 90-day mortality rates in patients undergoing pneumonectomy were 6.9 and 11.7 %, respectively. Furthermore, in patients undergoing pulmonary resection for primary lung cancer and interstitial pneumonia, Watanabe et al. [11], Saito et al. [12], and Yano et al. [13] reported the 30-/90-day mortality rates of 3.6/7.1, 0/3.6, and 1.6/4.8 %, respectively. These reports have indicated that the 90-day mortality rate after pulmonary resection was approximately double to that of the 30-day mortality rate, and this was consistent with our results. It seems important to recognize that the number of deaths occurred between 31 and 90 days after pulmonary resection was approximately similar to that of those occurred within 30 days after pulmonary resection.

In this study, it would be an advantage in using the 90-day mortality rate to assess the surgical risk, and in 2207 patients who underwent pulmonary resection, no death occurred due to recurrence within 90 days. If a treatment was selected based on an appropriate diagnosis, it was considered that the 90-day mortality rate could be considered as a result associated with only surgical complication.

The median of postoperative survival days of the patients who died from respiratory failure was 67 days (20–142 days) in the early period group and 100 (47–149 days) in the late period group; furthermore, all patients in the late period group died $\geq$31 days after pulmonary resection. Therefore, we consider that it would be necessary to make an assessment using the 90-day mortality rate for more accurate evaluation of the surgical risk. We found three patients in the early period group who died from respiratory failure within 30 days after pulmonary resection, on the other hand no patients died in the late period group. It is considered that standardization of treatment according to the guidelines for ARDS and improvement in intensive treatment management, including use of artificial respirators, would be related. In the three reports from Japan that examined surgical risk assessment of lung cancer patients with interstitial pneumonia [11–13], three died within 30 days and eight within 90 days after pulmonary resection. Five of those eight patients died in 31 days or more, and the cause of death was acute exacerbation of interstitial pneumonia. Considering these three reports [11–13], assessing patients who died from respiratory failure would be difficult using only the 30-day mortality rate, and the risk assessment for pulmonary resection should be conducted in combination with the 30- and 90-day mortalities.

We briefly indicate the reasons why the 90-day mortality rate is useful for risk assessment of pulmonary resection for primary lung cancer:

1. The 90-day mortality rate was approximately double to the 30-day mortality rate.
2. The postoperative survival of patients who died from recurrence after pulmonary recurrence was >91 days.
3. The patients died from respiratory failure in the late period group in 31 days or more after pulmonary resection, and therefore, it would be difficult to assess risk using only the 30-day mortality rate.

Conclusion

Not only the 30-day mortality rate but also the 90-day mortality rate is useful as one of the indices to assess the surgical risk of pulmonary resection for primary lung cancer.

Conflict of interest All authors declare no conflict of interest.

References

1. Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;65 Suppl 3:iii1–iii27.
2. The Japan Lung Society. The general rule for clinical and pathological record of lung cancer. Tokyo: Kanehara; 2010. p. 54.
3. Damhuis RA, Wijnhoven BP, Plaisier PW, Kirkels WJ, Kranse R, van Lanschot JJ. Comparison of 30-day, 90-day and in-hospital postoperative mortality for eight different cancer types. Br J Surg. 2012;99:1149–54.
4. Bryant AS, Rudemiller K, Cerfolio RJ. The 30- versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg. 2010;89:1717–22.
5. Kim AW, Boffa DJ, Wang Z, Detterbeck FC. An analysis, systematic review, andmeta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non-small cell lung cancer. J Thorac Cardiovasc Surg. 2012;143:55–63.
6. Little JP. Consistency of ASA grading. Anaesthesia. 1995;50:658–9.
7. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the

forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007;2:706–14.
8. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26:3552–9.
9. Watanabe S, Asamura H, Suzuki K, Tsuchiya R. Recent results of postoperative mortality for surgical resections in lung cancer. Ann Thorac Surg. 2004;78:999–1002.
10. Kuwano H, Amano J, Yokomise H. Thoracic and cardiovascular surgery in Japan during 2010: annual report by The Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg. 2012;60:680–708.
11. Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? J Thorac Cardiovasc Surg. 2008;5:1357–63.
12. Saito Y, Kawai Y, Takahashi N, Ikeya T, Murai K, Kawabata Y, et al. Survival after surgery for pathologic stage IA non-small cell lung cancer associated with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2011;92:1812–7.
13. Yano M, Sasaki H, Moriyama S, Hikosaka Y, Yokota K, Kobayashi S, et al. Post-operative acute exacerbation of pulmonary fibrosis in lung cancer patients undergoing lung resection. Interact CardioVasc Thorac Surg. 2012;14:146–50.

Surgical Results for Recurrent Hepatocellular Carcinoma after Curative Hepatectomy: Repeat Hepatectomy vs. Salvage Living Donor Liver Transplantation

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Running Title: Repeat Hx or salvage LDLT for recurrent HCC

Key Words: Hepatocellular carcinoma (HCC), Repeat hepatectomy (Repeat Hx), Salvage living donor liver transplantation (Salvage LDLT), Morbidity and mortality, 5-year survival, 5-year disease free survival.

Abbreviations: Hx, hepatectomy; LDLT, living donor liver transplantation; HCC, hepatocellular carcinoma; OS, overall survival; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; DFS, disease-free survival; KU, Kyushu University; DCP, des-gamma-carboxy prothrombin; AFP, α-fetoprotein; CT, computed tomography; vp, pathological portal venous infiltration; TACE, transarterial chemoembolization.

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Abstract

Background: The aims of this study were to evaluate the efficacy of repeat hepatectomy (Hx) and salvage living donor liver transplantation (LDLT) for recurrent hepatocellular carcinoma (HCC).

Methods: A retrospective cohort study was performed to analyze the surgical results of repeat Hx and salvage LDLT for patients with recurrent HCC within Milan criteria from 1989 to 2012. A total of 159 patients were divided into 2 groups: a repeat Hx group (n=146), and a salvage LDLT group (n=13). Operative results and patient prognoses were compared between the 2 groups.

Results: The operative invasiveness, including the operation time (229.1±97.7 vs. 862.9±194.4 min; p<.0001), and blood loss (596.3±764.9 vs. 24690±59014.4 g; p<.0001), were significantly higher in the salvage LDLT group. The early surgical results, such as morbidity (31% vs. 62%; p=0.0111) and the duration of hospital stay (20±22 vs. 35±21 days; p=0.0180), were significantly worse in the salvage LDLT group. There was no significant difference in the overall survival (OS) rate, but the disease-free survival rate of the salvage LDLT group was significantly better (p=0.0002). The OS rate of patients with grade B liver damage in the repeat Hx group was significantly worse (p<.0001), and the 5-year OS rate was quite low, i.e., 20% (liver damage A in the repeat Hx group, 77%; and the salvage LDLT group, 75%).

Conclusions: The prognosis of patients with grade B liver damage after repeat Hx for recurrent HCC is poor, and salvage LDLT would be one of a potent option for such patients.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] This disease burden is expected to increase in the future, in conjunction with the high prevalence of hepatitis B virus (HBV) in Asia and sub-Saharan Africa, and the rising incidence of hepatitis C virus (HCV) infections, alcoholic liver disease, and steatohepatitis in developed countries.[2] The mainstay of curative treatment for HCC is hepatectomy (Hx). With advances in surgical techniques and perioperative care,[3,4] the results of Hx for HCC have greatly improved. Nonetheless, the long-term survival after Hx remains unsatisfactory because of the high incidence of intrahepatic recurrence in up to 68-98% of patients.[5] Thus, effective therapeutic strategies for intrahepatic recurrence are critical to prolong the survival after Hx for HCC.

