[質疑応答]

伊東(座長):臨床的なことで先に確認したいのですが,提示した肝生検の材料はどこからどのような方法で採取したものでしょうか。

演者(金子):経皮的に肝生検針を使用し,門脈腫瘍栓をねらって採取したと聞いています。

伊東:門脈腫瘍栓を経皮的に採取したわけですか。

演者:そうです。

小尾(共同演者):当時,私が担当しましたが,この患者は肝内にはまったく腫瘍がなく,門脈腫瘍栓だけでてきたようなタイプでした。われわれも最初は診断がつかず,ただ張っているので腫瘍栓ではないかということで,エコーガイド下で針生検を行いました。

伊東:アプローチはどのようにされたのでしょうか。

小尾:普通に右肋間からです。

伊東:右肋間から右の一次分枝周辺部分の腫瘍栓を採取したということですか。

小尾:はい。

伊東:肝移植前のIFN/5-FU治療は外科病棟だったのですか。それとも内科病棟で治療されたのですか。

演者:内科です。

伊東:そして移植の時点で外科に移ったわけですか。

演者:はい。

病理コメント

移植前に行われた門脈本幹内腫瘍栓の生検組織には,非常に少領域ながら偽腺管構築を伴って増殖する異型肝細胞が認められる。中分化型肝細胞癌(Edmondson Ⅱ型)として矛盾しない組織像である。その後,生体肝移植のために摘出された肝臓内にも化学療法によって壊死に陥った腫瘍組織を門脈内に認める。組織学的には凝固壊死組織であり,鍍銀染色により組織構築や細胞骨格をある程度確認することができ,生検組織に認められた肝細胞癌に類似していた。与えられた標本内にはviableな腫瘍組織や肝実質内腫瘍性病変は認められなかった。背景肝組織は肝硬変である。生体肝移植前の臨床所見に矛盾しない所見である。

本症例は化学療法によるdownstage後に生体肝移植が行われ,移植後1年6か月で慢性拒絶による肝不全により再生体肝移植が行われている。この時摘出された移植肝臓には臨床的に再発は認められず,肝硬変の状態であったとされている。しかし,今後の移植治療の検討のためにも,摘出された移植肝臓の詳細な病理学的検索は必要と考えられる。

(尾島 英知)

[質疑応答]

伊東:そうすると,全摘標本のなかにはアクティブなHCCはなかったということですか。

尾島(病理コメンテーター):今回送られてきたのは1枚なのですが,そのなかにはありませんでした。

有井(東京医科歯科大学):この移植の適応というのは肝癌ではなしに,結局はいわゆる肝硬変ですか。

演者:そうです。T-Bil 2.5 mg/dlの非代償性肝硬変という判断です。

有井:一つお聞きしますが,HCC時の移植適応で,ミラノ基準などいろいろあるわけですが,こういう前治療を行いミラノ基準内にもっていくとすると,この患者もVp4であったが,そういう前治療が非常に効いたという場合にHCCとしてはミラノ基準内になったわけですね。

演者:そうです。

有井:もともとはミラノ基準外であったものを,前治療を行いミラノ基準内にもっていき手術した場合,その治療成績は最初からミラノ基準内であったものと同等と考えてよいのか,そういうスタディは恐らくないと思うのですが。

演者：比較したものはないと思いますが，勉強不足かもしれません。調べてみます。
有井：いったんたとえばVp4であれば，恐らく流血中にあって，どこかにオカルトの癌細胞が残っているかもしれません。それをいろいろな前治療で見掛け上，ミラノ基準内にもっていっても，もしかしたらまたそれがどこかで再燃するのではないかという危惧もあるわけです。最初からミラノ基準内であったものと前治療を行ってミラノ基準内にもっていったものとでは同じなのかどうかという質問なのですが。
澤田(獨協医科大学)：今年の国際移植学会でいくつかレポートがあったと思います。もともとミラノ基準内であったものと治療後ミラノ基準内になったが肝移植を行ったという症例報告はありますが，2年以降の長期成績の報告はまだないので，結果として判断はできていないと思います。
一つお聞きしたいのは，他病死されたということですが，病理解剖の標本は採取されているのでしょうか。
演者：病理解剖の標本は採取されていません。C型肝炎で肝硬変が早期に進行したので，一応再肝移植を行いました。
澤田：移植した肝臓がどうなっているのかはわからないということですね。
演者：移植した肝臓をみることができましたが，もう1回肝硬変になりました。しかし，特に再発などはありませんでした。
伊東：演者が他病死といっているのは，肝癌で亡くならなかったというだけで，肝臓病で亡くなったのですか。
演者：再肝移植後，しばらくして重症急性膵炎で亡くなりました。
伊東：治療関連死であれば，「他病死」とはいわないほうがよいですね。
演者：わかりました。
幕内(共同演者)：ミラノ基準外にあったものを治療してミラノ基準内になってどうかというのは，保険が絡んでいるものですから，治療してそうなったものとならないものとで日本肝移植研究会から厚労省に書類が提出されています。北海道大学の藤堂先生が日本で調査しデータを調べられて，それによると観察期間は短いのですが，ミラノ基準内とミラノ基準外では一般の意味で明らかに差があります。しかし，ミラノ基準外をミラノ基準内にして行った例とでは差がないというデータがでています。保険適用もミラノ基準内に戻せば差をつける必要はないのではないかというのが日本肝移植研究会の意見で，それが厚労省に提出してあるということでした。
伊東：それぞれの群の平均フォローアップ期間はどれくらいですか。
幕内：短いです。ただ，明らかに通常のミラノ基準内とミラノ基準外で行うと，明らかに差があるということです。
伊東：前治療でミラノ基準内にもっていった例でも，現時点での治療成績は特に悪くはなさそうだということでしょうか。
幕内：そうです。ですから前治療を行わずミラノ基準外で移植を行ったものと，治療後ミラノ基準内で行ったものとでは，生存曲線は違うということです。
福里(帝京大学)：診断が問題になるわけではありませんが，この患者のIFN receptorは調べていますか。
演者：調べておりません。
福里：治療効果ははっきりしていますので，こういうものを調べていただければと思います。それからp53 mutationは調べていますか。
演者：調べてないようです。
福里：できれば少しでも治療効果と関連した因子を調べた症例を蓄積していただいたほうがよかったと思います。

講 評

41歳，インド人男性が genotype 4 型の C 型慢性肝炎，肝硬変を基盤に，肝細胞癌(HCC)を発症した。肝内原発巣が不明のまま，診断時すでに高度の門脈内進展を呈していた。

入院時の精査にても，原発 HCC 病巣は同定不能であり，門脈右一次分枝から門脈本幹まで腫瘍栓が伸展，右肝門の腫瘍栓からの針生検材料で中分化 HCC の組織が確認された。

切除肝材料を前提とする本邦の「原発性肝癌取扱い規約」にはなじまない症例であるが，あえて staging を試みるなら「腫瘍個数不明，腫瘍径不明，Vp4」より StageⅣA の高度進行性 HCC となるであろう。著者らは StageⅡとしているが，この判定(規約の解釈)は疑問である。StageⅡなら，なぜ最初から切除しなかったのかと。

IFN 療法＋5-FU 肝動注が著効を奏し，門脈腫瘍栓は早期に消失，動注化学療法開始から1年後に生体肝移植手術が行われた。摘出肝の病理学的検討では肝実質内に HCC 原発巣を同定できず，P7 門脈枝に壊死化した腫瘍栓を認めたのみであった。

動注化学療法の奏効例では HCC 原発巣だけでなく，腫瘍被膜内外の浸潤域や脈管内腫瘍栓にも効果が及ぶことは従来よりよく知られている。本症例では，基盤が硬変肝のため同定が困難であったが，S7 領域のいずこかに被膜を形成せず，早期から浸潤型の進展を呈した原発病巣が存在したのであろう。

内科医には動注療法の有用性を再確認させ，外科医には集学的な downstaging と適切な術前診断により，初発時に高度進行性 HCC であっても移植外科の対象となる例が存在することを示す極めて教訓的な1例であった。

(伊東 和樹)

この論文は第34回肝癌症例検討会(2006年11月18日)で発表された

Surg Today (2008) 38:289–291
DOI 10.1007/s00595-007-3603-8

SURGERY TODAY

Reconstruction of the Middle Hepatic Vein Tributaries Draining Segments V and VIII of a Right Liver Graft by Using the Recipient's Own Middle Hepatic Vein and Vascular Closure Staples

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Abstract
A right liver graft lacking the middle hepatic vein can result in congestion of the anterior segment. We describe a method of reconstructing the middle hepatic vein tributaries by using the recipient's own middle hepatic vein with vascular closure staples. During a living donor right liver transplantation, the middle hepatic vein tributaries draining segments V (V5) and VIII (V8) of the right lobe graft were reconstructed using the recipient's own middle hepatic vein and secured with vascular closure staples. Computed tomography showed good venous outflow from the middle hepatic vein and no congestion or atrophy of the anterior segment of the right liver grafts. Thus, using the recipient's own middle hepatic vein is a suitable option for reconstructing the middle hepatic vein tributaries (V8 and V5) in right-liver living donor transplantation and the application of vascular closure staples helps to accomplish this.

