2．治　療

肝細胞がんの治療において，局所制御が最も重要である。肝機能が保たれた症例では，肝切除が第一選択[20]である。欧米ではミラノクライテリアを満たした肝がんは移植が第一選択となっている。しかしドナーの不足など問題が残っている。その中でPoonらが興味深い検討を行った[21]。ミラノクライテリアを満たす肝がんの腫瘍因子を切除群と移植群とで比較し長期生存への影響を検討した。その結果，予後因子としてC型肝炎，腫瘍径，個数，顕微鏡的静脈浸潤が挙げられた。切除か移植かは予後を規定しなかった。静脈浸潤の有無で層別化すると，長期予後において有意差は認められなかった。移植は肝機能が不良の症例に限定されるべきであろう。一方，腫瘍径の大きい肝がんや，脈管浸潤を伴った肝がんなど積極的な切除によって効果が期待できる症例もあり[22]挑戦も必要と思われる。

切除とラジオ波焼灼術（RFA）の比較試験は，Hongらから報告されている[23]。Child-Pugh 5点と肝機能良好で腫瘍径4cm未満の症例で比較検討した。その結果，局所再発率はRFA群で多かったが異所再発率では有意差を認めず，3年までの累積生存率と無再発生存率に有意差を認めなかった。ランダム化や観察期間に問題もあるが一つの結果である。今後本邦において，きちんとしたデザインによる比較試験が望まれる。

現在RFAは，局所療法の主軸を担っている。Child-Pugh A，Bで3cm，3個以内の症例において，従来のエタノール注入療法と比較した結果，局所制御に優れ，長期予後も改善した。安全性に関してもエタノール注入療法と比較して有意差を認めなかった[24]。さらに症例を重ねて有効性と安全性を検討した。1999年2月から2003年2月までに664例をRFAで治療した。2,140結節の肝がん治療に1,000セッションを要したが，治療関連死は0，major complicationは4%，minor complicationは1.7%であり，RFAの安全性が確認された[25]。また脈管や他臓器に隣接した合併症のリスクが高いと思われる腫瘍も安全に治療できた[26]。664例中319例がnaïve caseであったが，それらの症例の累積生存率は1年94.7%，2年86.1%，3年77.7%，4年67.4%，5年54.3%であり，RFAの長期予後における有効性も確認された[25]。しかし比較的早期に異所再発し腫瘍のコントロールが困難になる症例も存在する。Poonら[27]は，vascular endothelial growth factor（VEGF）に着目して術前のVEGFの血中レベルと予後を比較検討した。その結果術前のVEGF＞240 pg/mLの症例では生存率も無再発生存も有意に不良であった。今後このような症例に分子標的薬の効果が期待される。