In the past two decades, repeat Hx has been reported to be safe and to prolong survival after intrahepatic recurrence.[5-12] Our department has aggressively adopted repeat Hx as the main curative option for treating recurrent HCC, and reported good surgical results of repeat Hx for recurrent HCC.[13] Recently, salvage liver transplantation (LT) was proposed as a curative option for intrahepatic recurrence of HCC, but it is still not widely used because of the insufficient numbers of cadaveric donors and limited availability of appropriate living donors.[14-16] Salvage LT may offer a good strategy for relieving patients with a good prognosis after HCC recurrence, but concerns remain over the potential for increased difficulty of LT following a prior Hx to negate the benefit of a salvage LT.[17] A treatment strategy for patients with recurrent HCC within Milan criteria[18] should be established; however, there have been few reports comparing the results of different treatment for recurrent HCC, such as repeat Hx and salvage LT.[19,20]

In order to clarify the efficacy of salvage living donor liver transplantation (LDLT) for patients with recurrent HCC, we performed a retrospective review of patients undergoing repeat Hx or salvage LDLT for recurrent HCC within Milan criteria at our institution.

Methods

Patients

A total of 1354 Hx for HCC were performed at the Department of Surgery and Sciences, Kyushu University Hospital, between January 1989 and March 2012. Repeat Hx was performed in 146 patients with recurrent HCC within Milan criteria. All 146 patients had had a disease-free survival (DFS) of more than 1 year after the initial Hx for primary HCC. For patients with end-stage liver cirrhosis who had no modality except LDLT available to cure HCC, 13 LDLT for recurrent HCC after curative Hx against primary HCC (salvage LDLT) were performed. Although all patients with repeat Hx met Milan criteria in this series, there were no restrictions on tumor size, or number of nodules in candidates for salvage LDLT for recurrent HCC within Kyushu University (KU) criteria,[21, 22] therefore, 5 patients (38.5%) did not meet the Milan criteria. Since our proposal of the KU criteria,[22] we have not performed salvage LDLT for patients with recurrent HCC who have both tumor size>5 cm and des-gamma-carboxy prothrombin (DCP)> 300 mAU/ml. All our patients with repeat Hx also satisfied the KU criteria. The medical records of patients in this series were followed until March 2014, and the median follow-up periods were 72 months for the repeat Hx group, and 63 months for the salvage LDLT group.

Surgical Techniques and Follow-up Methods

The details of our surgical techniques and patient selection criteria for repeat Hx have been reported previously, and are almost identical to those of the initial Hx for primary HCC.[13,23]

Our transplantation procedures for both the donors and recipients have been described previously.[22,24,25] Donors were selected from candidates who hoped to be living donors. Donors were required to be within the third degree of consanguinity with recipients or spouses and to be between 20 and 65 years of age. Our criteria for choosing a graft type for recipients have been reported previously.[26] In this series, 8 left lobe+caudate grafts, 4 right lobe grafts, and 1 posterior segment graft were transplanted. Immunosuppression consisted of the combination of a tacrolimus (Prograf; Astellas

Pharma Inc., Tokyo, Japan) or cyclosporine (Neoral; Novartis Pharma K.K., Tokyo, Japan) with steroid and/or mycophenolate mofetil (MMF; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan).[26,27]

We mainly examined five surgical outcomes between the 2 groups: postoperative mortality, morbidity, the duration of hospital stay, overall survival (OS), and DFS. Any death that occurred in the hospital after Hx was recorded as a mortality. Complications were evaluated by Clavien's classification,[28] and those with a score of Grade II or more were defined as positive.

After discharge, all patients were examined for HCC recurrence by ultrasonography and tumor markers such as α-fetoprotein (AFP) and DCP every month, and by dynamic computed tomography (CT) every 3 or 4 months.[4] No patients received adjuvant chemotherapy or adjuvant lipiodolization in our series. We treated recurrent HCC by repeat Hx,[13] ablation therapy,[29] and lipiodolization[30] according to the previously described strategy.[7]

Statistical Analysis

Continuous variables were expressed as means ± standard deviation, and compared using a Student's *t*-test. Categorical variables were compared using either the χ^2 test or Fisher's exact test, as appropriate. The OS and DFS curves were generated by the Kaplan-Meier method and compared by the log-rank test. All analyses were performed with JMP® Pro 9.0.2 (SAS Institute Inc., Cary, NC). P-values of less than 0.05 were considered to indicate statistical significance.

