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一般講演

7. 久米秀明, 渡邊史生, 村岡 賢, 石濱 泰, 小寺義男，松下一之，松原久裕，朝長 毅：大腸癌組織膜タンパク質の大規模プロテオーム解析によるバイオマーカー探索とその検証．第 10 回日本プロテオーム学会，東京，2012 年 7 月 26-27 日
8. 原 康洋, 宮本泰豪, 加藤菊也, 福岡順也, 朝長 毅:細気管支肺胞上皮癌のプロテオーム解析によるバイオマーカー探索.日本ヒトプロテオーム機構第 10 回大会，東京，2012 年 7 月 26-27 日
9. 村岡 賢、久米秀明、渡邊史生、桑野晶喜、足立 淳、佐藤三佐子、川崎 直子、石濱 泰、石飛真人、稲治英生、小寺義男、宮本泰豪、加藤菊也、朝長 毅: 乳癌膜タンパク質の大規模 iTRAQ-shotgun と SRM 解析によるバイオマーカータンパク質の検証 日本プロテオーム学会 2012 年大会、東京、2012 年 7 月 26-27 日
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12. 村上達夫, 久家貴寿, 足立 淳, 白水 崇, 宮本泰豪, 加藤菊也, 石飛真人, 稲治英生, 小寺義男, 朝長 毅:大規模リン酸化プロテオーム解析と SRM/MRM によるヒト乳癌組織の検証法.日本プロテオーム学会 2012 年会, 東京, 2012 年 7 月 26-27 日
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G. 知的財産権の出願・登録状況（予定を含む）

１. 発明の名称：
「乳がん治療の予後判定方法」
発明者:朝長　毅、村岡　賢、村上達夫、加藤菊也、宮本泰豪
出願日 ：2012 年 5 月 23 日(国内出願)
出願番号:特願 2012-117961 (国内出願)
出願人 ：独立行政法人医薬基盤研究所

２. 発明の名称：「大腸癌治療剤」
発明者：朝長　毅、久家貴寿、久米秀明
出願日 ：2012 年 6 月 15 日(国内出願)
出願番号:特願 2012-135619 (国内出願)
出願人 ：独立行政法人医薬基盤研究所

３. 発明の名称:「大腸がんの判定方法」
発明者 ：朝長　毅、久米秀明
出願日 ：2012 年 12 月 27 日(国内出願)
出願番号：特願 2012-274638(国内出願)
出願人 ：独立行政法人医薬基盤研究所

４．発明の名称：
「癌が疑われる患者または患者由来の組織の癌部と非癌部との判別方法およびそれに用いる判別試薬」
発明者：清宮正徳、朝長　毅、宮崎　勝、野村文夫

出願日：2008 年 10 月 14 日(国内出願)
出願番号：特願 2008－264794(国内出願)
出願人：国立大学法人千葉大学、日東紡績株式会社
特許番号：特許第 5133842 号
登録日：2012年11月16日

Ⅲ. 研究成果の刊行に関する一覧

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
該当なし							

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肝炎等克服緊急対策研究事業

肝移植後Ｃ型肝炎に対する治療法の標準化を目指した臨床的ならびに基礎的研究

平成24年度　総括・分担研究報告書

【　研究成果の別刷（各１部）　】

研究代表者　上本　伸二

平成25(2013)年 5月

Living donor liver transplantation for recurrent hepatocellular carcinoma after liver resection

Toshimi Kaido, MD, PhD, Akira Mori, MD, PhD, Yasuhiro Ogura, MD, PhD, Koichiro Hata, MD, PhD, Atsushi Yoshizawa, MD, PhD, Taku Iida, MD, PhD, Shintaro Yagi, MD, PhD, *and* **Shinji Uemoto, MD, PhD,** *Kyoto, Japan*