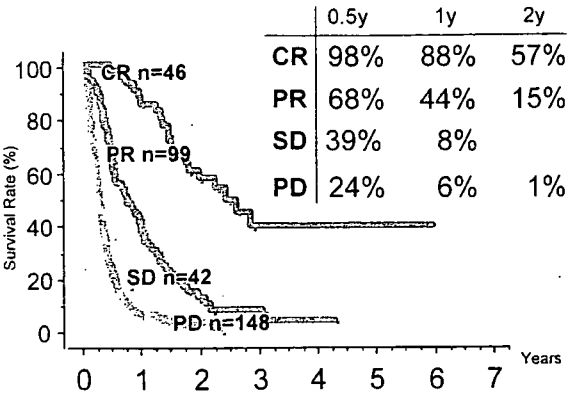

図1　治療効果別生存率（n＝335）2007.5.31現在

高度進行肝がんの治療でも進歩があった。門脈腫瘍浸潤を伴う進行肝細胞がんの予後は著しく不良であり，50%生存期間が約3か月，1年生存は見込めなかった。Sakonら[28]はインターフェロンα併用5-FU動注化学療法で，これら門脈腫瘍浸潤を伴う高度進行肝がん8例を治療し奏効率63%であったと報告した。さっそくわれわれは追試[29]を行った。Vp3，4の門脈腫瘍浸潤を伴う肝がん116例に対しインターフェロン併用5-FU動注化学療法を施行した。これらの症例と対症療法を中心としたhistorical control群40例とで累積生存率を比較した。その結果インターフェロン併用5-FU動注化学療法は有意に生存率を改善した。特にcomplete response群（16%）においては1年生存率81%，2年生存率59%，partial response群（36%）においては1年生存率43%，2年生存率18%であった。また重篤な副作用は認めず，コントロール可能な嘔気と食欲不振が主な副作用であった。われわれの症例はSakonらの症例と比較して，再発症例が多く肝機能も低下した症例が多かったため，奏効率や生存率がやや低い傾向があったが，Sakonらの報告[28]に近い有効性と安全性を証明できた。その後ペグインターフェロンが導入され天然型インターフェロンαと比較検討したが，奏効率や生存率に有意差を認めなかった。このため現在は利便性を鑑みペグインターフェロンを併用して5-FU動注化学療法を施行している。2007年5月現在，335例のVp3，4症例にインターフェロン併用5-FU動注化学療法を施行した。complete response 46例（14%），partial response 99例（30%），stable 42例（13%），progression 148例（44%）であり，奏効率43%であった。335例全体の累積生存率は，6か月50%，1年31%，2年15%，3年8%であった。治療効果別生存曲線を図1に示した。complete responseは1年88%，2年57%，partial responseは1年44%，2年15%と良好な成績であったが，progressionでは1年生存率がわずかに6%であった。本療法の特徴は，奏効す

れば必ず生存期間の得られることである。そこで予後予測因子および奏効予測を検討した。その結果予後規定因子は，腹水（+）（ハザード比0.383，95%CI 0.269～0.546，p<0.0001），Vp4（ハザード比0.635，95%CI 0.483～0.835，p=0.0011），Alb>3.4（ハザード比1.333，95% CI 1.008～1.764，p=0.0438）であった。効果予測因子は，血小板数<12.5×10⁴（ハザード比1.896，95% CI 1.165～3.084，p=0.01），腹水（−）（ハザード比2.000，95%CI 1.020～3.920，p=0.0436）であった。これらの結果より腹水無，Vp3，血小板数<12.5×10⁴の基準を満たす症例が，インターフェロン併用5-FU動注化学療法の良い適応と思われる。実際この基準を満たした症例は101/335例であったが，奏効率60%，median survival timeは9.6か月であったのに対して基準外の症例は奏効率36%，median survival time 5.1か月と不良であった。基準内の症例は有意に予後が良く，MSTはほぼ2倍となった。partial responseで肝機能良好な症例は，その後残存病変を積極的に切除して予後のさらなる改善を図っている。また術後のadjuvantとしても良好な成績が報告[22]されている。さらに遠隔転移のある症例に対してインターフェロンとS-1の併用療法が有効であった症例が報告[30]された。現在，肝外病変を伴う進行肝細胞癌に対するS-1/インターフェロンα併用化学療法の有効性第Ⅱ相ランダム化比較試験を大阪大学消化器外科門田守人教授によって多施設共同で展開中である。

近年，分子標的薬の開発が進み臨床試験の結果も報告[31]されている。sorafenibは，Raf kinaseとreceptor tyrosine kinasesを標的としたmultikinase経口阻害薬である。Abou-Alfaら[31]のphase Ⅱ trialでは，切除適応外となったChild-Pugh A，B（72%がA）肝細胞がん137例を対象とした。partial response 3例（2.2%），minor response 8例（5.8%），stable 46例（33.6%）であった。median survival timeは9.2か月であった。grade 3/4の有害事象は倦怠感（9.5%），下痢（8%）と皮膚反応（5.1%）であった。2007年のAmerican Society of Clinical OncologyでLlovetらはsorafenibのphase Ⅲ試験（SHARP: Sorafenib HCC Assesment Randomized Protocol）の結果を発表した。本試験はChild-Pugh Aで，組織学的に肝細胞がんと証明された，少なくとも未治療病変を1つ以上有する患者を対象に，主要評価項目を全生存期間と症状発現までの期間とし，sorafenibを1回400 mg，1日2回内服群299例とプラセボ群303例のrandomized placebo-controlled trialである。両群間で症状発現までの期間に有意な差を認めなかったが，sorafenib群の全生存期間の中央値は46週，プラセボ群は34週で，ハザード比0.60，p値0.00058と統計学的有意差を認めた。有害事象は，下痢がsorafenib群で11%，プラセボ群では2%であった。また手足皮膚反応は，sorafenib群では8%であったが，プラセボ群では1%であった。今後，肝細胞がんに対する分子標的治療の開発が促進されると思われる。