Results

Comparison of the patient background characteristics

The results of the comparison of patient background characteristics between the 2 groups are summarized in Table 1. There were significant differences in the age of patients between groups (repeat Hx: 68.2±9.6 years; and salvage LDLT: 56.2±5.6 years; $p<.0001$). The mean body mass indexes (BMI) of both groups were less than 25 (repeat Hx: 22.9±3.1; and salvage LDLT: 24.5±3.1; $p=0.0911$). The complication rate of esophageal varices was significantly higher in the salvage LDLT group (repeat Hx: 24%; and salvage LDLT: 92%; $p<.0001$). There were no significant differences in the positive rate of hepatitis B virus surface antigen or hepatitis C virus antibody. Patients in the repeat Hx group showed better maintenance of liver function and lower total bilirubin levels than those in the salvage LDLT group (repeat Hx: 0.7±0.3 mg/dl; and salvage LDLT: 2.4±0.1 mg/dl; $p<.0001$). There were significant differences in the Child-Pugh (repeat Hx: A in 96%; and salvage LDLT: A in 8%; $p<.0001$) and liver damage classifications defined by Liver Cancer Study of Japan[31] (repeat Hx: A in 81%; and salvage LDLT: A in 8%; $p<.0001$).

Comparison of the short-term surgical outcomes

The results of the comparison of short-term surgical outcomes are summarized in Table 2. The operation time was significantly prolonged in the salvage LDLT group (repeat Hx: 229.1±97.7 min; and salvage LDLT: 862.9±194.4 min; $p<.0001$). The intra-operative blood loss was significantly larger in the salvage LDLT group (repeat Hx: 596.3±764.9 g; and salvage LDLT: 24690.0±59014.4 g; $p<.0001$). Therefore, the intra-operative transfusion rate in the salvage LDLT group was significantly higher (repeat Hx: 18%; and salvage LDLT: 100%; $p<.0001$). There was one operative mortality in the salvage LDLT group (7.7%), but this rate was not significantly higher than that of the repeat Hx group (0%; p=0.0818). The morbidity rate in the salvage LDLT group was significantly higher (repeat Hx: 31%; and salvage LDLT: 62%; p=0.0111), and the mean duration of hospital stay was significantly prolonged in the salvage LDLT group (repeat Hx: 20±22 days; and salvage LDLT: 35±21 days;

p=0.0180). The morbidities of the salvage LDLT group were as follows; 3 septic complications (23%), 2 vascular complications including 1 re-operation (15%), 1 acute rejection (8%), 1 pneumonia (8%), and 1 graft versus host disease (8%).

Comparisons of the tumor-related factors

The results of the comparison of tumor-related factors are summarized in Table 3. The maximum tumor diameter in the salvage LDLT group was longer (repeat Hx: 1.9±0.9 cm; and salvage LDLT: 2.5±1.1 cm), but this difference was not statistically significant (p=0.0598). There were significant differences in the tumor number (repeat Hx: 1.3±0.5; and salvage LDLT: 4.0±5.1; $p<.0001$). There were no significant differences in the positive rate of pathological portal venous infiltration (vp) or pathological intrahepatic metastasis (im). The positive rate of histological cirrhosis in the salvage LDLT group was significantly higher (repeat Hx: 61%; and salvage LDLT: 100%; p=0.0191).

Comparisons of the OS and DFS rates

The OS and DFS curves after operation of the 2 groups are illustrated in Figure 1. There was no significant difference in the OS rate (p=0.1714); and the 5-year OS rate of the salvage LDLT group was 75%, and that of the repeat Hx group was 61%. The DFS rate in the repeat Hx group was significantly worse (p=0.0002), and the 5-year DFS rate of the salvage LDLT group reached 81%, but that in the repeat Hx group remained quite low at 16%.