Key words Living donor liver transplantation · Middle hepatic vein reconstruction · Vascular closure staples

Introduction

Living donor liver transplantation was developed primarily as a solution for the shortage of organs for pediatric recipients; however, its indications have been extended to include adult recipients. Right-liver living donor transplantation has become an increasingly popular option for adults, but if a right liver graft lacks a middle hepatic vein trunk, severe congestion of the anterior segment can develop because the hepatic venous outflow of the anterior segment drains mainly into the middle hepatic vein.[1,2] Several solutions have been devised to overcome this problem, including a right liver graft with reconstruction of the middle hepatic vein tributaries, using various interposition vein grafts.[3]

It has been reported that vascular closure staples, a relatively new device in vascular surgery, result in a shorter anastomotic time and fewer thrombotic complications.[4] Accordingly, we have found that compared with conventional suturing, vascular closure staples suturing carries a lower risk of anastomotic stenosis in portal vein reconstruction after living donor liver transplantation.[5] In this report, we describe how we used vascular closure staples in the reconstruction of the middle hepatic vein tributaries draining segments V (V5) and VIII (V8) of a right lobe graft by using the recipient's own middle hepatic vein.

Case Report

The recipient had decompensated liver cirrhosis caused by excessive alcohol consumption and his son offered donation of part of his liver. Three-dimensional computed tomographic imaging showed a large middle hepatic vein tributary draining segment 5. During retrieval of the donor organ, we identified a middle hepatic vein tributary (V8) draining segment 8 (4 mm) and a large middle hepatic vein tributary (V5) draining segment 5 (12 mm). The V5 and V8 tributaries were preserved until complete transection of the parenchyma. The recipient hepatectomy was completed with preservation of the middle hepatic vein tributaries as follows: after dividing the portal vein, hepatic artery, and bile duct in the hepatic hilum, the right and left hepatic veins were dissected. The middle hepatic vein was then clamped at its confluence with the inferior vena cava, and the hepatic parenchyma was resected from around the middle hepatic vein. The middle hepatic vein and its tributaries were carefully dissected using a Cavitron

Reprint requests to: H. Tashiro
Received: February 5, 2007 / Accepted: May 10, 2007

Fig. 1. The right liver lobe graft after *V5* and *V8* reconstruction

ultrasonic surgical aspirator. An approximately 10-cm segment of the main trunk, including the V5 and V8 branches, was isolated and preserved, and the recipient's liver was removed. After repairing tears in the middle hepatic vein with 6-0 or 7-0 proline sutures, we confirmed that the middle hepatic vein was intact, with a leak test. It took 19 min to prepare the middle hepatic vein. For graft implantation, the donor right hepatic vein was anastomosed to the native right hepatic vein orifice. The V8 tributary of the right liver graft was then anastomosed to the recipient's middle hepatic vein tributary (V8) by continuous suturing of the posterior wall with 7-0 proline sutures. Small vascular closure staples were then applied at 0.5-mm intervals to complete the anterior wall closure. After portal vein reconstruction using the vascular closure staples,[5] the portal vein was perfused. We then performed the hepatic artery and duct-to-duct bile duct reconstruction. Finally, the V5 was reconstructed by anastomosing the tributary (V5) of the middle hepatic vein of the right lobe graft to the recipient middle hepatic vein tributary (V5), using a continuous 7-0 proline suture in the posterior wall. Small vascular closure staples were then applied at 0.5-mm intervals to complete the anterior wall (Fig. 1). After reperfusion of the V5, we confirmed that there was no congestion of the anterior segments, including segments 8 and 5. Daily Doppler ultrasound showed good flow in the tributaries of the middle hepatic vein. The graft function was excellent and the recipient was discharged from hospital 35 days after surgery.

Results

Since January 2006, we have applied this technique successfully during liver transplantation in seven patients. We used the vascular closure staple technique in reconstruction of the V8 and V5 tributaries in six and three patients, respectively, using the recipient's own middle hepatic vein. None of the patients experienced vascular complications and all had good venous flow postoperatively.

Discussion

When a cadaveric venous graft is not available, a variety of vein grafts have been used for the reconstruction of middle hepatic vein tributaries. These include the great saphenous vein and the inferior mesenteric vein, which require no extensive dissection for removal, but are much smaller than the middle hepatic vein; and the jugular and iliac veins, which have a similar caliber to the middle hepatic vein, but require extensive dissection for removal.[6–8] The advantages of using the recipient's middle hepatic vein over these other vein grafts are as follows.[9] First, it has a similar caliber to the donor vein and good patency. We confirmed the triphasic or biphasic waveform on follow-up Doppler ultrasonography done 3 months postoperatively in all of our patients. Second, neither the recipient nor the donor requires additional surgery. By clamping the root of the middle hepatic vein, dissection of the recipient's own middle hepatic vein entails no risk of bleeding. One possible disadvantage of using the recipient's own middle hepatic vein is that it may be too short for reconstruction of the V5.[10] However, to our knowledge, there have been no reports on reconstruction of the V5 using the recipient's own middle hepatic vein. In our experience, the recipient's middle hepatic vein is long enough to allow reconstruction of the V5. If the recipient's middle hepatic vein is too short for reconstruction of the V5, the recipient's portal vein and the great saphenous vein can be used as an interposition graft between the V5 of the liver graft and the recipient's middle hepatic vein.

We applied vascular closure staples when reconstructing the tributaries of the middle hepatic vein of a liver graft. In our previous series of living donor liver transplantations, we reported that vascular closure staple suturing was associated with a low risk of anastomotic stenosis in portal vein reconstruction.[5] The major advantages of the vascular closure staples are as follows: they do not penetrate the vessel; they do not disrupt the endothelium; they do not have an intraluminal component; the anastomosis can be performed faster with vascular closure staples than with continuous suturing; and the interrupted anastomosis allows for dilatation and growth of the vessel.[4] We observed no stenosis or obstruction of the anastomotic site of the V5 or V8 tributaries of the liver graft.

In conclusion, we used the recipient's middle hepatic vein to reconstruct the middle hepatic vein tributaries

(V8 and/or V5) by applying vascular closure staples in seven right-lobe living donor liver transplantations with excellent results. Further studies are warranted to evaluate the efficiency and outcome of the application of vascular closure staples in reconstruction of the middle hepatic vein V8 and V5 tributaries using the recipient's middle hepatic vein in living donor liver transplantation.