3．予　防

すでに述べたように本邦の肝細胞がんは80%以上がC型慢性肝炎に由来する。よって抗ウイルス療法を行うことによって，発がんの予防が可能である[4-6]。しかしながらペグインターフェロンとリバビリン併用療法でも，患者の高齢化，副作用，奏効率などが問題となり理論的にいかないこともある。このような症例に瀉血療法を行って肝炎を沈静化させることによって肝線維化を改善する可能性[32]があり，結果として発がん予防につながると思われる。現在本邦ではインターフェロン不応例や適応外例にグリチルリチン製剤を用いることが多い。この際少量の瀉血を繰り返し良好な成績が報告[33]された。今後さらなる工夫で発がん阻止に取り組むべきであろう。

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症例報告

門脈本幹腫瘍栓で発症した肝細胞癌に対してインターフェロン/5-FU動注療法後，腫瘍栓消失し，生体肝移植を施行した1例

金子 順一*1 菅原 寧彦*1 田村 純人*1 松井 郁一*1
冨樫 順一*1 佐野 圭二*1 今村 宏*1 國土 典宏*1
幕内 雅敏*1 建石 良介*2 小俣 政男*2 小尾俊太郎*3

A case of liver transplantation for advanced hepatocellular carcinoma with portal venous tumor thrombosis after 5-FU and interferon therapy

Junichi Kaneko*1, Yasuhiko Sugawara*1, Sumihito Tamura*1, Yuichi Matsui*1, Junichi Togashi*1, Keiji Sano*1, Hiroshi Imamura*1, Norihiro Kokudo*1, Masatoshi Makuuchi*1, Ryosuke Tateishi*2, Masao Omata*2 and Shuntaro Obi*3
*1*Hepato-Biliary-Pancreatic Surgery, Artificial Organ and Transplantation Division, Dept. of Surgery, *2Dept. of Gastroenterology, University of Tokyo, Tokyo, Japan, *3Dept. of Hepatology, Kyoundo Hospital, Tokyo, Japan*

Summary : The simply combined 5-FU and interferon therapy was first reported by Sakon at Osaka University using advanced hepatocellular carcinoma with portal venous invasion in 2002. Our protocol is based on Sakon and his colleagues report. This is our first case for 5-FU + interferon therapy. A 41-year-old Indian male was referred to our institute with tumor invasion to the main trunk of portal vein. It was pathologically diagnosed as hepatocellular carcinoma by biopsy. After administration of 5-FU interferon combination therapy, PIVKA-Ⅱ went down rapidly and maintained within normal limit for a year. Finally, he received living donor liver transplantation. Hepatocellular carcinoma had been no recurrence for a year and six months. However, this patient died from severe acute pancreatitis.

Key words : hepatocellular carcinoma, liver transplantation, chemotherapy
〔*Liver Cancer* **13**(1) : 43-47, 2007〕

はじめに

肝細胞癌による門脈腫瘍栓が診断された場合，肝移植の適応とならない。再発の危険因子の一つであるからである。今回われわれは，門脈腫瘍栓の存在が診断された後，化学療法を試み complete response(CR)を得た。約1年間の無再発の経過を経て，生体肝移植を施行した例を経験したので報告する。

*1 東京大学医学部附属病院・肝胆膵・人工臓器移植外科
*2 同 ・消化器内科
*3 杏雲堂病院・肝臓科

受理：2006年12月22日，採用：2007年2月1日

I. 症 例

患者：41歳，男性，インド人。

家族歴：慢性肝疾患歴なし。

既往歴：10歳時黄疸(詳細不明)，28歳時熱傷(輸血あり)，刺青なし。

生活歴：1日5本×15年間の喫煙歴あり，飲酒歴なし。

現病歴：1997年10月よりGOTおよびGPTの高値を指摘され，C型慢性肝炎が判明した。1997年11月からインターフェロン(interferon-α：IFN)とリバビリンの治療を受けたが，C型肝炎ウイルスは消失せず，治療を中止し経過観察されていた。C型肝炎ウイルスのgenotypeは4型であった。2000年10月に腹部超音波検査で異常を指摘され，当院を紹介された。