The repeat Hx group was divided according to the Child-Pugh classification (Child A: 140 cases; and Child B: 6 cases), and survival curves were compared among the 3 groups (Figure 2). However, the impact of division of the repeat Hx group according to Child-Pugh classification was not certain. In contrast, the impact of division of the repeated Hx group according to liver damage classification (liver damage A: 118 cases; and liver damage B: 28 cases) was quite clear (Figure 3). The OS ($p<.0001$) and DFS ($p<.0001$) rates of repeat Hx in patients with grade B liver damage were significantly worse, and the 5-year OS rate of repeat Hx in patients with grade B liver damage remained quite low at 20%, and there were no patients with 5-year DFS. The 5-year OS rate of repeat Hx in patients with grade A liver damage reached 77%,

which was approximately the same value as in the salvage LDLT group.

Discussion

Primary liver transplantation is recognized as the most effective treatment for HCC within Milan criteria, but its practical use is limited by organ shortage.[32] Primary Hx is the main option for HCC treatment with reasonable long-term survival outcomes but is associated with high rates of disease recurrence. We recently reported that the 5-year OS rate of primary Hx for HCC had reached 78%.[4] Poon et al. suggested a treatment strategy of primary Hx for HCC within Milan criteria, with SLT reserved for HCC recurrence[33] This strategy may potentially reduce disease progression for patients awaiting LT and reduce the number of LTs required. Based on our results, in comparison with primary LDLT, although the salvage LDLT is associated with increased operation difficulties, it also provides the relatively good OS and DFS, therefore, primary Hx with salvage LDLT should be a potent option for treatment of patients with HCC within Milan criteria. Nevertheless, the high incidence of intrahepatic recurrence in up to 68-98% of patients after Hx for HCC remains a problem.[5] Thus, effective therapeutic strategies for intrahepatic recurrence are critical to prolong patient survival. We reported that the DFS of patients was not improved after Hx for HCC, and 5-year DFS remains low as 34%.[4]

Repeat Hx for recurrent HCC was first reported to be effective more than two decades ago.[5-12] Chan et al. performed a systemic review of repeat Hx comparing 1125 patients in 22 eligible studies, the reported that the median mortality was low (0%; 0-6%) and median 5-year OS rate was also fairly good (52%; 22-83%).[5] In the present study, we also reported a good 5-year OS rate (up to 61%) for the repeat Hx group. However, the 5-year DFS rate of the repeat Hx group remained low (16%). It has been established that HCC recurrence is mainly due to micro-metastases or multi-centric recurrence.[34,35] All 146 patients with repeat Hx in this series had 1-year or more DFS from initial Hx for HCC and recurrent HCC within Milan criteria, and thus the main recurrent type of patients with repeat Hx would be multi-centric recurrence. Chan et al. also reported that the independent prognostic factors for survival after repeat Hx for recurrent HCC are severe liver dysfunction (Hazard ratio 2.53), macrovascular portal vein invasion (Hazard ratio 2.25), vp (Hazard ratio 1.81), and time to recurrence> 12-18

months (Hazard ratio 0.52).[5] Patients with severe liver dysfunction are at high risk for HCC re-recurrence, and the treatment for re-recurrence would be restricted in such cases.[13] Pre-operative selection criteria for severe liver dysfunction which affects the patients' poor survival would be important. In this series, as shown in Fig. 2 and 3., those selection criteria were based not on the Child-Pugh but the liver damage classification. Liver damage classification was defined by the value of indocyanine green retention rate at 15 min (ICGR15) in addition to the degree of ascites, and that of total bilirubin, albumin, and prothrombin time.[23, 31] Many papers reported that the ICGR15 value is the best discriminating preoperative test for evaluating hepatic functional reserve in patients with HCC in cirrhosis,[36, 37] and we previously reported that patient survival after initial Hx for primary HCC could be better stratified by liver damage A/B than Child-Pugh A/B classification,[23] and Japanese evidence-based clinical guidelines for the treatment of HCC demonstrated a treatment algorithm according to the degree of liver damage.[38] In this series, the 5-year OS of patients with grade A liver damage after repeat Hx reached 77%, which is identical to the maximum value after salvage LDLT. The drawbacks of LT include the insufficient numbers of cadaveric donors, lack of appropriate living donors, relatively high mortality of recipients, mortality and morbidity of the living donors,[24,25] and need for lifelong immunosuppressant therapy and high cost. Although we have no mortality of the living donors in more than 500 hepatic resections so far and reported relatively low morbidity ≥Clavien II of the living donors as 12.4%,[39, 40] the physical and psychological burdens of the living donors should be major concerns in LDLT. Therefore, repeat Hx should be recommended for patients with grade A liver damage against recurrent HCC. On the other hand, the 5-year OS rate of patients with grade B liver damage after repeat Hx was quite low (20%), and salvage LDLT would be recommended in such patients. Taken into consideration the Japanese guidelines for HCC treatment and our previous and recent results,[7,38] our treatment strategy for recurrent HCC can be summarized as shown in Table 4. For an intrahepatic recurrence, the repeat Hx is indicated when liver function is well-preserved (liver damage A) and fewer than 3 recurrent liver nodules (Nodular type). In patients with more than 4 recurrent liver nodules (Multiple type), lipiodolization (LPD)[41, 42] is indicated. For an extrahepatic recurrence, especially in lung metastasis, surgical resection is indicated only when the recurrence is isolated and