Background. *Little is known about outcomes and indications for living donor liver transplantation in patients with recurrent hepatocellular carcinoma after liver resection.*
Methods. *We analyzed retrospectively 176 patients with hepatocellular carcinoma who underwent living donor liver transplantation at our institute between February 1999 and December 2009. Among 128 of 176 patients with a history of pretreatment for hepatocellular carcinoma, 19 patients underwent radical liver resection. We compared patient characteristics, intraoperative blood loss, operative duration, and long-term outcomes including overall survival and recurrence rates between patients who had received hepatectomy, other pretreatments, and no pretreatments.*
Results. *The surgical duration was significantly longer in patients with pretransplant hepatectomy than in those who had undergone other types of pretreatment (n = 109) or none (n = 48), whereas intraoperative blood loss did not differ among the 3 groups. Overall survival and recurrence rates did not significantly differ among the 3 groups. In patients with pretransplant hepatectomy, survival rates were significantly higher among patients who met the Kyoto criteria (≤10 tumors, all ≤5 cm in diameter and serum des-gamma-carboxy prothrombin levels ≤400 mAU/mL; n = 15) than those with values that exceeded the Kyoto criteria (n = 4) (5-year survival rates, 93% vs 25%, P = .005). Similarly, recurrence rates were significantly lower among patients meeting than exceeding the Kyoto criteria (5-year recurrence rates, 10% vs 67%, P = .011).*
Conclusion. *Patients with hepatocellular carcinoma recurrence after liver resection can safely undergo living donor liver transplantation. Long-term outcomes can be particularly favorable in patients who meet the Kyoto criteria. (Surgery 2012;151:55-60.)*

From the Department of Surgery, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

LIVER TRANSPLANTATION (LT) now plays an important role in the treatment of patients with hepatocellular carcinoma (HCC), as it provides good long-term overall survival. However, tumor progression during the waiting period is still the biggest problem associated with deceased donor LT (DDLT) for HCC. Therefore, tumors that progress while waiting for a transplant have been controlled frequently using bridge therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and hepatic resection.[1-4] With respect to DDLT after prior liver resection, 2 representative reports have examined the value of salvage for patients with recurrent HCC or deteriorated liver function after liver resection.[5,6] One report concluded that liver resection before transplantation does not increase the morbidity or impair long-term survival after LT,[5] whereas the other report associated LT after resection with higher operative mortality, an increased risk of recurrence, and a poorer outcome than primary LT.[6] Living donor LT (LDLT) can also be performed as salvage LT. To date, only 1 report has analyzed the results of salvage LDLT after liver resection for HCC.[7] Therefore, little is known about the short- and long-term outcomes of LDLT and DDLT in patients with recurrent HCC after liver resection.

Several extended criteria have been proposed beyond the Milan criteria for LT to treat primary HCC with acceptable results.[8-11] In contrast, the

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Reprint requests: Toshimi Kaido, MD, PhD, Department of Surgery, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: kaido@kuhp.kyoto-u.ac.jp.

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criteria for LT to treat recurrent HCC has not reached consensus. Recently, we proposed the following new expanded selection criteria (Kyoto criteria) for LDLT to treat HCC: tumor number ≤10, the maximal diameter of each tumor was ≤5 cm and serum des-gamma-carboxy prothrombin (DCP) levels of ≤400 mAU/mL.[11] The Kyoto criteria comprise 3 independent significant risk factors for recurrence, tumor number, and tumor size based on the findings of pretransplant imaging and tumor markers. Consequently, the Kyoto criteria effectively exclude patients with biologically aggressive tumors before LT, with a recurrence rate of 5% at 5 years according to a retrospective analysis of 136 patients.[11] The value of the Kyoto criteria for patients with recurrent HCC after liver resection is unclear.

Here, we investigated the short- and long-term outcomes of salvage LT for patients with recurrent HCC after hepatectomy. We also examined the relevance of our extended selection criteria to salvage LT.

PATIENTS AND METHODS

Patients. Between February 1999 and December 2009, a total of 176 patients (122 men and 54 women) underwent LDLT for HCC at Kyoto University Hospital. Our Institutional Review Board approved the study, which proceeded in accordance with the 1975 Declaration of Helsinki.

The median patient age was 56 years (range, 22–69). Pretreatment for HCC included TACE, RFA, hepatic resection, and a combination of these strategies implemented with curative intent. Patients with uncontrolled recurrent HCC were subsequently referred to our institute for LDLT as a second- or third-line treatment. Tumor morphology was evaluated using contrast-enhanced multidetector computed tomography within 1 month before LDLT.