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Repeat hepatectomy for recurrent hepatocellular carcinoma

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Background. *Long-term prognosis of patients with hepatocellular carcinoma (HCC) after partial hepatectomy remains unsatisfactory because of the high incidence of recurrence in the liver remnant. Controversy exists about the efficacy of repeat hepatectomy for recurrent HCC patients. The purpose of this study was to retrospectively examine and clarify the significance of repeat hepatectomy in the treatment of recurrent HCC.*

Methods. *From January 1990 to December 2004, 84 patients with recurrent HCC underwent a second hepatectomy with curative intent. Survival rates in these 84 patients were analyzed retrospectively.*

Results. *After the second hepatectomy, the overall 5-year survival rate was 50% for the 84 patients included in this study; the corresponding recurrence-free survival rate was 10%. Multivariate analysis showed that the second hepatectomy performed between 1997 and 2004 ($P < .001$) and the absence of microscopic vascular invasion at the second hepatectomy ($P = .001$) were the significant and independent prognostic factors for overall survival after the second hepatectomy. The overall 5-year survival rate after the second hepatectomy was 80% in 46 patients who had both these prognostic factors. However, even in the subgroup with good long-term survival, the 5-year recurrence-free survival rate was only 6%. The more times hepatectomy was repeated, the shorter the recurrence-free interval became.*

Conclusions. *Repeat hepatectomy for recurrent HCC had survival benefits, especially for patients without microscopic vascular invasion. However, the incidence of re-recurrence after the second hepatectomy was high, and the recurrence-free interval was short, even in the subgroup with survival benefits. The effectiveness of repeat hepatectomy for curing recurrent HCC is limited.*
(Surgery 2007;141:589-97.)

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PARTIAL HEPATECTOMY is the first choice of treatment for patients with hepatocellular carcinoma (HCC) and preserved liver function. The prognosis of HCC patients has improved because of advances in radiologic assessment, patient selection, operative techniques, and perioperative care;[1,2] however, long-term prognosis of patients with HCC after partial hepatectomy remains unsatisfactory because of the high incidence of recurrence in the liver remnant. Cumulative 5-year recurrence rates after curative partial hepatectomy is 70% to 80%.[3-5] Therefore, appropriate management of recurrent HCC is important for improving long-term outcome after hepatectomy. Treatment modalities for recurrent HCC include repeat partial hepatectomy, ablation therapy and transcatheter arterial chemoembolization. The 5-year survival rates after repeat hepatectomy that have been reported recently[6-11] has ranged from 41% to 69%; however, various factors, such as impaired liver function, preclude repeat hepatectomy in over 70% of patients with recurrent HCC,[9-14] and the re-recurrence rate after repeat hepatectomy is also high.[6]

Liver transplantation (LT) for selected HCC patients, by which the whole cirrhotic liver and all gross tumors, occult tumors, and dysplastic nodules are removed at the same time, results in a better prognosis with a low rate of cancer recurrence than does curative partial hepatectomy.[15-18] Although LT is a first-line treatment for small HCC concom-

Accepted for publication December 27, 2006.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2006.12.014

itant with decompensated liver cirrhosis, it has been proposed recently that LT should be applied even to patients with HCC who have preserved liver function.[19,20] The severe disparity between the demand for transplantation and the supply of organs from deceased donors has precluded an expansion of the selection criteria to include patients with HCC and preserved liver function.[21]

We have performed repeat hepatectomy for recurrent HCC as we have done for initial hepatectomy for primary HCC. We present here the results of 94 repeat hepatectomies for 84 patients with recurrent HCC after initial hepatectomy. Our study includes the largest number of patients with recurrent HCC who underwent repeat hepatectomy at a single center. The purpose of this study was to retrospectively clarify the significance of repeat hepatectomy in the treatment of recurrent HCC.

METHODS

From January 1990 to December 2004, 483 consecutive patients underwent an initial hepatectomy with curative intent for HCC at Hiroshima University Hospital (Hiroshima, Japan) by a single team. Among the 483 patients, 279 (58%) developed intrahepatic recurrence, and 70 patients underwent a second hepatectomy (rate of repeat hepatectomy, 25%). During the same time period, 21 additional patients also underwent a second hepatectomy; 4 of these patients had undergone initial hepatectomy at our institute before January 1990 and 17 patients had undergone initial hepatectomy at other hospitals. Of the total of 91 patients, 7 patients received a second hepatectomy with palliative intent, such as mass reduction surgery for large HCC concomitant with multiple intrahepatic metastases or distant metastases; these patients were excluded from this study. The remaining 84 patients underwent a second hepatectomy with curative intent and were included in this retrospective study. Among the 84 patients, 8 patients underwent third hepatectomies for second recurrences, and 2 patients underwent fourth hepatectomies for third recurrences. There were 64 men and 20 women with a mean age of 66 years (range, 39 to 84 years) who underwent a second hepatectomy.

Cancer stage was classified according to the new American Joint Committee on Cancer (AJCC)/Internal Union Against Cancer (UICC) Tumor, Node, Metastasis (TNM) staging system.[22] Hepatectomy of less than 1 segment according to Couinaud's segmentation[23] was defined as limited resection. For patients undergoing multiple resections, the most important procedure was considered to be the main type of hepatectomy. When a patient had insufficient hepatic functional reserve within which all tumors could be resected, an intraoperative ablation therapy, such as ethanol injection, microwave coagulation, or radiofrequency ablation (RFA), was added to hepatectomy for a limited number of small residual tumors.

Indication of repeat hepatectomy for recurrent HCC and operative procedure. The selection of type of hepatectomy was made on the basis of liver function and tumor location. Liver function was assessed by the Child-Pugh classification[24] of severity of liver disease and indocyanine green retention rate at 15 minutes. Child-Pugh class C was regarded as a contraindication for hepatectomy. Hepatectomy was indicated when all tumors detected by preoperative imaging modalities could be resected within the hepatic functional reserve or could be treated with the addition of intraoperative ablation therapy to hepatectomy. In contrast, when the recurrent HCC tumors were 2 cm or less in size and the number of tumors was 3 or less, percutaneous ablation therapies were preferable despite the feasibility of repeat hepatectomy, depending on tumor location in the liver. The indication for repeat hepatectomy for patients with recurrent HCC throughout the period of the present study did not change.

Intermittent hepatic inflow occlusion was performed during hepatic parenchymal transection if necessary. The main inflow occlusion technique used primarily was a Pringle maneuver, which was maintained for 15 minutes and released for 5 minutes, and was performed using a soft bowel clamp or tourniquet.[25] Parenchymal transection was performed using an ultrasonic dissector (Sonop 5000; Aloka Co, Ltd, Tokyo, Japan) combined with a bipolar electrocautery.

Statistical analysis. Statistical analyses using standard tests (chi-square test, *t* test) were performed when appropriate. Overall survival rates and recurrence-free survival rates were computed by the Kaplan-Meier method and compared between groups by the log-rank test. Factors that were found to significantly influence survival were then used in the stepwise Cox proportional hazards regression model for multivariate analysis. Significance was defined as a P value $<.05$. Statistical analyses were performed using StatView for Windows, version 5.0 (SAS Institute, Cary NC).

Follow-up. Follow-up evaluation after hepatectomy consisted of physical examinations, blood chemistry tests, and measurements of levels of tumor markers, including alpha-fetoprotein and des-gamma-carboxy prothrombin, every month for 2 years. After 2 years, the patients were assessed every

3 months. Patients were examined by ultrasonography every 3 months and by chest and abdominal computed tomography (CT) every 6 months. Helical CT and multidetector-row CT were introduced at our institute in April 1995 and March 1999, respectively. When recurrence was indicated by any of these examinations, patients underwent hepatic angiography. CT during hepatic arteriography and CT during arterial portography were introduced at our institute in January 1999 and have been used routinely since that time. The mean and median follow-up periods after the second hepatectomy were 36 and 31 months (range, 4 to 143 months), respectively.