resectable.[43] Surgical treatments should be indicated for patients with DFS≥1 year from initial Hx and vp 0/1 at primary Hx.

Chan et al.[5] reported in their systemic review of salvage LT that the mortality rate of salvage LT was significant (5%), but only 3 studies reportied mortality rates> 10%.[44-46] In our series, one patient (7.7%) died at 1 post-operative day due to the hemorrhagic shock caused by excessive intra-operative bleeding. This patient had underwent S7 partial Hx for primary HCC, and intra-peritoneal portal hypertension was developed because of the intrahepatic portal vein thrombosis due to RFA for recurrent HCC. The mobilization of the liver was quite difficult at salvage LDLT due to severe adhesion to the retroperitoneal space and diaphragm, and massive hemorrhaging occurred. From our own experience, the proceeding Hx at S7 would be a potent risk factor for excessive intra-operative bleeding at salvage LDLT. Chan et al. also reported the following median values for morbidities and duration of the hospital stay: biliary complication, 8%; infectious complication, 11%; bleeding, 7%; vascular complication, 7%; reoperation or re-transplant, 0%; acute rejection, 0%; and duration of hospital stay, 19 days.[5] Maggs et al. suggested in their systemic review that the rates of morbidity were comparable between primary LT and salvage LT.[32] However in our series, compared to repeat Hx, the operative invasiveness of salvage LDLT was far greater, especially with respect to operative blood loss (596 vs. 24690 g; $p<.0001$). This excessive operative invasiveness of salvage LDLT compared to repeat Hx should always be taken into consideration, and for patients with grade B liver damage in which the primary HCC is located at S7, primary LDLT should be selected rather than primary Hx.

There have been 2 reports comparing surgical results between the salvage LT and non-transplant therapies. Ng et al. reported that the prognoses of patients with non-transplant therapy (5-year OS rate: 40.8%) and those with LT (5-year OS rate: 53.8%) for transplantable HCC are similar.[19] Chan et al. also reported that there were no differences in survival between repeat Hx (5-year OS rate: 48%) and salvage LT (5-year OS rate: 60%).[20] However, these studies included too few cases with non-salvage LT, and their survival data on salvage LT were worse than ours.

We reported in this series that the prognosis of patients with grade B liver damage after repeat Hx was quite poor, but this result does not necessarily mean that

non-surgical treatments such as RFA or transarterial chemoembolization (TACE) are indicated for such patients. Pathological examination of totally explanted livers after RFA for HCC showed that complete tumor necrosis rarely occurred (46.7%)[44], and increased intra-tumoral pressure during ablation might also induce tumor dissemination into the adjacent portal vessels.[48] It is also known that partial necrosis promotes tumor recurrence after TACE.[49]

Baseline tumor or surgical characteristics at the initial Hx of the 2 groups are not significantly different such as the positive rate of vp, im, anatomical resection, and transfusion rate in our own series. However, the mean time from primary resection to the salvage LDLT (5.3±4.2 years) was significantly longer than that to the repeat Hx (2.9±3.4 years; p=0.0124). The positive rate of liver directed therapy (LDT) such as RFA or LPD of the salvage LDLT group (69.2%) is significantly higher than that of the repeat Hx group (3.4%; p<.0001). The inferiority of the remnant liver function of the salvage LDLT group should be the main cause of this difference, and LDTs would lead the longer observation time from initial Hx of the salvage LDLT group.