Our institutional selection criteria and indication for LDLT to treat HCC have not been different between primary and recurrent HCC. Our selection criteria until December 2006 included any size or number of tumors provided that distant metastasis or gross vascular involvement on preoperative imaging was absent. Since January 2007, we have implemented the Kyoto criteria as described previously.[11]

A total of 96 patients were hepatitis C virus antibody positive, 57 were hepatitis B surface antigen positive, and 7 had coinfection. The Child-Turcotte-Pugh classifications were C, B, and A for 79 (44.9%), 69 (39.2%), and 28 (15.9%) patients, respectively. The median model for end-stage liver disease (MELD) score was 17 (range, 3–43). Preoperative imaging revealed that 100 patients met and 76 did not meet the Milan criteria. The selection criteria for the donor and recipient as well as surgical techniques for both donor and recipient operations have been described in detail elsewhere.[12-14] The standard immunosuppression protocol consisted of tacrolimus and low-dose steroid.[15,16] No patients were switched to mammalian target of rapamycin inhibitor. As of the end of April 2010, the median follow-up period was 77 months (range, 11–141).

Among 128 (72.7%) of 176 patients with a history of treatment for HCC, 19 patients underwent liver resection before LDLT (hepatectomy group). Right or left hepatectomy as performed in 7 patients, segmentecomy in 2 patients, and partial resection in 10 patients. Other pretreatments including TACE, RFA, and a combination of these approaches were delivered to 109 patients (other pretreatment group), and 48 patients received no pretreatment (no pretreatment group). We compared MELD scores, etiology of underlying liver disease, tumor markers such as alpha-fetoprotein (AFP) and DCP, intraoperative blood loss, operative duration, graft-to-recipient weight ratios, and long-term outcomes including overall survival and recurrence rates among the 3 groups.

We examined the overall survival and recurrence rates of 19 patients in the hepatectomy group according to the Kyoto, Milan and University of California, San Francisco (UCSF) criteria.

Statistical analysis. The quantitative data are expressed as means ± standard deviation. The data were analyzed statistically using the 1-way analysis of variance. Any variable identified as significant ($P < .05$) in univariate analysis using the preceding tests was considered a candidate for multivariate analysis using multiple logistic regression models. Cumulative overall survival and recurrence rates were calculated using the Kaplan-Meier method, and the differences between curves were evaluated using the log-rank test. All statistical data were generated using JMP 5.0.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Characteristics of patients at the time of LDLT. Age, sex, etiology of underlying cirrhosis, and tumor markers (Table I) did not significantly differ among the 3 groups at the time of LDLT. However, the proportion of Child-Pugh classification A was significantly higher in the hepatectomy group than in the other pretreatment and no pretreatment groups ($P < .001$). The MELD score was likewise significantly lower in the hepatectomy group than in

Table I. Comparison of patient characteristics at the time of liver transplantation among hepatectomy, other pretreatment, and no pretreatment groups

	Hepatectomy	*Other pretreatment*	*No pretreatment*	P
Number of patients	19	109	48	
Age (years)	52.3 ± 11.4	56.0 ± 7.9	54.3 ± 6.7	.1524
Male sex	14 (74%)	75 (69%)	33 (69%)	.9067
Etiology of cirrhosis				.0629
Viral hepatitis C	9 (47%)	69 (63%)	18 (38%)	
Viral hepatitis B	7 (37%)	29 (27%)	21 (44%)	
Viral hepatitis C/B	2 (11%)	2 (18%)	3 (6%)	
Others	1 (5%)	9 (8%)	6 (13%)	
Child-Pugh classification				.0002
A	9 (47%)	18 (17%)	1 (2%)	
B	6 (32%)	44 (40%)	19 (40%)	
C	4 (21%)	47 (43%)	28 (58%)	
MELD score	10.9 ± 5.5	15.6 ± 6.6	19.1 ± 7.4	<.0001
AFP (ng/mL)	408 ± 864	480 ± 1,656	560 ± 1,735	.7377
DCP (mAU/mL)	112 ± 125	356 ± 944	414 ± 1,165	.3210
Within MC	6 (32%)	61 (56%)	33 (69%)	.0199

MC, Milan criteria.