RESULTS

Patients' characteristics and operative procedures of the 94 repeat hepatectomies for the 84 patients are summarized in Table I. Data are shown separately for second, third, and fourth hepatectomies. Among the 84 patients, 62% of the patients undergoing resection had hepatitis C infection, and 67% had histologically confirmed cirrhosis at the second hepatectomy. The remaining 33% had evidence of chronic hepatitis. Mean tumor sizes in diameter at the second and third hepatectomies were 2.8 cm and 2.7 cm, respectively. At the second hepatectomy, 31 patients (37%) had multiple tumors; at the third hepatectomy, 7 patients (88%) had multiple tumors. A total of 18 patients (21%) at the second hepatectomy and 3 patients (38%) at the third hepatectomy had macroscopic vascular invasion (tumor thrombus in the vasculature). According to the TNM staging system, cancer stages at the second hepatectomy were stage I in 40 patients (48%), stage II in 34 patients (40%), and stage IIIA in 10 patients (12%). Types of initial hepatectomy performed in the 84 patients were hemihepatectomy in 6 patients, bisegmentectomy in 7 patients, segmentectomy in 17 patients, and limited resection in 54 patients. Although anatomic resections, including hemihepatectomy, bisegmentectomy, or segmentectomy, were performed in 24 (26%) of the patients at the second hepatectomy and in 3 (37%) of the patients at the third hepatectomy, most procedures performed for recurrent HCC were limited resection. A total of 9 patients (10%) at the second hepatectomy and 2 patients (25%) at the third hepatectomy underwent multiple resections for multiple, recurrent HCC. Intraoperative ablation therapy was added in 15 patients (16%) at the second hepatectomy.

Intraoperative and postoperative data for the 94 repeat hepatectomies in 84 patients with recurrent HCC are summarized in Table II. The mean operation times in the second and third hepatectomies were 265 minutes (range, 90 to 650 minutes) and 300 minutes (range, 170 to 370 minutes), respectively. The mean blood losses in the second and third hepatectomies were 603 mL (range, 10 to 5300 mL) and 502 mL (range, 170 to 1250 mL), respectively. Eight patients (10%) received perioperative blood transfusion at the second hepatectomy or during their perioperative periods; however, no patient received perioperative blood transfusion at the third or fourth hepatectomy. Postoperative complications occurred in 19 of the 84 patients (23%) who underwent a second hepatectomy and

Table I. Patients'characteristics and operative procedures for 94 repeat hepatectomies in 84 patients

	Second Hx (n = 84)	*Third Hx (n = 8)*	*Fourth Hx (n = 2)*
Age at operation (y)	65.5 ± 7.8	69.2 ± 9.0	60, 66
Gender: Male	64 (76)	4	1
HCV-positive	52 (62)	5	2
HBV-positive	27 (32)	3	0
Cirrhotic liver	56 (67)	4	1
Child-Pugh class A	71 (85)	8	2
ICG-R_{15} (%)*	17.7 ± 9.0	18.0 ± 10.4	13.2, 20.0
Tumor size in diameter (cm)	2.8 ± 1.9	2.7 ± 1.5	1.5, 2.0
Single tumor	53 (63)	1	2
Macroscopic vascular invasion	18 (21)	3	0
AJCC/UICC TNM stage†			
I	40 (48)	1	2
II	34 (40)	5	0
IIIA	10 (12)	2	0
Meeting the Milan criteria	56 (67)	5	2
Type of initial Hx: Major‡	13 (15)		
Type of repeated Hx: Major‡	11 (13)	2	0
Intraoperative additional procedures§	15 (18)	0	0

n, Number of patients; *Hx*, hepatectomy; *HCV*, hepatitis C virus; *HBV*, hepatitis B virus.

Data are expressed as means ± standard deviation or as number of patients (% of total patients).

*ICG-R_{15}, indocyanine green retention rate at 15 minutes.

†Cancer stage was classified according to the new AJCC/UICC TNM staging.[22]

‡Hepatectomy of 2 or more segments according to Chuinard's segmentation.[23]

§Ethanol injection therapy, microwave coagulation therapy, or radiofrequency ablation therapy.

Table II. Intraoperative and postoperative data of 94 repeat hepatectomies for 84 patients with recurrent hepatocellular carcinoma

	Second Hx (n = 84)	*Third Hx (n = 8)*	*Fourth Hx (n = 2)*
Operation time (min)	265 ± 111	300 ± 77	145, 210
Inflow occlusion	51 (61)	7 (88)	0
Blood loss (ml)	603 ± 876	502 ± 408	50, 50
Perioperative blood transfusion	8 (10)	0 (0)	0 (0)
Postoperative complications			
Major	9	1	0
Minor	11*	2	0
Morbidity (%)	23	38	0
30-day mortality	0	0	0
90-day mortality	0	1	0

n, Number of patients; *Hx*, hepatectomy.
Data are expressed as means ± standard deviation or as number of patients (% of total patients).
*One patient had two minor complications.

in 3 of the 8 patients (38%) who underwent a third hepatectomy; no postoperative complications occurred in the 2 patients who underwent a fourth hepatectomy. Although there were no deaths within 30 days after repeat hepatectomy, 1 patient died on postoperative day 41 after a third hepatectomy due to cardiac complications. The inhospital death rate in patients who underwent the 94 repeat hepatectomies was 1%.

The 1-, 3-, and 5-year overall survival rates of the 84 patients after the second hepatectomy were 88%, 67%, and 50%, respectively. The corresponding recurrence-free survival rates of those 84 patients after the second hepatectomy were 56%, 25%, and 10%, respectively (Fig 1). Mean recurrence-free intervals after initial hepatectomy in the 84 patients, after the second hepatectomy in the 57 patients, and after the third hepatectomy in the 7 patients were 29 months, 13 months, and 8 months, respectively. There were differences between recurrence-free intervals after the initial hepatectomy compared to the second hepatectomy ($P < .001$) and between recurrence-free intervals after the initial hepatectomy compared to those after the third hepatectomy ($P = .017$) (Table III).

All significant factors affecting overall survival after the second hepatectomy in univariate analysis included tumor diameter larger than 3 cm ($P = .017$), tumor(s) exceeding the Milan criteria ($P = .002$), TNM stage IIIA according to the AJCC/UICC classification system ($P = .021$), presence of

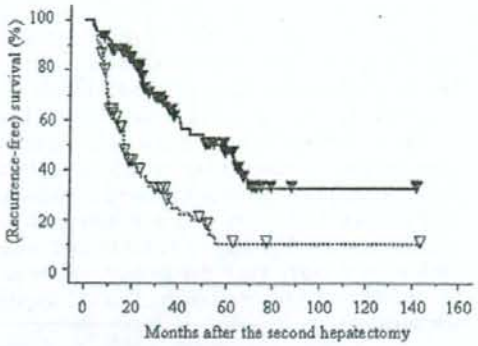

Fig 1. Overall survival (*solid line*) and recurrence-free survival (*dotted line*) curves for 84 patients after second hepatectomy.

Table III. Comparison of recurrence-free intervals

		Recurrence-free interval (m)		
	n	*Mean*	*Median*	*Range*
After initial hepatectomy	84	28.9	22.4	(2.7-102.6)
After second hepatectomy	57	13.3	8.9	(0.4-50.3)
After third hepatectomy	7	7.5	5.2	(1.3-14.7)

macroscopic vascular invasion ($P < .001$), presence of microscopic vascular invasion ($P = .001$), second hepatectomy performed between 1990 and 1996 ($P < .001$), blood loss of more than 1000 mL ($P = .007$), and perioperative blood transfusion ($P = .001$) (Table IV). There were no significant factors at initial hepatectomy affecting the overall survival after the second hepatectomy (data not shown).

In the multivariate analysis according to the stepwise Cox proportional hazards model, a second hepatectomy performed between 1990 and 1996 ($P < .001$) and the presence of microscopic vascular invasion at a second hepatectomy ($P = .001$) were the significant and independent adverse prognostic factors for overall survival after the second hepatectomy (data not shown).

To evaluate the differences between backgrounds of patients who underwent a second hepatectomy in different eras, a subgroup that underwent a second hepatectomy between 1997 and 2004 was compared with a group that underwent a second hepatectomy between 1990 and 1996 with regard to prognostic factors that were shown by univariate analysis to have affected overall survival

Table IV. Overall survival rates after second hepatectomy according to clinicopathologic factors at the second hepatectomy

Variables at the second Hx	*n*	*Survival after second Hx (%)* 3-year	5-year	P *value*
Tumor size in diameter (cm)				
≤3	53	70	60	.017
>3	31	59	33	
Milan criteria				
Meet	56	83	62	.002
Exceed	28	38	29	
AJCC/UICC TNM stage*				
I	40	86	61	.021
II	32	54	48	
IIIA	12	33	22	
Macroscopic vascular invasion				
No	66	79	61	<.001
Yes	18	30	18	
Microscopic vascular invasion				
No	57	81	62	.001
Yes	28	37	22	
Tumor differentiation†				
Well	14	83	61	.077
Moderately	60	66	48	
Poorly	9	37	—	
Year of second Hx				
1990-1996	20	40	10	<.001
1997-2004	64	78	71	
Blood loss (ml)				
≤1,000	69	72	52	.007
>1,000	15	36	24	
Perioperative blood transfusion				
No	76	72	54	.001
Yes	8	42	28	

n, Number of patients; *Hx*, hepatectomy.
The other factors did not reach statistically significant values.
*Cancer stage was classified according to the new AJCC/UICC TNM staging system.[22]
†Two patients had uncertain pathologic diagnoses of tumor differentiation due to entire necrosis of the tumor induced by preoperative transcatheter arterial chemoembolization.