In conclusion, with respect to the treatment for recurrent HCC within Milan criteria, repeat Hx is indicated for patients with grade A liver damage. The prognosis of patients with grade B liver damage after repeat Hx for recurrent HCC is poor, and therefore, salvage LDLT would be a potent option for such patients.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61: 69-90.
2. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011; 365: 1118-27.
3. Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T, Shirabe K, Shimada M, Maehara Y. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg. 2007; 204: 580-7.
4. Yamashita Y, Tsuijita E, Takeishi K, Ishida T, Ikegami T, Ezaki T, Maeda T, Utsunomiya T, Nagasue N, Shirabe K, Maehara Y. Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1,000 consecutive cases over 20 years in a single institution. Am J Surg. 2014; 207: 890-6.
5. Chan DL, Alzahrani NA, Morris DL, Chua TC. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol. 2014; 29: 31-41.
6. Lee PH, Lin WJ, Tsang YM, Hu RH, Sheu JC, Lai MY, Hsu HC, May W, Lee CS. Clinical management of recurrent hepatocellular carcinoma. Ann Surg. 1995; 222: 670-6.
7. Shimada M, Takenaka K, Taguchi K, Fujiwara Y, Gion T, Kajiyama K, Maeda T, Shirabe K, Yanaga K, Sugimachi K. Prognostic factors after repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg. 1998; 227: 80-5.
8. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg. 1999; 229: 216-22.
9. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg. 2003; 238: 703-10.
10. Itamoto T, Nakahara H, Amano H, Kohashi T, Ohdan H, Tashiro H, Asahara T. Repeat hepatectomy for recurrent hepatocellular carcinoma. Surgery. 2007; 141: 589-97.

11. Parfitt JR, Marotta P, Alghamdi M, Wall W, Khakhar A, Suskin NG, Quan D, McAllister V, Ghent C, Levstik M, McLean C, Chakrabarti S, Garcia B, Driman DK. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. Liver Transpl. 2007; 13: 543-51.

12. Kubo S, Takemura S, Uenishi T, Yamamoto T, Ohba K, Ogawa M, Hai S, Ichikawa T, Kodai S, Shinkawa H, Tanaka H. Second hepatic resection for recurrent hepatocellular carcinoma in patients with chronic hepatitis C. World J Surg. 2008; 32: 632-8.

13. Yamashita Y, Shirabe K, Tsuijita E, Takeishi K, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Utsunomiya T, Maehara Y. Third or more repeat hepatectomy for recurrent hepatocellular carcinoma. Surgery. 2013; 154: 1038-45.

14. Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology. 2012; 55: 132-40.

15. Liu F, Wei Y, Wang W, Chen K, Yan L, Wen T, Zhao J, Xu M, Li B. Salvage liver transplantation for recurrent hepatocellular carcinoma within UCSF criteria after liver resection. PLoS One. 2012; 7: e48932.

16. Wu L, Hu A, Tam N, Zhang J, Lin M, Guo Z, He X. Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One. 2012; 7: e41820.

17. Chan DL, Alzahrani NA, Morris DL, Chua TC. Systematic review of efficacy and outcomes of salvage liver transplantation after primary hepatic resection for hepatocellular carcinoma. J Gastroenterol Hepatol. 2014; 29: 31-41.

18. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334: 693-9.

19. Ng KK, Lo CM, Liu CL, Poon RT, Chan SC, Fan ST. Survival analysis of patients with transplantable recurrent hepatocellular carcinoma: implications for salvage liver transplant. Arch Surg. 2008; 143: 68-74; discussion 74.