入院時血液検査(Table 1)：汎血球減少，肝機能低下とPIVKA-IIの高値を認めた。Child-Pugh scoreは9点であった。

腹部超音波検査：当院初診時に施行した腹部超音波検査では，門脈本幹から門脈右枝にかけて，わずかに高エコーで膨張性に発育する腫瘤を認めた。

腹部CT検査(Fig. 1)：門脈本幹から門脈右枝にかけて低吸収値の欠損像を認めた。血栓ないし腫瘍栓が疑われたが，伸展が膨張性のため門脈腫瘍栓と考えた。肝実質には腫瘍像を認めなかった。また，腹水を認めないが肝表は不整であり，肝硬変と診断した。

経動脈的門脈造影(Fig. 2)：経動脈的門脈造影検査を施行したところ，固有肝動脈造影において著明な肝動脈門脈シャントを認めた。門脈本幹から右前区域枝と右後区域枝の分岐部にかけて，陰影欠損像を認めた。肝内に明らかな腫瘍濃染像を認めなかった。

腫瘍生検(Fig. 3)：腹部超音波下に，右肋間より肝生検(腫瘍生検)を施行したところ，腫瘍細胞はわずかで構造も崩れており，判断が難しいが厚い索状構造と偽腺管構造がみられ，中分化型肝細胞癌(Edmondson II型)と考えた。

化学療法(Fig. 4, 5)：肝細胞癌T2, N0, M0, Stage IIの診断で，2000年12月より肝動注化学療法併用IFN療法を施行した(5-FU 500 mg/day×5 days＋天然型IFN-α 500万単位×3/week×4 weeks×2 kur)。治療後，PIVKA-IIは著明に低下し正常化した。その後門脈腫瘍栓は消失し，引き続きIFN療

Table 1 Laboratory data on admission

WBC	$3.1\times10^3/\mu l$	TP	6.4 g/dl
RBC	$282\times10^4/\mu l$	Alb	2.5 g/dl
Hb	808 g/dl	GOT	62 U/l
Hct	26.8%	GPT	36 U/l
Plt	$5.4\times10^4/\mu l$	T-Bil	2.5 mg/dl
AFP	14 ng/ml	LDH	205 IU/l
PIVKA-II	15,229 mAU/ml	ALP	199 IU/l
PT-INR	1.43	γ-GTP	58 IU/l
PT	53%		

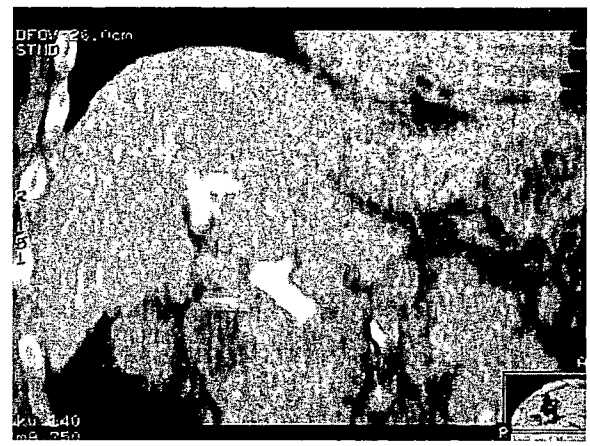

Fig. 1 Tumor thrombosis invaded the main trunk of the portal vein.

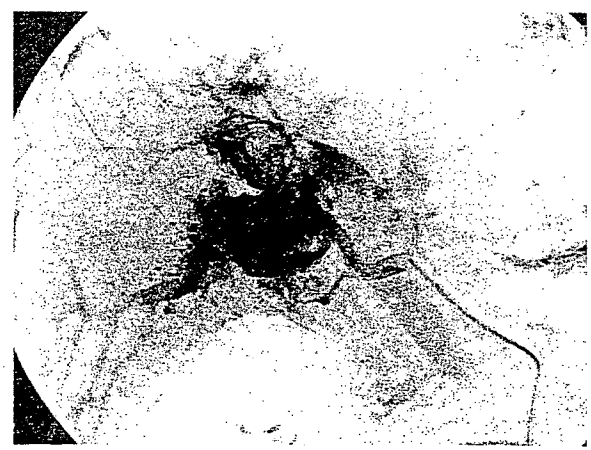

Fig. 2 Abdominal angiography showed arterioportal shunt and filling defect in the portal vein.

Fig. 3 Histological findings of biopsy specimen showed Edmondson grade II hepatocellular carcinoma.

法のみ施行した(500万単位筋注×3/week×2 months)。

生体肝移植(Fig. 6, 7):約1年間の経過観察中,腫瘍マーカーの正常が維持された。腹部CT検査で再発病変を認めず,骨シンチグラフィや胸部CT検査においても肝外病変は確認できなかった。肝機能は初回入院時より,T-Bil 2.5 mg/dl, Alb 2.5 g/dl, Child-Pugh score 9点の肝硬変が存在したため,2001年12月に生体肝移植を施行した。摘出肝の肉眼像および組織像ともに典型的な硬変肝であった。病理学的検索では肝実質に腫瘍は認めず,完全壊死

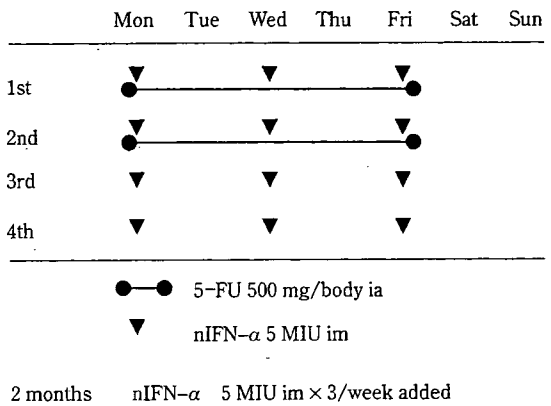

Fig. 4 According to our protocol, 5-FU 500 mg/body ia and nIFN-α 5 MIU im were given first 2 and 4 weeks. Thereafter, nIFN-α 5 MIU im was added subsequent 2 months.
5-FU : 5-fluorouracil, nIFN : natural interferon, MIU : million international unit, ia : intraarterial, im : intramuscularly

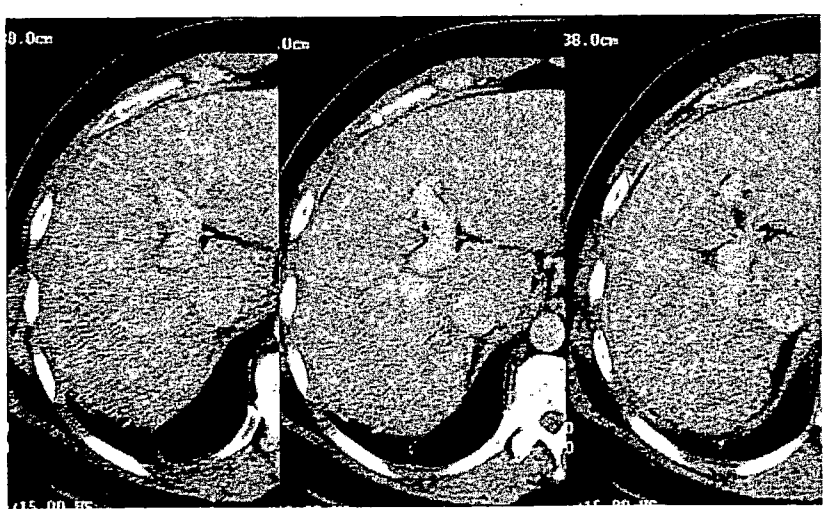

Fig. 5 Computed tomography was taken after chemotherapy. Portal vein tumor thrombosis disappeared.

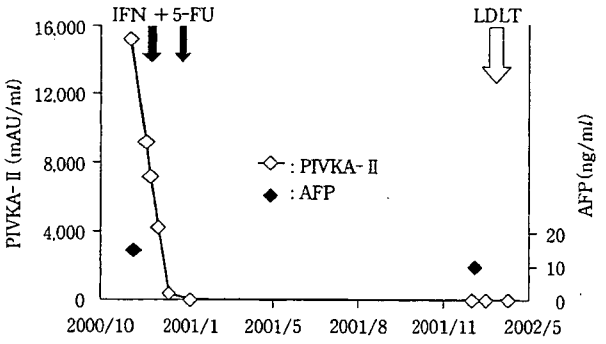

Fig. 6 After administration of 5-FU + interferon combination therapy, PIVKA-II declined rapidly and stayed under the normal limit for a year. Finally, he received living donor liver transplantation.
LDLT: living donor liver transplantation

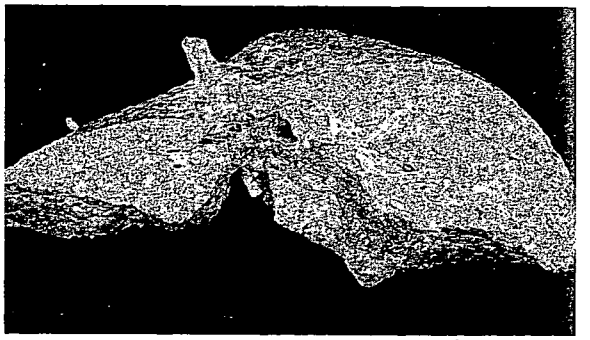

Fig. 7 Examination of the specimen revealed complete necrosis of the tumor thrombosis and there was no carcinoma in the liver parenchyma.

に陥った門脈内腫瘍栓をP7の枝に認めた。

移植術後の経過：その後約1年6か月にわたり肝細胞癌の再発を認めなかったが，慢性拒絶による肝不全に至った。腫瘍マーカーを含めた血液検査と胸腹部CT検査では再発を認めず，再生体肝移植を施行した。摘出肝に再発腫瘍を認めなかった。しかし，再生体肝移植後6か月目に重症急性膵炎により治療関連死した[1]。

II. 考　察

進行肝細胞癌に対する化学療法は，Urabe ら[2]がIFN/5-FU 動注療法を含むプロトコールで試みたことが最初に報告された。Sakon ら[3]は副作用軽減のために，進行肝細胞癌11例に対し，IFN/5-FU動注療法のみで治療を試み，partial response(PR) 45%，CR 27% を得られたと報告した。Obi ら[4]はSakon らと同様のプロトコールで，今回提示したこの症例を含め116例に対し治療を行い，PR 36%，CR 16% の効果を得たと報告し，さらに非治療群より予後が改善されたと報告した。IFN/5-FU 動注療法は，今後の進行肝細胞癌に対する重要な治療法になると思われる。

一方，肝硬変合併肝細胞癌に対する肝移植については，Mazzaferro らはミラノ基準として，肝細胞癌の直径5 cm 以下または3個，直径3 cm 以下であれば，4年生存率は85% と良好なことを1996年に報告した[5]。それとともに，危険因子とされる脈管侵襲[6]を術前に認めないことが，日本における脳死肝移植の待機患者登録基準と生体肝移植の保険適応基準となっている。提示した症例は脈管侵襲を認めていたため，われわれはCRを得られるまで肝移植は不適であると考えていた。

抗癌剤化学療法後にミラノ基準内に downstage したものと，元から合致していたものに対する移植の予後の差については，Yao らは治療によりミラノ基準(正確には，米国の The United Network for Organ Sharing の T2 stage)に downstage したものと，最初から T2 stage 以内であった例に対する肝移植の平均観察期間16か月の比較では差がなかったと報告した[7]。よってこの症例に対しても downstage 後に肝移植が適応となる可能性が考えられた。

肝移植を施行するまでの観察期間については，肝細胞癌の再発や背景肝機能が問題となる。Yao らは治療終了後に，downstage が成功したかどうかを確認するために，観察期間3か月以上をおいて肝移植を施行したと報告したが，われわれは肝移植の目的はCRを得られた後の背景肝硬変に対する治療と考え，腫瘍消失後約1年間の経過観察期間をおいた。この症例のように C型肝炎合併肝硬変の Child-Pugh class B の自然予後は，Planas ら[8]の2004年の報告によると1年生存率，3年および5年生存率はそれぞれおおよそ 80%，70%，50% である。一方，Obi ら[4]の報告によると，この症例のように化学療法でCRが得られた後の予後は，1年生

存率と2年生存率がおおよそ70%と50%であった。また，C型肝炎肝硬変に対する生体肝移植の予後は，日本肝移植研究会の2005年肝移植症例登録報告[9]によると，1年生存率と3年生存率は75%と70%であった。われわれの施設での90例の成績は，1年生存率と3年生存率が86%と84%であり肝移植によって予後の改善が見込めると考えた。

また，この症例は初回肝移植後の1年6か月後に慢性拒絶となり再肝不全となった[1]。しかし，慢性拒絶は報告[10]によると3～5%と頻度が少ない。われわれの施設でも，この症例を含め肝移植を施行した380例のなかで，慢性拒絶の発症は2例と約0.5%の頻度であった。再肝移植についての報告では，C型肝炎合併移植肝不全に対する再肝移植は2年生存率が35%で術後合併症が多発するとされる[11]。この症例のように，術後重症急性膵炎の合併した報告はないが，再肝移植は再考の余地があったといえる。

今後も，肝細胞癌に対して積極的な化学療法を含めた集学的治療の展開が期待される。また，肝硬変合併肝細胞癌の予後を決するのは，腫瘍因子だけでなく肝機能も問題となる。この症例のように内科と外科の連携で，肝移植も含めた医療を患者に提供することは重要であろう。

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[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

HIROTAKA TASHIRO, TOSHIYUKI ITAMOTO, HIDEKI OHDAN, AKIHIKO OSHITA, YASUHIRO FUDABA, KOHEI ISHIYAMA, TOSHIHIKO KOHASHI, HIRONOBU AMANO, SABURO FUKUDA, and TOSHIMASA ASAHARA

Second Department of Surgery, Faculty of Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

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

Toshiyuki Itamoto, MD, PhD, Hideki Nakahara, MD, PhD, Hironobu Amano, MD, PhD, Toshihiko Kohashi, MD, PhD, Hideki Ohdan, MD, PhD, Hirotaka Tashiro, MD, PhD, *and* **Toshimasa Asahara, MD, PhD,** *Hiroshima, Japan*

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.)

From the Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, Japan

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.

Reprint requests: Toshiyuki Itamoto, MD, PhD, Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan. E-mail: titamoto@hiroshima-u.ac.jp.

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)/International 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

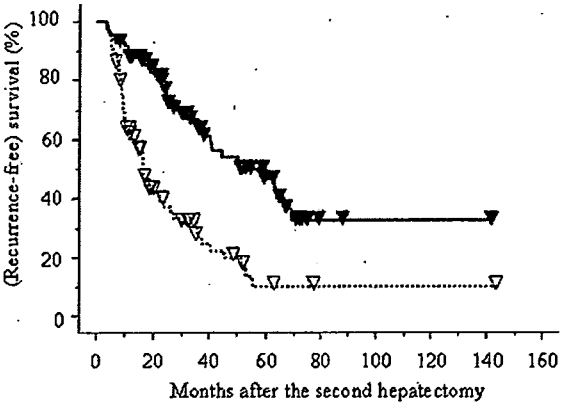

Fig 1. Overall survival (*solid line*) and recurrence-free survival (*dotted line*) curves for 84 patients after second hepatectomy.

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.

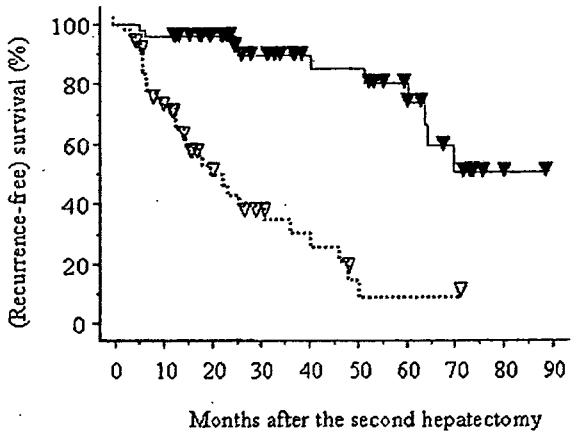

Fig 2. Overall survival (*solid line*) and recurrence-free survival (*dotted line*) curves for 46 patients who underwent a second hepatectomy between 1997 and 2004 and who had no microscopic vascular invasion at the second hepatectomy.

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