Table II. Comparison of operative and pathological characteristics among hepatectomy, other pretreatment and no pretreatment groups

	Hepatectomy	*Other pretreatment*	*No pretreatment*	P
Graft-to-recipient weight ratio (%)	1.07 ± 0.28	1.02 ± 0.23	1.03 ± 0.26	.6726
Surgical duration (min)	941 ± 250	796 ± 171	763 ± 123	.0024
Intraoperative blood loss (mL)	9,999 ± 12,188	7,528 ± 8,653	6,846 ± 5,909	.4486
Tumor characteristics*				
Size of largest tumor (cm)	3.7 ± 5.0	3.0 ± 1.9	3.1 ± 1.9	.5627
Number of nodules	9.6 ± 7.9	6.9 ± 4.4	2.5 ± 2.0	<.0001
Differentiation				.1399
Well	1	16	4	
Moderately	13	69	37	
Poorly	5	24	7	
Microvascular invasion	7 (37%)	43 (39%)	10 (21%)	.0638
In-hospital death	1 (5%)	12 (11%)	4 (8%)	.6650

*Tumor characteristics are those found on the pathology of the explant after transplantation.

the other pretreatment and no pretreatment groups ($P < .001$). The patient rate within the Milan criteria diagnosed by preoperative imaging was significantly lower in the hepatectomy group than in the other pretreatment and no pretreatment groups ($P = .020$).

The duration from the diagnosis of HCC at the time of liver transplantation was 41.7 ± 31.3, 30.3 ± 26.4, and 3.8 ± 2.7 months in the hepatectomy, other and no pretreatment groups, respectively. The duration from the diagnosis of HCC at the time of liver transplantation was significantly longer in the hepatectomy and the other pretreatment groups compared with the no pretreatment group ($P < .001$).

Operative and pathologic characteristics. Surgical duration was significantly longer in the hepatectomy group than in the other pretreatment and no pretreatment groups ($P = .002$, Table II). Intraoperative blood loss did not differ among the groups. Multivariate analysis revealed that the MELD score ($P = .085$), Child-Pugh classification ($P = .130$), and Milan criteria ($P = .424$) were not significant risk factors for massive (>5 L) intraoperative blood loss. Significantly more tumors were found in the hepatectomy group than in the other pretreatment and no pretreatment groups ($P < .001$), whereas the tumor size did not differ among the groups. One patient died of pneumonia 39 days after LDLT. The in-hospital mortality rate in the hepatectomy group was 5.3%, which was similar to that in the other pretreatment and no pretreatment groups.

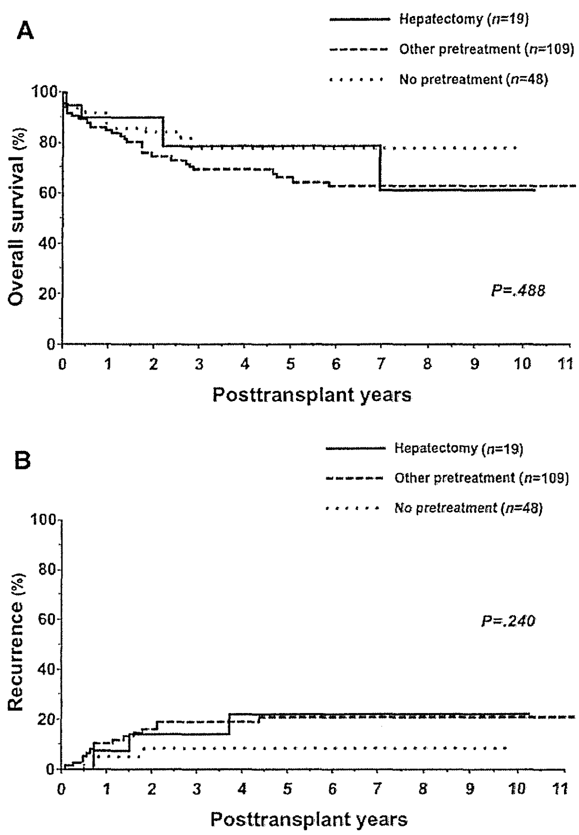

Fig 1. (*A*) Comparison of the overall survival rates among hepatectomy, other pretreatment and no pretreatment groups. (*B*) Comparison of the recurrence rates among hepatectomy, other pretreatment and no pretreatment groups.

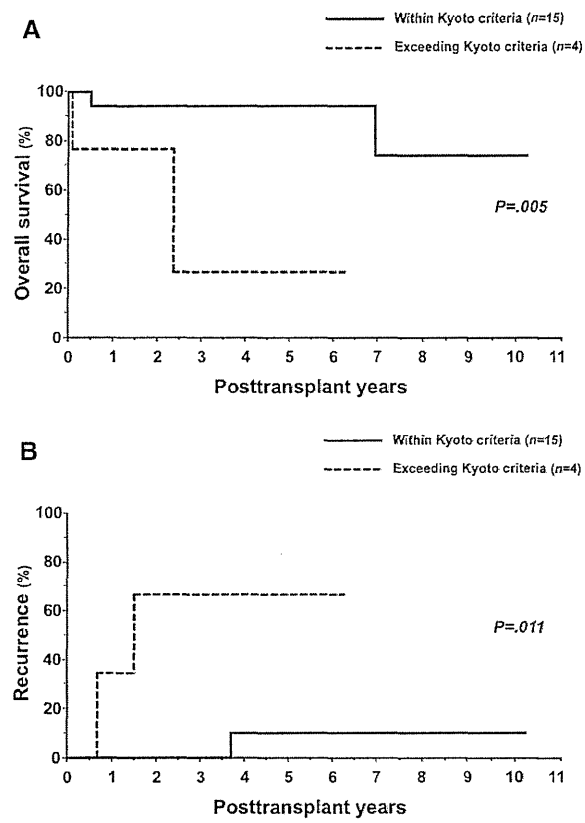

Fig 2. (*A*) Comparison of the overall survival rates in the hepatectomy group according to the Kyoto criteria. (*B*) Comparison of the recurrence rates in the hepatectomy group according to the Kyoto criteria.

Long-term outcomes in the 3 groups. Long-term overall survival rates did not differ significantly among the hepatectomy (n = 19), other pretreatment (n = 109), and no pretreatment (n = 48) groups (5-year rates, 77%, 66%, and 76%, respectively, Fig 1, *A*). The 5-year recurrence rates also did not significantly differ among the groups (22%, 21%, and 8%, respectively, Fig 1, *B*).

Long-term outcomes in the hepatectomy group according to selection criteria. Of the 19 patients who underwent LDLT after hepatectomy, the survival rates were significantly higher in those who met the Kyoto criteria (≤10 tumors, all ≤5 cm in diameter and DCP ≤400 mAU/mL; n = 15) compared with those who exceeded (n = 4) the Kyoto criteria (5-year survival, 93% vs 25%, P = .005; Fig 2, *A*). The recurrence rates were also lower among patients who met the Kyoto criteria than among those who exceeded the criteria (n = 4; 5-year recurrence rates, 10% vs 67%, P = .011, Fig 2, *B*).

In contrast, the overall survival and recurrence rates did not significantly differ between patients who met (n = 6) and those who exceeded (n = 13) the Milan criteria (Fig 3, *A* and *B*). The 5-year overall survival and recurrence rates in 10 patients in the hepatectomy group who met the Kyoto criteria but who were beyond the Milan criteria were 90% and 0%, respectively. Nine of 19 patients (47.3%) in the hepatectomy group were within the UCSF criteria. The overall survival and recurrence rates did not significantly differ between patients within and exceeding these criteria (P = .242 and P = .860).

DISCUSSION

The role of bridge therapy before LT differs somewhat between societies such as East Asia, where LDLT predominates, and other societies where it does not. Bridge therapy to prevent dropout from the waiting list is theoretically not required for patients who underwent elective LDLT. However, pretreatment using approaches such as TACE, RFA, and liver resection usually proceed in the clinical setting because LDLT is

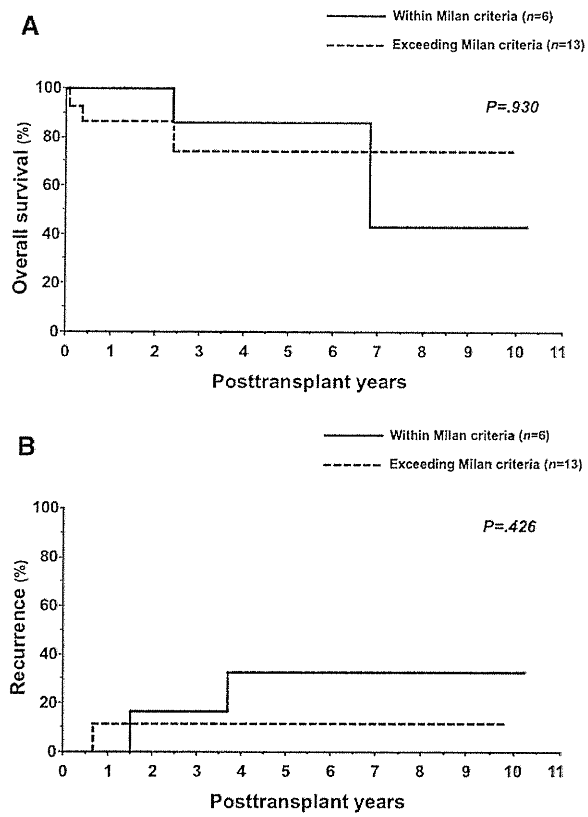

Fig 3. (*A*) Comparison of the overall survival rates in the hepatectomy group according to the Milan criteria. (*B*) Comparison of the recurrence rates in the hepatectomy group according to the Milan criteria.

regarded as a second- or third-line option in Asian countries. Therefore, the goal of such therapies usually is to cure patients with HCC rather than to serve as bridge therapy, unless they cannot proceed because deteriorated liver function. Among these treatment options, liver resection is often selected, because it is considered the most curative therapy for HCC if the patient has a functioning liver. However, LT after liver resection is associated with technical difficulties and risks caused by intra-abdominal adhesion.

Here, we found favorable short- and long-term outcomes in 19 patients who underwent LDLT for recurrent HCC after liver resection. This group represents the most patients of this type ever reported. Belghiti et al[5] analyzed 18 patients who underwent secondary DDLT after liver resection, including 11 with morphologic evidence of recurrence. They reported that liver resection before LT does not increase morbidity or impair long-term survival after LT. In contrast, Adam et al[6] associated a higher operative mortality, more intraoperative bleeding, an increased risk of recurrence, and a poorer overall survival for patients who underwent DDLT after liver resection (n = 17; 5-year survival rate, 41%) than primary LT (n = 195; 5-year survival rate, 61%). Hwang et al[7] examined the outcomes of 17 patients who underwent salvage LDLT, including 15 with recurrent HCC. They found that bleeding complications occurred more frequently in patients after salvage than after primary LDLT. However, the overall 5-year survival rates did not significantly differ between the 2 groups (54% and 72%, respectively). The current study found that intraoperative bleeding in LDLT after liver resection did not differ from that in primary LDLT, whereas the surgical duration was significantly longer for patients after liver resection. Moreover, overall survival and recurrence rates were similar to those in primary LDLT. These findings indicated that salvage LDLT for recurrent HCC could be performed safely with favorable outcomes.

The hepatectomy group had better liver function (higher incidence of Child-Pugh classification A) and lower MELD scores at the time of LDLT than the other pretreatment and no pretreatment groups ($P < .001$). For this reason, the patients in the hepatectomy group had sufficient remnant liver function to undergo hepatectomy at least at the time of liver resection, whereas the patients in the other pretreatment and no pretreatment groups could not undergo liver resection partly because of impaired liver function. Moreover, the indication for LDLT in the hepatectomy group in our study was not deteriorating liver function but tumor recurrence. Therefore, the better liver function and overall status of the hepatectomy group might have positively affected short-term as well as long-term outcomes. In contrast, the number of tumors and the rate of patients who exceeded the Milan criteria were significantly larger in the hepatectomy group than in the other pretreatment and no pretreatment groups, whereas tumor marker levels, tumor size, differentiation, and vascular invasiveness did not differ among the 3 groups. These findings indicate that the number of tumors might not affect prognosis significantly.

Selection criteria for salvage LT have not been established. The current study found that the survival rates were similar between patients who exceeded and those who were within the Milan criteria (5-year rate, 83%). The recurrence rate also did not differ between patients who were within and those who exceeded the Milan criteria. In contrast, the survival rates of patients within the Kyoto criteria were significantly higher (5-year rate, 93%) and recurrence rates were significantly lower (5-year rate, 10%) compared with those who exceeded the Kyoto criteria (5-year rates, 25% and 67%, respectively). Although the patient cohort in this study was small, these findings suggest that the Kyoto criteria, including a surrogate marker of tumor biological aggressiveness, are useful as selection criteria and also for salvage LT to treat recurrent HCC. However, serum DCP level usually cannot be measured in the Western countries. In fact, a representative tumor marker for HCC, serum AFP level >800 ng/mL, was also a significant risk factor for recurrence in univariate analysis, whereas it was not an independent risk factor in multivariate analysis.[11] Considering the availability of AFP in clinical settings, it would be possible to use AFP as a surrogate for DCP in the Western countries.

In practice, taking into consideration the problem of organ shortage and the risks for live donors, salvage LT would be a useful treatment strategy for patients with HCC who undergo either DDLT or LDLT. In contrast, liver resection as bridge therapy might impair patient transplantability as well as the long-term survival of patients with cirrhotic liver and HCC. Adam et al[6] demonstrated a 25% rate of transplantable patients with tumor recurrence treated by resection while initially eligible for transplantation. They also reported that 5-year overall and disease-free survival is decreased in transplantable resected patients compared with primary transplanted patients. The total number and long-term prognosis of transplantable resected patients was unclear in the current study because most of the patients who underwent LDLT at our institution were referred from other hospitals. Although transplantability is affected partly by selection criteria, some risk of low transplantability might be associated with LDLT. An intention-to-treat analysis of a nationwide database is required to elucidate such risks in LDLT.

In conclusion, LDLT can be performed safely in patients with HCC recurrence after liver resection. In particular, favorable long-term outcomes can be obtained for patients who meet the Kyoto criteria.

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Applied nutritional investigation

Pre- and perioperative factors affecting infection after living donor liver transplantation

Toshimi Kaido M.D. *, Akira Mori M.D., Yasuhiro Ogura M.D., Kouhei Ogawa M.D., Koichiro Hata M.D., Atsushi Yoshizawa M.D., Shintaro Yagi M.D., Shinji Uemoto M.D.

Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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ABSTRACT

Objective: Infectious complications, including sepsis, that often occur after liver transplantation (LT) comprise the most frequent causes of in-hospital death. This study investigated the predictors of post-transplantation infectious complications to establish a strategy with which to improve short-term outcomes after LT.
Methods: We used univariate and multivariate analyses to assess pre- and perioperative risk factors for post-transplantation infectious complications in 100 consecutive patients who underwent living donor LT from February 2008 through February 2010 at our institute.
Results: Multivariate analysis showed that low preoperative body cell mass and the absence of preoperative supplementation with branched-chain amino acids were of prognostic significance for post-transplantation sepsis. In addition, Child–Pugh classification C and massive operative blood loss were independent risk factors for post-transplantation bacteremia, and preoperative low body cell mass was an independent risk factor for in-hospital death from infection.
Conclusion: Pretransplantation nutritional intervention and decreases in operative blood loss would help prevent post-transplantation infectious complications from developing during living donor LT. Branched-chain amino acid supplementation before LT affects the occurrence of infectious complications.

Introduction

Infections after liver transplantation (LT) are the most frequent causes of morbidity and in-hospital death [1]. Patients who undergo LT are regarded as at unusually high risk for perioperative infection. For example, protein–energy malnutrition, which is common in patients with end-stage liver disease requiring LT, is considered to confer a vulnerability to preoperative infection, including spontaneous bacterial peritonitis and pneumonia from a deteriorated immune function [2,3]. LT is a massive invasion of the host. The number of intraoperatively transfused cellular blood products is also a risk factor for infections [4]. Furthermore, immunosuppression and multiple catheter insertions increase the risk of post-transplantation infection. Consequently, infectious complications, including sepsis and bacteremia, often occur after LT and are the most frequent causes of in-hospital death. Therefore, the prevention of post-transplantation infection plays a crucial role in improving short-term outcomes after LT.

Malnutrition is a risk factor for postoperative complications and mortality rates in patients with a cirrhotic liver who undergo surgery [5,6]. However, the impact of preoperative nutritional status and of nutritional interventions on postoperative infectious complications in LT remains controversial [7–10], especially in patients undergoing living donor LT (LDLT). Patients with advanced cirrhosis characteristically show a decrease in plasma concentrations of branched-chain amino acids (BCAAs). These BCAAs not only serve as an essential substrate in the synthesis of body proteins, but also act as an important regulator of protein turnover. Moreover, BCAAs have beneficial effects on hepatic encephalopathy through the promotion of ammonia detoxification and the correction of the plasma amino acid imbalance, liver regeneration, and hepatic cachexia in patients with liver diseases [11]. Improving systemic conditions, including nutritional status, to the greatest extent possible before LT facilitates early postoperative recovery. Supplementation with a BCAA-enriched nutrient mixture is reportedly beneficial not only for patients with liver cirrhosis but also for patients undergoing hepatectomy

* Corresponding author. Tel./fax: +81-75-751-4322.
E-mail address: kaido@kuhp.kyoto-u.ac.jp (T. Kaido).

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