(Table V). The former group had a higher ratio of patients meeting the Milan criteria than did the latter group ($P = .004$). The former group had lesser ratios of patients whose HCC had macroscopic vascular invasion ($P = .020$), patients whose blood loss during the second hepatectomy was less than 1000 mL, and patients who received no blood transfusion during the perioperative periods than did the latter group ($P = .003$ and $P < .001$, respectively).

Table V. Comparison of patients' backgrounds according to the period in which the second hepatectomy was performed

Variables	*Time periods in which second Hx was performed* 1990-1996 (*n* = 20)	1997-2004 (*n* = 64)	P *value*
At second Hx			
Milan criteria			
Meet	8	48	.004
Exceed	12	16	
Macroscopic vascular invasion			
No	12	54	.020
Yes	8	10	
Blood loss (ml)			
≤1,000	12	57	.003
>1,000	8	7	
Perioperative blood transfusion			
No	13	63	<.001
Yes	7	1	

n, Number of patients; *Hx*, hepatectomy.
The other factors did not reach statistically significant values.

The 1-, 3-, and 5-year overall survival rates after the second hepatectomy in 46 patients who underwent the second hepatectomy between 1997 and 2004 and who had no microscopic vascular invasion at the second hepatectomy were 96%, 90%, and 80%, respectively. The corresponding recurrence-free survival rates after the second hepatectomy in those 46 patients were 71%, 33%, and 6%, respectively (Fig 2).

DISCUSSION

Most studies addressing the role of repeat hepatectomy for recurrent HCC have included small numbers of patients.[7-14] The main reason is the low rate of resectability in patients with intrahepatic recurrence because of poor hepatic functional reserve and/or unresectable tumor dissemination in the liver remnant at the diagnosis of recurrence. The rate of repeat hepatectomy for HCC recurrence after initial hepatectomy has been reported recently to be 10% to 31%.[6,9-11] In our series, the rate of re-resection was 25%. This study is the largest series of patients who have undergone repeat hepatectomy for recurrent HCC. Thus, the results obtained from the present retrospective study might provide useful information on treatment strategy for recurrent HCC.

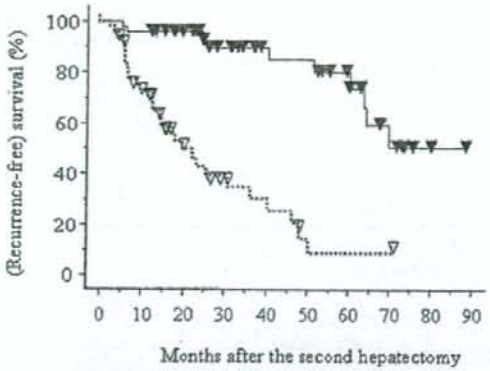

Fig 2. Overall survival (*solid line*) and recurrence-free survival (*dotted line*) curves for 46 patients who underwent a second hepatectomy between 1997 and 2004 and who had no microscopic vascular invasion at the second hepatectomy.

Repeated hepatectomy has good long-term results; the cumulative 5-year survival rates after a second hepatectomy have been reported to be 41% to 69%,[6-11] and the rate was 50% in our series. Percutaneous ablation therapies have been the preferable treatment modalities for small-sized and a small number of HCC. There have been, however, few studies on percutaneous thermal ablation therapies to evaluate the superiority of local ablation therapies for recurrent HCC compared to repeat hepatectomy.[26,27] We reported previously the results of percutaneous microwave coagulation therapy for recurrent HCC after curative hepatectomy. Local recurrence after the ablation therapy occurred in one half of the patients, and the 4-year survival rate was 50%.[26] In a recent study on percutaneous RFA for HCC recurrence after hepatectomy, the overall 5-year survival rate after RFA was only 18%, and the local recurrence rate was 13.6%.[27] Moreover, these therapies are sometimes ineffective for neoplasms on the liver surface or near large vessels. Postoperative adhesions between the remnant liver and the gastrointestinal tract may prevent patients with recurrent HCC after hepatectomy from undergoing percutaneous thermal ablation therapy. Repeat hepatectomy, at the present time, is the first choice of treatment when recurrent HCC can be treated by local treatment, and the patient has preserved liver function.

A few studies have revealed the poor prognostic factors after a second hepatectomy.[6,9] Shimada et al[9] reported that microscopic portal vein invasion at initial hepatectomy was the only independent poor prognostic factor. They suggested that micrometastases occur through the portal vein in primary HCC, and a few of them grow as large as present diagnostic devices could detect. The detectable tumor masses were resected, but any remaining metastases from the primary HCC still might grow after repeat hepatectomy, indicating the limits of diagnostic accuracy.[9] Minagawa et al[6] reported that independent poor prognostic factors were a recurrence-free interval of less than 1 year, tumor multiplicity at initial hepatectomy, and microscopic portal vein invasion at the second hepatectomy. In the present study, a second hepatectomy performed before 1996 and the presence of microscopic vascular invasion at the second hepatectomy were the independent adverse prognostic factors. Recent advances in imaging modalities have made it possible to select patients who are true candidates for repeat hepatectomy. Not only advances in imaging modalities but also technical refinement in hepatectomy might be involved in the significant improvement of survival after the second hepatectomy, as indicated in the present study. Regarding the recurrence-free interval between an initial and a second hepatectomy, approximately 60% of recurrent neoplasms observed within 1 year after initial hepatectomy in our series were single nodules in the liver remnant (data not shown), and the majority of these recurrences might have occurred as de novo tumor development in the liver remnant. Therefore, the prognosis of patients who developed recurrence within 1 year after initial hepatectomy was not so poor that the recurrence-free interval after initial hepatectomy would not affect the prognosis after the second hepatectomy.

We performed repeat hepatectomy for recurrent HCC based on the same criteria for indication as those for initial hepatectomy for primary HCC. Accordingly, recurrent HCC with macroscopic vascular invasion is within the indication of a second hepatectomy. Therefore, approximately 20% of the patients included in the present study had macroscopic vascular invasion at the second hepatectomy. The 5-year survival rate of patients with recurrent HCC without microscopic vascular invasion who underwent a second hepatectomy in the recent period reached 80%, and these patients with preserved liver function should be considered as candidates for repeat hepatectomy. A disappointing result in this study, which also was seen in another study,[6] was the high rate of recurrence after the second hepatectomy: 5-year recurrence-free survival rate was only 10%. The rate was only 6% even in patients without microscopic vascular invasion who underwent the second hepatectomy during

the recent period. Moreover, the more times hepatectomy was repeated, the shorter the recurrence-free interval became. These results indicate the limits of repeat hepatectomy for cure of recurrent HCC.

Liver transplantation is the best option for patients with decompensated cirrhosis and with single HCC smaller than 5 cm or showing up to 3 nodules, each of which is less than 3 cm.[15] A major controversy persists over whether primary LT or partial hepatectomy is the optimal initial treatment for patients with resectable and transplantable HCC who have preserved liver function. Results of several retrospective studies showing that primary LT was associated with superior recurrence-free survival are the basis for the argument in favor of primary LT for resectable and transplantable HCC even in patients with preserved liver function, whereas overall long-term survival after partial hepatectomy was similar to that after primary LT.[16-18] Application of primary LT for patients with resectable HCC and preserved liver function would result in a greater shortage of deceased donor livers and an increase in the dropout rate on waiting lists. Partial hepatectomy is applicable immediately and results in a cure of HCC in some patients. The establishment of a strategy of primary LT for patients with resectable HCC might result in patients undergoing unnecessary LT and subsequent unnecessary immunosuppression. Without solving these problems, the approach is not realistic. There have been no prospective, randomized studies comparing partial hepatectomy with primary LT for early HCC in patients who could be eligible for both treatments.

In contrast, LT for patients with recurrent HCC or decompensated liver cirrhosis after curative hepatectomy, a concept that has been called "salvage LT" in the broad sense of the word "salvage," also has been debated for cure of HCC.[28-32] Initial studies suggested that salvage LT would offer poorer results.[28] Belghiti et al[29] reported that the survival after salvage LT was not significantly less; indeed, the 5-year survival rate after salvage LT in their study was 61%. Moreover, the Barcelona Clinic Liver Cancer Group[30] proposed salvage LT for patients in whom pathologic examination of a resected specimen indicated a high risk of recurrence even in the absence of proven residual disease. This concept is salvage LT in the narrow sense of the word "salvage." This approach may reduce the dropout rate on a waiting list and the effect of a long waiting list and donor shortage by selection of patients with HCC who are likely to obtain the maximum benefit from LT.[31] Expectations from the scenario depend on various assumptions and have not been proven by a prospective study.

Controversy also exists about whether salvage LT or repeat hepatectomy is the optimal surgical treatment for patients with resectable and transplantable recurrent HCC who have preserved liver function. The majority of patients with recurrent HCC after initial hepatectomy for small HCC have transplantable recurrent tumors in the remnant liver.[31-33] Considering our results showing the 5-year recurrence-free survival rate after the second hepatectomy was only 10%, and our results showing that the more times hepatectomy was repeated, the shorter the recurrence-free interval became, salvage LT may be the best treatment choice even for patients with resectable recurrent HCC and preserved liver function. If salvage LT is indicated for patients with recurrent HCC meeting the Milan criteria[15] who are younger than 60 or 65 years, only 10% or 15% of patients with HCC who underwent a second hepatectomy in this study would have benefited from salvage LT (data not shown), because the mean age of the patients with recurrent HCC at the time of the second hepatectomy was 66 years. Actually, LT has been performed in less than 20% of patients with recurrent HCC.[21,28,30,34] The low applicability of salvage LT for patients with recurrent HCC results from the older ages of the candidates at diagnosis of recurrence.[34]

Living-donor LT offers the potential for earlier transplantation for patients with HCC, which would result in lesser dropout rates and improved outcomes. Modeling studies have suggested that acceptable life expectancy and cost-effectiveness could be reached if waiting-time exceeded 7 months for patients with early HCC.[35] Thus, living-donor LT, even for patients with recurrent HCC, seems justified when there is little likelihood of a cadaveric organ becoming available in a timely manner. If a cirrhotic patient with recurrent HCC that is resectable and transplantable has a suitable living donor, living-donor LT can result in long-term survival without HCC recurrence. However, when a patient with recurrent HCC has no suitable living donor or has no indication for LT due to advanced age or associated diseases, repeat hepatectomy, which might enable total removal of cancer tissue, remains the first line of treatment for patients with resectable recurrent HCC and preserved liver function, even if the possibility of re-recurrence is extremely high.

In conclusion, repeat hepatectomy for patients with recurrent HCC resulted in good long-term survival and had survival benefits especially

for patients without microscopic vascular invasion. The incidence of re-recurrence after the second hepatectomy, however, was very high, and the recurrence-free interval was short, even in the subgroup with good long-term survival. The effectiveness of repeat hepatectomy for curing patients with recurrent HCC is limited. Salvage LT might be appropriate for treating patients with recurrent HCC, even if recurrent HCC in patients with preserved liver function is resectable.

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World J Surg (2007) 31:2222–2229
DOI 10.1007/s00268-007-9217-x

Biliary Complications after Duct-to-duct Biliary Reconstruction in Living-donor Liver Transplantation: Causes and Treatment

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Published online: 22 September 2007

Abstract
Background In living-donor liver transplantation (LDLT), biliary complications are recognized as a significant cause of post-transplantation morbidity.
Methods Eighty patients who underwent LDLT with duct-to-duct biliary reconstruction at Hiroshima University Hospital were enrolled in this study. The mean follow-up was 24 months (range, 3–72 months). Eighteen patients underwent the basiliximab-based immunosuppressive therapy, and 62 patients underwent non-basiliximab-based immunosuppressive therapy. The development of biliary complications after LDLT was retrospectively analyzed. Biliary complications were initially treated by endoscopic or radiological modalities.
Results Biliary leakages and strictures occurred in 12 (15%) and 20 (25%) of the 80 patients, respectively. Stepwise multivariate analysis demonstrated bile leakage to be an independent risk factor for the development of biliary stricture ($p = 0.001$) and basiliximab-based immunosuppressive therapy to be an independent protective factor for postoperative biliary leakage ($p = 0.005$). The 1-week total doses of steroids were significantly lower in the basiliximab-based immunosuppressive regimes (mean dose: 573mg) than in the non-basiliximab-based ones (mean dose: 1,121mg) ($p = 0.01$). All patients with biliary leakage were successfully treated with endoscopic or radiological modalities, except one patient who was treated by surgical treatment. Endoscopic or radiological modalities were successful as primary treatment modalities in 12 (60%) of 20 patients with biliary strictures. Lastly, six patients were treated surgically with long-term success, except for one patient with chronic cholangitis who died after 16 months.
Conclusions Steroid-sparing basiliximab-based immunosuppressive therapy reduced the incidence of biliary leakage, and biliary leakage was the independent factor for biliary stricture. The non-surgical and surgical treatments for biliary complications were satisfactory.

Various refinements in surgical techniques, postoperative management, and immunosuppressive management have reduced the incidence of complications after liver transplantation. Biliary complications, however, continue to be a significant cause of morbidity after liver transplantation [1, 2]. In living-donor liver transplantation (LDLT), the biliary system is usually reconstructed by performing a Roux-en-Y hepaticojejunostomy (RYHJ), which results in biliary complications in 12%-18% of recipients [3, 4]. In 1998, Wachs et al. first reported duct-to-duct reconstruction for LDLT [5]. Duct-to-duct direct biliary reconstruction has been performed in many institutes, and the advantages of duct-to-duct biliary reconstruction over hepaticojejunostomy have been pointed out in several reports. For example, it preserves the physiological bilioenteric and bowel continuity, thus preventing delayed bowel movements. Further, it permits easy endoscopic access to the biliary tree for diagnostic and therapeutic instrumentation and assists the prevention and management

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of ascending cholangitis [6–9]. As the number of patients who have undergone LDLT with duct-to-duct biliary reconstruction has increased, however, a variety of biliary complications have emerged [10–12]. Some reports have addressed the occurrence of late biliary complications, particularly biliary strictures, in many patients with a significant median follow-up duration (>12 months) [9, 13]. In the present study, to evaluate the safety of duct-to-duct biliary reconstruction in LDLT, we retrospectively analyzed the biliary complications observed, with focus on biliary leakage and stricture.

Materials and methods

Patients and surgical procedures

Between May 2000 and September 2006, 85 patients underwent LDLT at Hiroshima University. Among these patients, the 80 patients who underwent duct-to-duct biliary reconstruction along with LDLT were enrolled in this study. Patient, graft, and operative characteristics are summarized in Table 1. The series comprised 47 men and 33 women (average age: 50 years). The most common indications for LDLT were viral hepatitis and cirrhosis with or without hepatocellular carcinoma (n = 54), followed by fulminant hepatic failure (n = 10), primary biliary cirrhosis (n = 8), autoimmune hepatitis (n = 6), and others (n = 2). The most commonly used graft type was a right hemi-liver (n = 66), followed by a left hemi-liver (n = 14). The donors included 49 men and 31 women (average age: 35 years).

The mean model for end-stage liver diseases (MELD) score at the time of LDLT was 17.9 (range: 5–50). The mean graft-to-recipient weight ratio (GRWR) was 1.08 (range: 0.5–2.4); moreover, none of the grafts included a middle hepatic vein. The mean operative time was 12 h 8 min (range: 9–25 h). The mean total ischemic time was 108 min (range: 43–240 min), and the warm ischemic time was 45 min (range: 32–220 min).

The immunosuppressive regimen comprised cyclosporine with mycophenolate mofetil (MMF) and methylprednisolone and basiliximab (n = 18), or cyclosporine with MMF and methylprednisolone (n = 8), or tacrolimus with methylprednisolone (n = 56). The steroid-sparing basiliximab-based immuosuppressive therapy was indicated for viral hepatitis, because the steroid might contribute to the acceleration of hepatitis viral replication. Basiliximab 20 mg was given intravenously on both day 0 and day 4 after surgery. Tacrolimus was administered with a level of 5 ng/ml for the first 48 h postoperatively in order to maintain renal function. Then, the dose of tacrolimus was adjusted to maintain a level of 10–15 ng/ml during the first month, and afterward tapered to achieve a level of 5–10 ng/ml. Cyclosporine was also administered at a level of 50–100 ng/ml for the first 48 h postoperatively in order to maintain renal function. Then, the dose of cyclosporine was adjusted to maintain a level of 250–300 ng/ml during the first month, after which it was tapered to achieve a level of 150–250 ng/ml. Dose reductions of both tacrolimus and cyclosporine were performed primarily on the basis of renal and liver function. For patients with renal insufficiency, tacrolimus or cyclosporine was not given until renal function improved. After oral medication capsules were tolerated, MMF was given at a dose of 500–1,000 mg a day. Mycophenolate mofetil was tapered and discontinued, based on gastrointestinal toxicity and myelosuppression. Treatment with steroids was discontinued 2–3 months after LDLT. In basiliximab-based immuosuppressive therapy, patients either received no methylpredonisolone or they received 250 mg methylpredonisolone intravenously during surgery, followed by daily tapering (starting at 120 mg/day and ending at a baseline 40 mg/day, intravenously).

Table 1 Living-donor liver transplantation patient demographics

Characteristics	Number = 80
Age (range, years)	50 (20–69)
Male	47 (59%)
MELD (range)	17.9 (5–50)
Indication	
Liver cirrhosis (HCC)	54 (35)
Cholestatic disease	8
Fulminant hepatic failure	10
Autoimmune hepatitis	6
Others	2
Donor	
Age (range, years)	35 (18–64)
Male	49 (31)
Graft	
Left lobe	14
Right lobe	66
GRWR	1.08 (0.5–2.4)
Immunosuppresive therapy	
Tac + steroid	54
CyA + steroids + MMF	8
CyA + steroids + MMF + Bax	18
Operation	
Time (range)	12 h 8 min (9h–25h)
Blood loss (range)	4875ml (345–39500)
Total ischmic time (range)	108min (43–240)
Warm ischmic time (range)	45min (32–220)

MELD model for end-stage liver disease; GRWR graft: recipient weight ratio; Tac tacrolimus; CyA cyclosporin; MMF mycophenolate mofetil; Bax basiliximab

Treatment with oral methylpredonisone (32 mg/day) was initiated on postoperative day 7–10. In non-basiliximab based immunosuppression therapy, patients received 500 mg methylpredonisolone intravenously during surgery, followed by daily taper (starting at 250 mg/day and ending at a baseline 40 mg/day, intravenously). Treatment with oral methylpredonisone (32 mg/day) was initiated on day 7–10. Subsequent adjustment in maintenance methylpredonisolone was dependent on the patient's clinical course.

Donor assessment and surgery

The donors underwent several preoperative examinations, including computed tomography (CT) and drip-infusion cholangiography-CT, in order to assess the biliary and vascular system. The surgical techniques for donor hepatectomy have been described elsewhere [14]. Briefly, prior to parenchymal transection, routine intraoperative cholangiography was performed with fluoroscopy to determine the transection point of the hepatic duct. Minimal dissection was performed at the hilar plate around the hepatic duct. The liver was then transected with an ultrasonic dissector without inflow occlusion. The hepatic duct was sharply severed near the confluence, and the remnant stump was carefully closed with 6–0 polydioxanone monofilament sutures (PDS; Ethicon, Inc., Tokyo, Japan). The liver graft was perfused with University of Wisconsin (UW) solution. The diameters of the bile duct and vessels of the graft and the graft weight were directly measured. The average intraoperative blood loss was 310 ml. None of the 80 donors were given a blood transfusion.

Recipient surgery

In total hepatectomy, the hilar plate was dissected sharply at or distal to the second-order branch of the bile duct. In the dissection, careful attention was paid in order to preserve as much as possible of the surrounding tissues with an adequate blood supply to the bile duct. To maintain the blood supply to the bile duct from the right hepatic artery, dissection between the right hepatic artery and the bile duct was avoided. Bile duct anastomosis was performed after completion of all vascular anastomoses and reperfusion of the liver graft. Wherever possible, we prospectively performed duct-to-duct biliary reconstruction. An end-to-end anastomosis between the graft and recipient bile ducts was performed using an interrupted 6–0 PDS, beginning from the posterior wall and terminating at the anterior wall. In the case of more than one ductal opening in the graft, if the openings were adjacent to each other, ductoplasty was performed to suture them to form a single orifice. If two ductal openings in the graft were far apart, separate duct-to-duct anastomoses were performed without ductoplasty. A stent tube was routinely placed through the anastomosis as a splint and was pulled out through the common bile duct above the duodenum. A cholangiogram was obtained by using the inserted stent tube 1 month after LDLT, and then the stent tube was clamped. The tubes for bile duct stenting were removed 3 months after LDLT.

Diagnosis and treatment of biliary complications

Biliary leakage was diagnosed clinically and radiologically on the basis of a bile leak through abdominal drains, evacuation of extrahepatic biloma through a newly inserted drain under ultrasound guidance, or identification of a leak by endoscopic retrograde cholangiography (ERC) or cholangiography via an inserted stent tube. For biliary leakage, endoscopic retrograde nasobiliary drainage (ENBD) or percutaneous drainage under ultrasound guidance were the techniques most commonly undertaken.

Biliary stricture is primarily suspected when cholestatic enzymes that are assessed by liver function tests, including alkaline phosphatase and γ-glutamyl transpeptidase, are elevated and/or if there is sonographic evidence of a dilated biliary system. If the total bilirubin was not elevated, drip-infusion cholangiography-CT was performed. The presence of strictures was confirmed by ERC and/or percutaneous transhepatic cholangiography (PTC). Biliary stenosis was diagnosed on the basis of an abrupt luminal narrowing with an overt dilatation of the intrahepatic duct.

Primary transpapillary intervention was attempted in all patients who underwent duct-to-duct biliary reconstruction. Endoscopic retrograde balloon cholangioplasty was performed; this was followed by the placement of a plastic internal stent tube. When endoscopic treatment failed, percutaneous management of the biliary stricture was undertaken. Surgical revision was indicated when both these modalities failed.

Statistical analysis

Category variables were compared with the chi-square test. Continuous data were compared by the Mann-Whitney test. Patient survival after liver transplantation was analyzed by the Kaplan-Meier survival method. The statistical comparison of survival data was performed with the log-rank test. Stepwise logistic regression analysis was carried out in order to identify the independent predictors of biliary complications. A p value < 0.05 was considered to be significant. All statistical analyses were performed with the statistical software package SPSS version 11.0 (SPSS Inc Chicago, IL).

Results

Type of biliary reconstruction

Table 2 shows the type of bile duct reconstruction with the corresponding incidence rate of biliary stricture. Forty-eight (60%) grafts had a single duct for anastomosis, 29 grafts (36%) had two ducts, and 3 grafts (4%) had three ducts. After ductoplasty in 14 grafts, 62 grafts had a single duct for anastomosis, 15 grafts had two ducts for anastomosis, 2 grafts had three ducts for anastomosis, and 1 graft had two ducts for anastomosis.

Overall incidence of biliary complications, risk factors, and outcomes after LDLT

Biliary leaks developed in 12 patients (15%), and 20 (25%) of the 80 patients suffered from a post-transplantation biliary stricture (Table 2). The mean follow-up was 24 months (range: 3–72 months). The onset of biliary leakage was 20 ± 8 days. No patient developed a de novo biliary stricture beyond 20 months after LDLT. Seven patients (8.8%) developed both the biliary complications. None of the five patients that underwent hepaticojejunostomy developed a biliary stricture. Further, there were no hepatic arterial complications in our series. By univariate analysis, we found two variables to be associated with an increased risk of biliary stricture: a postoperative bile leakage and non-basiliximab-based immunosuppressive therapy (Table 3). After stepwise multivariate analysis, one variable remained significant, i.e., postoperative bile leakage ($p = 0.001$) (Table 3). There were no significant differences in the incidence of biliary stricture with respect to donor age, MELD score, graft type, the number of bile ducts, and ductoplasty. There was no significant difference in the incidence of biliary stricture with respect to the number and mode of anastomotic sutures. However, in the grafts that had three ducts, we observed a high incidence of biliary stricture (2/3, 66.6%) (Table 2). We next examined the incidence of biliary stricture according to the diameter of the anastomosis. Graft duct sizes were classified into small (diameter <4 mm), medium (diameter 4–5 mm), and large (diameter >5 mm). Recipients with two or three biliary ducts were excluded in order to avoid bias from complex biliary reconstructions. We observed no association between the diameter of the bile ducts and the incidence of anastomotic suture.

Interestingly, both biliary leaks and strictures developed less frequently in patients with basiliximab-based immunosuppressive regimes. In stepwise multivariate analysis, non-basiliximab-based immunosuppressive therapy was associated with an increased risk for postoperative bile leakage ($p = 0.005$) (Table 4). Further, we found that the 1-week doses of methylpredonisolone after LDLT were significantly lower in basiliximab-based immunosuppressive regimes than in non-basiliximab-based ones ($p = 0.01$) (Fig. 1).

Freedom from biliary stricture was 73% at 1 year and 69% at 2 years (Fig. 2). The 1-year and 5-year survival rates for patients with biliary stricture were 69% and 53%, respectively, compared with 79% and 70% for those without biliary strictures ($p = 0.31$) (Fig. 3).

Table 2 Biliary complications after duct-to-duct biliary reconstruction in living donor liver transplantation

	n	Leakage (%)	stricture (%)
Number of bile ducts and anastomoses	80	12 (15)	20 (25)
1 duct / 1 anastomoses	48	5 (10.4)	11 (22.9)
2 ducts / 1 anastomoses (plasty)	14	3 (21.4)	5 (35.7)
2 ducts / 2 anastomoses	15	2 (13.3)	2 (13.3)
3 ducts / 3 anastomoses	2	1 (50)	2 (100)
3 ducts / 2 anastomoses (plasty)	1	0	0

Table 3 Univariate and multivariate analysis of risk factors for biliary strictures

Risk factors	No. of patients with biliary stricture	*p* Value (Univariate)	*p* Value (Multivariate)
Immunosuppression		0.044	0.124
Bax (*n*=18)	1 (5%)		
Non-Bax (*n*=62)	19 (30.6%)		
Biliary leakage		0.0001	0.001
Yes (*n*=12)	7 (58%)		
No (*n*=68)	13 (19%)		
No. of bile ducts		0.501	0.165
Single (*n*=48)	11 (22.9%)		
Non-single (*n*=32)	9 (28.1%)		
Ductoplasty		0.216	0.121
Yes (*n*=15)	5 (33.3%)		
No (*n*=65)	15 (23.1%)		
Donor age		0.072	0.152
> 50 year (*n*=28)	10 (35.7%)		
< 50 year (*n*=52)	10 (19.2%)		
Graft		0.647	0.917
Right (*n*=66)	17 (25.7%)		
Left (*n*=14)	3 (21.4%)		
MELD		0.837	0.806
> 25 (*n*=17)	4 (23.5%)		
< 25 (*n*=63)	16 (25.3%)		

Table 4 Univariate and multivariate analysis of risk factors for biliary leakage

Risk factors	No. of patients with biliary leakage	*p* Value (Univariate)	*p* Value (Multivariate)
Immunosuppression		0.033	0.005
Bax (*n*=18)	0 (0%)		
Non-Bax (*n*=62)	12 (19%)		
No. of bile ducts		0.569	0.901
Single (*n*=48)	6 (12.5%)		
Non-single (*n*=32)	6 (19%)		
Ductoplasty		0.639	0.702
Yes (*n*=16)	3 (18.8%)		
No (*n*=64)	9 (14%)		
Donor age		0.066	0.065
> 50 year (*n*=28)	7 (25%)		
< 50 year (*n*=52)	5 (9.6%)		
Graft		0.636	0.512
Right (*n*=66)	9 (13.6%)		
Left (*n*=14)	3 (21%)		
MELD		0.674	0.42
> 25 (*n*=17)	2 (12.5%)		
< 25 (*n*=63)	10 (15.6%)		

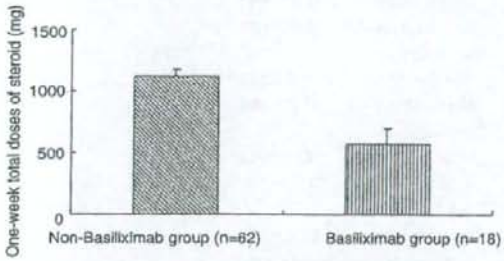

Fig. 1 Total doses of methylpredonisolone that were administered for one week after living donor liver transplant (LDLT). All values are expressed as the mean ± standard error

Management of biliary complications

For biliary leakage, ENBD was possible in five patients. Six patients with bilairy leakage underwent percutaneous drainage under ultrasound guidance. One patient underwent Roux-en-Y hepaticojejunostomy. All patients were successfully treated by these modalities (Fig. 4).

Figure 5 shows the summary of the various modalities used for the treatment of biliary strictures. Initially, the patients with biliary strictures were referred for ERC. In 10 of the 20 patients, a guidewire could pass through the stricture, and these patients were treated by endoscopic internal stent placement. In the remaining 10 patients, the guidewire could not be passed through the biliary stricture because it was too tight and the bile ducts were too kinked. No symptoms of biliary stricture were observed in two patients after ERC. Seven patients required percutaneous transhepatic biliary drainage (PTBD), and five patients underwent stenting. Consequently, six patients underwent Roux-en-Y reconstruction to repair the stricture; however, 16 months after transplantation, one patient died of sepsis secondary to chronic cholangitis.

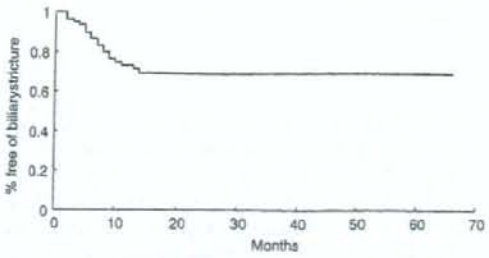

Fig. 2 Biliary stricture-free rate after LDLT

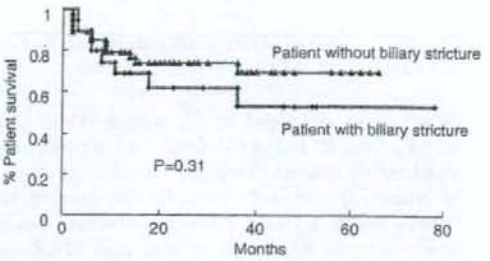

Fig. 3 Impact of biliary strictures on patient survival (Kaplan-Meier) in months

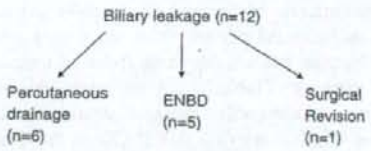

Fig. 4 Summary of the treatment modalities used for biliary leakage: endocsopic retrograde nasobiliary drainage (ENBD), percutaneous drainage, and surgical revision

Discussion

In the present study we observed that post-transplantation anastomotic biliary leakages and strictures occurred, respectively, in 15% and 25% of our patients who