20. Chan AC, Chan SC, Chok KS, Cheung TT, Chiu DW, Poon RT, Fan ST, Lo CM. Treatment strategy for recurrent hepatocellular carcinoma: salvage transplantation, repeated resection, or radiofrequency ablation? Liver Transpl. 2013; 19: 411-9.

21. Yoshizumi T, Shirabe K, Soejima Y, Taketomi A, Ikegami T, Uchiyama H, Harada N, Ijichi H, Maehara Y. Living donor liver transplantation in patients who have received pretransplant treatment for hepatocellular carcinoma. Transplantation. 2011; 91: e61-2.

22. Taketomi A, Sanefuji K, Soejima Y, Yoshizumi T, Uhciyama H, Ikegami T, Harada N, Yamashita Y, Sugimachi K, Kayashima H, Iguchi T, Maehara Y. Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. Transplantation. 2009; 87: 531-7.

23. Yamashita Y, Taketomi A, Itoh S, Kitagawa D, Kayashima H, Harimoto N, Tsujita E, Kuroda Y, Maehara Y. Long-term favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 Years of Experience. J Am Coll Surg 2007; 205: 19-26.

24. Taketomi A Morita K, Toshima T, Takeishi K, Kayashima H, Ninomiya M, Uchiyama H, Soejima Y, Shirabe K, Maehara Y. Living donor hepatectomies with procedures to prevent biliary complications. J Am Coll Surg. 2010; 211: 456-64.

25. Ikegami T, Shirabe K, Yamashita Y, Yoshizumi T, Harimoto N, Takeishi K, Tsujita E, Itoh S, Maehara Y. Small upper midline incision for living donor hemi-liver graft procurement in adults. J Am Coll Surg. 2014; 219: e39-43.

26. Yoshizumi T, Ikegami T, Yoshiya S, Motomura T, Mano Y, Muto J, Ikeda T, Soejima Y, Shirabe K, Maehara Y. Impact of tumor size, number of tumors and neutrophil-to-lymphocyte ratio in liver transplantation for recurrent hepatocellular carcinoma. Hepatol Res. 2013; 43: 709-16.

27. Harimoto N, Shirabe K, Nakagawara H, Toshima T, Yamashita Y, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y. Prognostic factors affecting survival at recurrence of hepatocellular carcinoma after living-donor liver transplantation: with special reference to neutrophil/lymphocyte ratio. Transplantation. 2013; 96: 1008-12.

28. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R,

Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009; 250: 187-96.

29. Chan AC, Poon RT, Cheung TT, Chok KS, Chan SC, Fan ST, Lo CM. Survival analysis of re-resection versus radiofrequency ablation for intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. World J Surg. 2012; 36: 151-6.
30. Furuta T, Kanematsu T, Matsumata T, Shirabe K, Yamagata M, Utsunomiya T, Sugimachi K. Lipiodolization prolongs survival rates in postoperative patients with a recurrent hepatocellular carcinoma. Hepatogastroenterology. 1990; 37: 494-7.
31. Liver Cancer Study Group of Japan: General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Engle d 3. Tokyo, Kanehara, 2010.
32. Maggs JR, Suddle AR, Aluvihare V, Heneghan MA. Systematic review: the role of liver transplantation in the management of hepatocellular carcinoma. Aliment Pharmacol Ther. 2012 May; 35: 1113-34.
33. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002; 235: 373-82.
34. Shirabe K, Kanematsu T, Matsumata T, Adachi E, Akazawa K, Sugimachi K. Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. Hepatology. 1991; 14: 802-5.
35. Shirabe K, Takenaka K, Taketomi A, Kawahara N, Yamamoto K, Shimada M, Sugimachi K. Postoperative hepatitis status as a significant risk factor for recurrence in cirrhotic patients with small hepatocellular carcinoma. Cancer. 1996; 77: 1050-5.
36. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg. 84: 1255-9, 1997.
37. Fan ST, Lai EC, Lo CM, Ng IO, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg. 130: 198-203, 1995.
38. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular