Table 1　Differences between CP type A and CP type B

	CP type A	CP type B
Indication		
Liver function (Liver damage) or liver resection	A/B or 2 ≦ Segment	B/C or 2 ≧ Segment
Parenteral nutrition	Common parenteral fluids are administered through a peripheral venous catheter	Hyper alimentation is administered through a central venous catheter and fresh frozen plasma
Hospital discharge	POD 8 ～ 10	POD 10 ～ 12

Table 2　Patient characteristics in each CP

	CP type A	CP type B	*P* value
No. of patients	100	15	
Age (years)	64 (37—87)	63 (52—78)	*NS**
Sex (M/F)	73/26	12/3	*NS*§
Disease			
Hepatocellular carcinoma	56	12	*NS*§
Liver metastases of colorectal/gastric carcinoma and others	43	3	
Liver resection			
Partial resection	79	2	
Minor (1 ≧ Segment)	11	2	*< 0.0001*§
Major (2 ≦ Segment)	9	11	

Values represent (mean (range), NS. not significant)

* : Statistical significance between groups was analyzed by Mann-Whitney's U test

§ : Statistical significance between groups was analyzed by Chi-square test

度の違いを一つのパスにまとめることは困難と考えられたため，肝機能・肝切除量に着目し周術期管理を分けて術後輸液内容の異なる2種類のパスを作成した(医療用，患者用を分けると計4種類)．肝機能が肝障害度AもしくはBの症例または2区域切除以下の肝切除量を予定する症例のパス（以下，肝切除Aのパス）と肝障害度BもしくはCの症例または2区域切除以上の大量肝切除を予定する症例のパス（以下，肝切除Bのパス）を作成した．主な相違点はTable 1に示すように肝切除Aのパス（CP type A）では末梢血管確保のみによる通常の1号，3号液を中心とした組成の輸液指示を，肝切除Bのパス（CP type B）では術前より中心静脈ラインを確保し術後の輸液内容は新鮮凍結血漿投与も予定にいれた糖やナトリウム，カリウムなどの組成を計算した輸液内容でパスを作成した．また，肝切除Bのパスを選択する際は高度肝機能不良あるいは大量肝切除といった大きな手術侵襲が加わり，回復期間を要すると思われたため，予定退院日を肝切除Aで術後8～10日目，肝切除Bで術後10～12日目と違いをもたせて設定した．肝切除パスAとBの大きな相違はこの2点でその他ドレーン抜去は術後3～5日目，経口摂取は術翌日昼より全粥（朝から水分可）を開始，離床・歩行開始も術翌日からとAB同じ設定とした．各症例に対しどちらのパスを採用するかは明確な基準を設けず各担当医が決めることとした．患者の体格指数（body mass index；BMI）の違いや術直後の尿量，経口摂取の増減に応じての輸液の追加，減量はパス逸脱とせず，アウトカムの一つである予定退院日を守れないような合併症が生じた場合，バリアンス発生，パス逸脱とした．また，こうした起こりうる術後合併症については術前より文書を用いて説明し，実際に合併症が起こ

Table 3 Preoperative liver function and surgical stress in each CP

	CP type A (n = 100)	CP type B (n = 15)	*P* value
Preoperative liver function			
Total bilirubin (mg/dl)	0.9 (0.3—1.7)	0.9 (0.4—1.5)	*NS* *
Albumin (g/dl)	3.9 (3.1—4.8)	3.7 (3.2—4.1)	*NS* *
Prothrombin time (PT) (%)	79.6 (39.4—109.8)	75.9 (58.3—91.0)	*NS* *
ICG R15 (%)	13.5 (3.3—36.3)	14.4 (7.0—30.9)	*NS* *
Platelet ($\times 10^4/\mu l$)	17.7 (4.5—35.6)	19.1 (7.0—42.2)	*NS* *
Hemoglobin (g/dl)	13.3 (9.0—15.8)	13.2 (11.3—15.2)	*NS* *
Surgical stress			
Operative time (min.)	201 (55—515)	318 (160—558)	*< 0.0001* *
Hepatic ischemic time (min.)	68 (15—176)	87 (25—148)	*0.02* *
Blood loss (ml)	919 (10—7,270)	3,245 (605—14,399)	*< 0.0001* *
Resected liver weight (g)	216 (5—1,780)	779 (190—2,000)	*< 0.0001* *

Values represent (mean (range), NS : not significant)

* : statistical significance between groups was analyzed by Mann-Whitney's U test

Table 4 Variance in each CP

	CP type A (n = 100)	CP type B (n = 15)	*P* value
Variances (total)	16 (16%)	7 (47%)	*0.0112*
Postoperative complications	14 (14%)	7 (47%)	
Bile leakage	5	1	
Poor oral intake	2	2	
Pulmonary infarction	0	1	
Wound infection	1	2	
Intestinal tract injury	3	1	
Cholangitis	2	0	
Prolonged jaundice	1	0	
Change of operative procedure	2 (2%)	0	

Data are shown as numbers of patients (percentage) and analyzed by chi-square test.

りバリアンスが発生した際にはそれに対する必要な処置（例えば絶飲食など）を患者に説明し，パス逸脱とした．

なお，各解析結果は連続変数に関しては平均値（範囲）で表記，統計学的検定はMann-Whitney's U検定にて比較検定および単回帰分析を，名義変数に関してはカイ2乗検定により比較検定を行った．また術後バリアンス発生に寄与する独立因子検索にはロジスティック回帰分析を用いた．いずれも $P<0.05$ をもって有意差ありと判定した．

結　果

パス適応となった115例のうち100例に肝切除Aが，15例に肝切除Bのパスが用いられた．肝切除AとBにおける患者背景（年齢・性別）および疾患内訳に有意差を認めなかったが，肝切除術式として肝切除A群に肝部分切除が，肝切除B群に2区域以上の肝切除が多く行われている傾向が認められた(Table 2)．同様に手術侵襲因子の比較検討でも手術時間，肝阻血時間，出血量，肝切除重量のすべてにおいて肝切除B群で有意差が認められた(Table 3)．一方で術前の血液・生化学検査

Table 5　Outcomes in cases without variances

	CP type A (n = 84)	CP type B (n = 8)	*P* value
Removal drains (POD)	3.7	4.5	*NS*
Postoperative hospital stay (days)	8.9	10	*0.0035*
Oral intake			
POD1 diet (%)	43.7	38.1	*NS*
POD2 diet (%)	69.4	70.0	*NS*

Data are analyzed by Mann-Whitney's U test.

Table 6　Clinical factors associated with failure of CP type A

Clinical factors	*P* value
Age	*NS*
Sex	*NS*
Disease	*0.0108*
Operative procedure	*0.0381*
Preoperative liver function	
Total bilirubin	*NS*
Albumin	*NS*
Prothrombin time	*NS*
ICG R15	*NS*
Platelet	*NS*
Hemoglobin	*NS*
Surgical stress	
Operative time	*< 0.0001*
Hepatic ischemic time	*NS*
Blood loss	*0.0025*
Resected liver weight	*NS*
Blood transfusion	*< 0.0001*
Oral intake	
POD1 diet	*NS*
POD2 diet	*0.0167*

* : Statistical significance between CP type A with/without variances groups was analyzed by Logistic regression. NS : not signiticaut

結果については，肝切除AとBにおいて各数値間に有意差を認めなかった．

バリアンスが発生することなくパスが完遂された症例は肝切除AとB群合わせて115例中92例(80%)であった．それぞれでみるとバリアンスが発生した症例は肝切除A群で16例(16%)，肝切除B群で7例(47%)で，肝切除B群においてパス完遂率が低かった(Table 4)．術後合併症については胆汁漏，経口摂取不良，肺梗塞，創感染，術中腸管損傷による術後絶飲食，胆管炎による発熱，遷延性の黄疸などが認められた(Table 4)．術後合併症以外でパス逸脱の原因として術式の変更が2例あった．1例は転移性肝癌症例で開腹時に腹膜播種を認め試験開腹のみとなり，もう1例は同じく転移性肝癌症例で胃への直接浸潤があり胃全摘を併施した症例であった．

バリアンスのなかった症例におけるパスのアウトカム解析においてはTable 5に示すように肝切除AとB群それぞれにおいてドレーン抜去は術後平均3.7日目と4.5日目で有意差はなかった．ドレーン抜去と同様，術後の経口摂取量は術後1日目と2日目ともに肝切除AとBにおいて有意差を認めなかった．術後平均在院日数についてはパス間で設定が異なるため，8.9日と10日で有意差を認めた．術後在院日数に関してはバリアンス発生のなかった症例では肝切除AとB群合わせても平均9.0日で，バリアンスの発生したパス逸脱症例も含めたすべての症例では平均11.7日であった．術後第1，2日目の経口摂取量はバリアンスの発生しなかった症例を対象とすると手術侵襲程度に差があっても同程度摂取していた．

パス逸脱率が高く，有効性の低かった肝切除B群を除いた肝切除A群の症例群において検討した結果，バリアンス発生に寄与する臨床的因子は術前としては疾患内訳と術式で，手術侵襲因子としては手術時間，出血量，輸血の有無であった．また，術後の経口摂取量において術後2日目の摂取不良はバリアンス発生に寄与していた(Table 6)．さらにこの術後2日目の経口摂取量と背景因

Table 7 Correlation between oral intake on POD2 and Clinical factors

Clinical factors	*P* value
Age	*NS§*
Sex	*< 0.0001**
Disease	*0.0126**
Operative procedure	*NS**
Preoperative liver function	
Total bilirubin	*NS§*
Albumin	*NS§*
Prothrombin time	*NS§*
ICG R15	*NS§*
Platelet	*NS§*
Hemoglobin	*NS§*
Surgical stress	
Operative time	*0.0070§*
Hepatic ischemic time	*0.0024§*
Blood loss	*NS§*
Resected liver weight	*NS§*
Blood transfusion	*0.0076**
Morbidity	*NS**

* : Statistical significance between CP type A with/without variances groups was analyzed by Logistic regression. § : Simple regression analysis was done to evaluate the relation between specific variables. NS : not significant

子について相関を解析したところ，Table 6に示したパス逸脱とほぼ同様の相関関係を認めたが，他の因子として女性であることと術中肝阻血時間が長くなるにつれ術後第2日目の経口摂取が不良となる傾向を認めた（Table 7）．

考　察

一般的に他の消化器外科手術に比べて肝切除術は手術にともなう危険性が高く術後合併症も生じやすい．しかし，そうした肝切除術も年間手術件数の多い施設では術後の安全性は高いとされている[10]．当科における肝切除術は年間100例を越え，いわゆるhigh volume centerとして肝切除術の手術成績は安定しており，バリアンス発生も少なくパス導入は可能であると考えられた．

佐野[11]や及川ら[12]は予備能良好な正常肝に対する肝切除の術後輸液管理は他の腹部手術後の輸液管理と同様でよいとしている．我々もこれまでの肝切除後の輸液内容を見直すと症例毎に輸液指示が異なるものの大きく分けて2通りに分けることができ，一方は通常の腹部手術と同様の輸液管理を行っていた．そこで今回肝切除術に対するパス導入に際してはこの2通りのパスを作成した．こうした我々の工夫により予定していた胆道再建を伴わない肝切除術のほとんどの症例にパスを適応することができ80%の完遂率が達成された．

しかし，パスを実際に使用してみて2種類のパスのうち高度肝機能不良，大量肝切除症例への適応を想定して作られた肝切除Bのパスは逸脱率が高かったことが問題点として挙げられる．さらに，Table 3に示したように2種類のパスの使い分けは術前肝機能によらず，手術侵襲の大きさによってなされていたことが明らかとなった．肝切除Bのパスは術後指示が肝切除Aに比べるとあらゆる点で煩雑となっている．大きな手術侵襲を想定して作成したので肝切除Bの煩雑さはやむをえないがAとBの選択基準を設けなかったためにAとBどちらを選択してもよいと考えられる症例には術後指示のシンプルな肝切除Aが選択される傾向が強かったと思われる．そのため，肝切除Aのパスに比べBのパスは選択率が低くなった（15/115；13%）と推測される．手術侵襲が大きいという選択バイアスが強く働いているものの肝切除Bのパスは完遂率も低かった（8/15；53%）．さまざまな術式・手術侵襲に対応すべく2種類のパスを作成したが，結果的には肝切除Bのパスは使用頻度，完遂率ともに低いという有効性があまり認められなかった．

次にパス完遂率も高く，有効性も認められた肝切除Aのパスについて検討すると，原発性よりも転移性肝癌の手術症例にバリアンス発生を高率に認めた（Table 6）．転移性肝癌の手術症例では癒着剥離操作があり，その影響で術後腸管蠕動の回復遅延から嘔気，食思不振の遷延や剥離操作の際の腸管損傷により術直後からの絶飲食という要因でバリアンスが多く発生していた．術前肝機能因子はパス逸脱に影響はなく，手術侵襲，特に手術時間，出血量，輸血の有無がバリアンス発生に大きく寄与していた．また，経口摂取量でみると術翌日の摂取量よりも術後2日目の経口摂取量がパス

Table 8　Indication of CP in hepatectomy

Surgical stress	Cut off point	Incidence of variance in CP type A	
		Sensibility	Specificity
Operative time (min.)	300	8/16 (50%)	80/84 (95%)
Hepatic ischemic time (min.)	90	6/16 (38%)	69/84 (82%)
Blood loss (ml)	3,000	3/16 (19%)	83/84 (99%)
Resected liver weight (g)	800	2/16 (13%)	82/84 (98%)

逸脱に関与していることが認められた．これは術後2日目まで経口摂取不良が続くとその後の経過中，バリアンスが発生しパスから逸脱する可能性が高くなる，という非常に興味深い結果を得た．そこでその背景因子について検討を行ったところ，パス逸脱とほぼ同様の因子と相関関係を認めたが，それ以外では術後2日目の経口摂取量不良例は女性に多く，また術中肝阻血時間と相関していた(Table 7)．性別因子についてはカイ2乗検定にて疾患内訳因子と強い相関を認め($p=0.0120$)，今回の検討では転移性肝癌の切除例が女性に多かったためによる2次的な相関関係であると考えられた．また，手術侵襲としては肝阻血時間が術後2日目の経口摂取量へ影響していることが明らかとなり，腸管循環の阻血が術後の経口摂取量に関与しているのではないかと推測された．

以上，今回のバリアンス，アウトカム解析結果から肝切除Aのパスでは術後管理が難しいと考えられる症例は肝切除Bのパスを適応しても逸脱する確率は高く，また肝切除Bのパスの適応と考えられる症例そのものが年間を通じて少ないため，そういった症例は肝切除パスの適応外としてもよいと考えられた．具体的な適応基準設定を目的とし判別分析も行ったが，良好な予測式を得ることができなかった．しかし，逸脱率の高かった肝切除Bのパス群におけるTable 3に示した手術侵襲因子の各平均数値を参考にカットオフ値を推定し，肝切除Aの症例で検証すると感度・特異度の両面から特に手術時間5時間がパス適応の一つの指標として有効ではないかと考えられた (Table 8)．今後，当院での肝切除における術後管理の方針としてはAとBという手術侵襲で2種類のパスを使い分けるよりも肝切除Aのパスで一本化し，術前評価の中で予定手術時間が5時間以上，かつ他の手術侵襲因子のカットオフ値も越えることが予想されるような場合はパスの適応外とした方がよいのではないかと考えられた．

また従来，大量肝切除あるいは障害肝の肝切除の術後管理は新鮮凍結血漿投与も予定にいれた糖やナトリウム，カリウムなどの組成を計算した輸液が必要とされてきた[11)12)]．しかし，新しく我々が提案した肝切除Aのパスが適応可能となるような手術侵襲が想定される場合，正常肝だけでなく軽度の障害肝における葉切除例に対してもそうした厳密な輸液管理を行わずに通常の腹部手術と同等の輸液管理で安全に術後管理が行えるのではないかと考えられた．一方で中等度以上の肝機能障害を有する手術侵襲の大きい大量肝切除例には術後バリアンス発生頻度が高く，パス適応は難しく輸液管理もいまだ厳密に行う必要性が示唆される．

文　献

1) 武藤正樹：日本におけるクリニカルパスの現状と最近の話題．臨外　56：439—447, 2001
2) 関戸　仁，永野靖彦，三浦靖彦ほか：クリニカルパスにおけるバリアンス分析の有用性．日消外会誌　35：233—236, 2002
3) Pitt HA, Murray KP, Bowman HM et al：Clinical pathway implementation improves outcomes for complex biliary surgery. Surgery 126：751—758, 1999
4) Pritts TA, Nussbaum MS, Flensch LV et al：Implementation of a clinical pathway decreases length of stay and cost for bowel resection. Ann Surg 230：728—733, 1999
5) Porter GA, Pisters PWT, Mansyur C et al：Cost and utilization impact of a clinical pathway for patients undergoing pancreaticoduodenectomy. Ann Surg Oncol 7：484—489, 2000
6) 袴田健一，鳴海俊治，豊木嘉一ほか：臨床的・経

済的アウトカムと患者満足度からみた膵頭十二指腸切除術に対するクリニカルパス導入の意義. 日消外会誌 37：369—374, 2004
7) 前田貴司, 橋元宏治, 三浦奈央子ほか：肝臓外科におけるクリニカルパスの有用性と課題. 広島医 57：819—821, 2004
8) 吉村弥須子, 久保正二, 白田久美子：肝切除術のクリニカルパス導入におけるバリアンス要因の検討. 看技 49：52—55, 2003
9) 桂巻 正：肝切除術のクリニカルパス. 消外 26：425—434, 2003
10) Glasgow RE, Showstack JA, Katz PP et al：The relationship between hospital volume and outcomes of hepatic resection for hepatocellular carcinoma. Arch Surg 134：30—35, 1999
11) 佐野圭二：輸液メニューの決め方. 幕内雅敏, 高山忠利編. 肝臓外科の要点と盲点. 文光堂, 東京, 1998, p265—267
12) 及川昌也, 海野倫明, 片寄 友ほか：肝切除術後管理（術後肝不全対策も含めて）. 消外 28：459—463, 2005

Indication of a Clinical Pathway for Hepatectomy on Variance Analysis

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Purpose：We studied the incidence of variance and outcome of a clinical pathway（CP）for hepatectomy. **Patients and Methods**：From January 2003, a CP was introduced in management of hepatectomy without reconstruction of the bile duct. From January to December 2004, a CP was implemented for 115 patients undergoing hepatectomy without reconstruction of the bile duct. **Results**：Patients completing the CP were 80%. Mean postoperative hospitalization stay was 9.0 days. Clinical factors correlated with the incidence of variance were the type of disease（primary liver cancer or metastatic liver tumor), surgical procedure, operating time, blood loss, blood transfusion, and the amount of diet on postoperative day（POD）2. **Conclusions**：We evaluated indications of a CP for hepatectomy. The most useful clinical factor was operating time. The frequency of incidence of variance will be probably high if we cannot conduct hepatectomy within a 5-hour operation.
Key words：clinical pathway, hepatectomy, hepatocellular carcinoma, variance, outcome
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早期胆道癌の治療／胆管癌の外科療法

肝内胆管癌の手術

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B. 胆道癌 VII. 胆道癌の治療
早期胆道癌の治療／胆管癌の外科療法

肝内胆管癌の手術

Surgical treatment for intrahepatic cholangiocarcinoma

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Key words　肝内胆管癌，拡大肝切除術，門脈合併切除，肝外胆管切除，肝動脈合併切除

はじめに

肝内胆管癌(intrahepatic cholangiocarcinoma)は進行癌の状態で診断されることが多く，門脈・肝動脈・胆管などに直接浸潤を認める頻度が高い．したがって，肝内胆管癌に対して治癒切除を達成するためには，肝断端を十分確保した拡大肝切除に加えて，しばしば門脈・肝動脈・肝外胆管などの合併切除が必要となる．これまで著者らの施設では，血管合併切除および肝外胆管切除を伴う拡大肝切除を積極的に施行してきた．しかし，他施設の報告と同様に，こうした進行肝内胆管癌の予後は依然として不良である．こうした拡大手術が有効であるというエビデンスも現在まで十分には示されていない．一方，リンパ節転移を有する肝内胆管癌の予後は極めて不良であり，リンパ節転移陽性例に対するリンパ節郭清の意義も明らかではない．したがって，肝内胆管癌に関する外科治療には依然として多くの課題が残されているのが実状である．

本稿では肝内胆管癌に対する切除成績と手術の実際を概説するとともに，外科治療上の問題点および最新の知見について紹介する．

1. 肝内胆管癌の切除成績

a. Stage別の成績

1992年10月から2005年5月まで間に，国立がんセンター東病院上腹部外科において切除された肝内胆管癌は43例であった．Kaplan-Meier法で計算した切除例全体の1年，3年，5年生存率は各々55%，40%，28%であり(図1)，MST(median survival time)は17カ月であった．最近の主な報告でも，肝内胆管癌切除例の5年生存率は20-40%程度と報告されている[1-6]．

UICC第6版[7]によるStage別の5年生存率は，Stage I(n=9)で89%，Stage II(n=13)で42%と比較的良好であったが，Stage III/IV(n=21)では0%と極めて不良であった(図2)．Stage III/IVのMSTは6カ月で，1年以上生存したのは21例中4例にすぎなかった．Stage IとStage III/IV($p<0.0046$)，Stage IIとStage III/IV($p<0.0096$)の間には各々有意差を認めた．

b. 治癒切除例の成績

肝内胆管癌に対する手術の有効性に関しては，組織学的に切除断端癌陰性(R0)の治癒切除後には良好な治療成績・生存率が得られるとの報告が多い[4,8,9]．なかでもLangらはR0切除例の3

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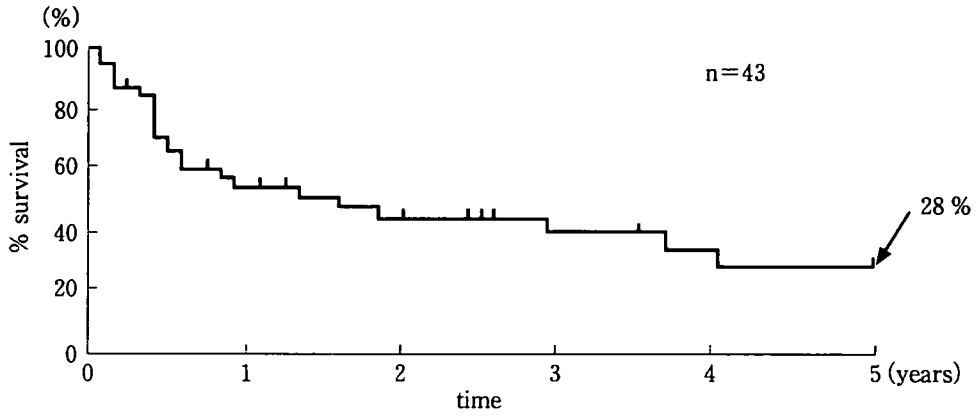

図1 肝内胆管癌切除例の生存率

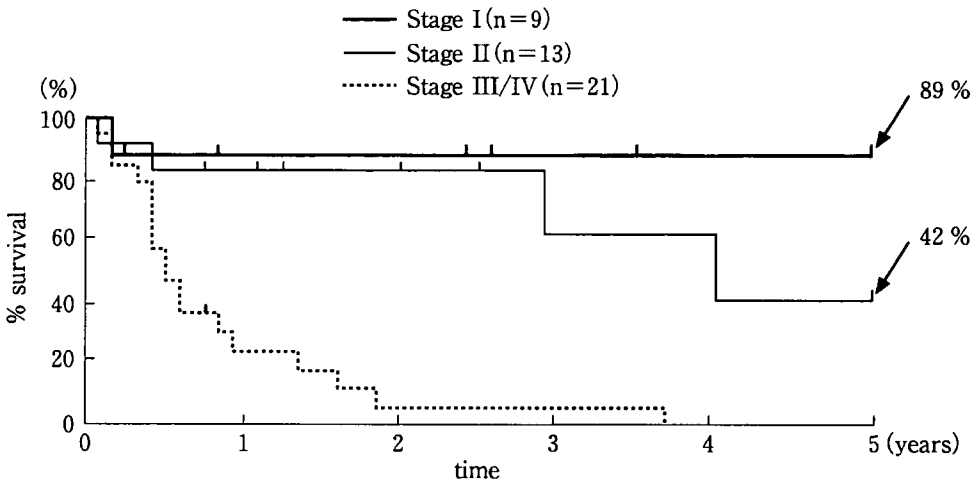

図2 肝内胆管癌Stage別の生存率

年生存率82%と極めて良好な成績を報告している．逆に切除断端癌陽性(R1)となった非治癒切除例のMSTは5カ月，開腹のみに終わった例のMSTは7カ月と極めて予後不良であったことを報告している[9]．著者らのR0切除例(n=31)の1年，3年，5年生存率は各々63%，52%，37%で，MSTは38カ月と比較的良好であった．R1切除例(n=12)のMSTは6カ月と極めて不良であった．

c. 肝門浸潤型と末梢型の成績

以前著者らは，肝内胆管癌を肝門浸潤型(hilar-invasive type)と末梢型(peripheral type)に分類し，肝門浸潤型の5年生存率4%に対して，末梢型の5年生存率は43%と有意に良好であることを報告した[1]．今回当センターの切除例で再検討したところ，肝門浸潤型(n=23)の5年生存率は7%と極めて不良であるのに対して，末梢型(n=20)の5年生存率は58%と有意(p=0.02)に良好であった(**図3**)．したがって，肝内胆管癌を肝門浸潤型と末梢型に分類することは，予後の推測および手術適応の検討のために有用であると思われた．**図4-6**は左右肝管合流部に浸潤を認める肝門浸潤型のCT，胆管像，および門脈像である．本症例に対しては肝外胆管切除および門脈合併切除を伴う拡大右肝切除術を施行した．

2. 肝内胆管癌に対する拡大肝切除術の実際

a. 拡大肝切除術

一般に肝内胆管癌は進行癌として診断されることが多いので，拡大肝切除術に加えて肝外胆

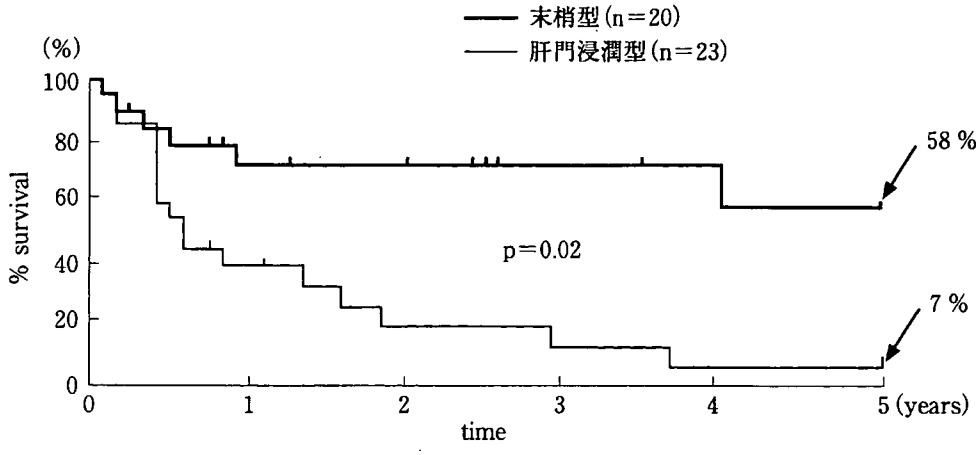

図3 肝門浸潤型と末梢型の生存率

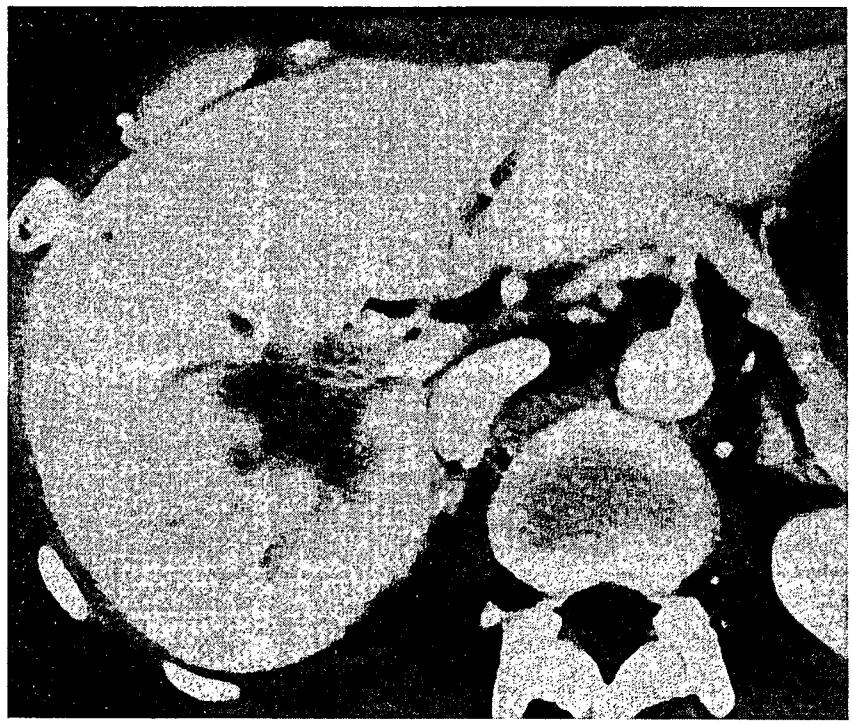

図4 造影CT
肝右葉に不正型の肝内胆管癌を認める.

管および肝門部血管合併切除が必要となる頻度が高い. 当センターでは, 肝内胆管癌切除例43例中36例(84%)に肝葉切除以上の肝切除術を施行した. 更に, 肝門部血行再建を7例, 肝外胆管切除を20例に施行した.

b. 血管合併切除

肝内胆管癌に対する血管合併切除の適応については, 国の内外で明確なコンセンサスがないのが実状である. 著者らの施設では, 肝内胆管癌に対して門脈再建を伴う拡大肝切除を5例, 右肝動脈切除再建を伴う拡大左肝切除を1例, 門脈分岐部および左肝動脈への直接浸潤を認め, 右肝動脈と腫瘍が癒着していた1例に門脈と右肝動脈の切除再建を伴う拡大左肝切除術を施行した. 肝動脈再建は原則としてマイクロサージャリーによる吻合で行っている. **図7**は門脈・下大静脈合併切除を伴う拡大右肝切除術のシェーマである[10]. **図8**は門脈合併切除・再建を伴

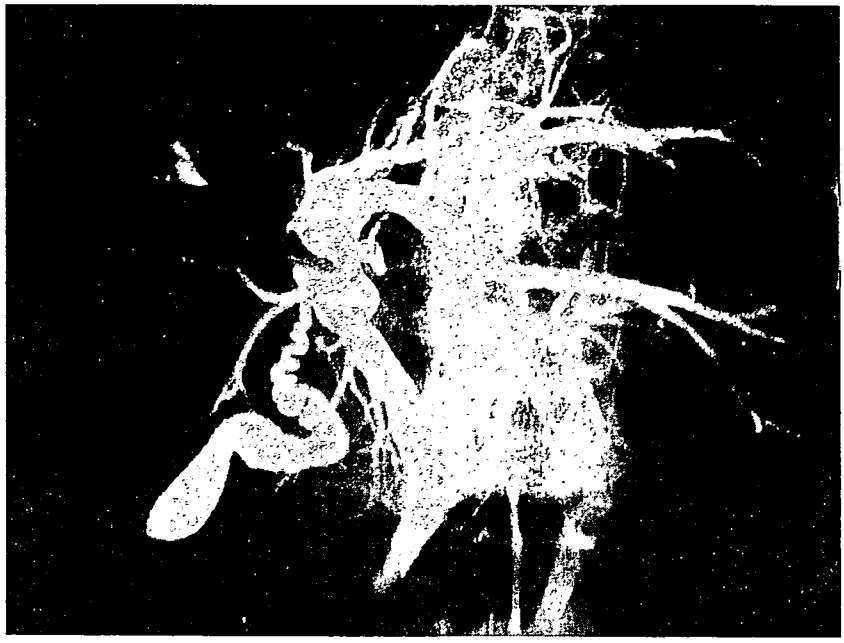

図5 胆管像
左右肝管合流部に肝内胆管癌の浸潤を認める.

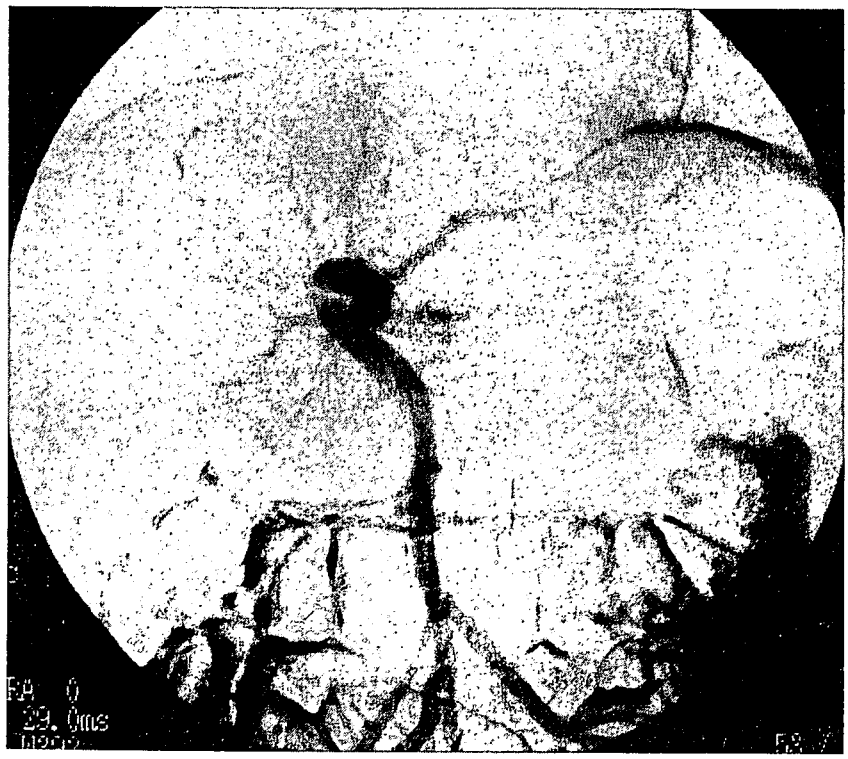

図6 門脈造影
右門脈は直接浸潤のため全く造影されない.

う拡大左肝切除後の術中スナップである. これら肝門部血行再建を施行した7例は全員退院可能であり手術は安全に施行可能であった. しかし退院後の早期再発が多く, 1年生存率は25%, MSTは7カ月であった. Langらは, 門脈切除・再建または下大静脈合併切除を8例に施行し, そのうち3例がR0切除となったことを報告しているが, 1年以上生存したのは8例中2例の

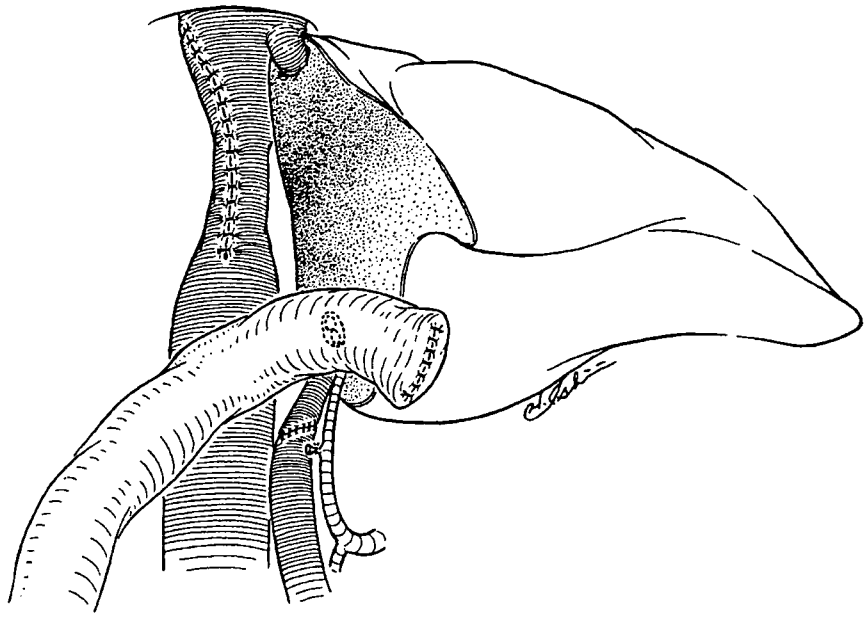

図7 門脈・下大静脈合併切除を伴う拡大右肝切除術のシェーマ
(J Hepatobiliary Pancreat Surg **7**(6): 600, 2000. より許可を得て転載)

図8 門脈合併切除・再建を伴う拡大左肝切除後の術中スナップ

ようである[9]. 肝内胆管癌に対する血管合併切除が有効であるという明確なエビデンスがない現状では, 肝内胆管癌に対する血行再建を伴う拡大肝切除術は, R0の治癒切除となる可能性が高い場合に限って施行すべきであろう. 著者らは, 両側門脈と両側肝動脈ともに明らかな直接浸潤を認め, 血行再建困難と考えられる場合は局所進行癌(locally advanced cancer)として手術適応から除外している.

c. 肝外胆管切除と尾状葉切除

肝外胆管切除の適応に関しては, 左右肝管合流部浸潤のあるBD4症例では必須であるが, 右肝管または左肝管のみに浸潤を認めるBD3症例では胆管断端の癌遺残がなければ必ずしも必要ではないと考えている. 尾状葉切除も肝実質切離断端に癌を認めなければ必ずしも必要で

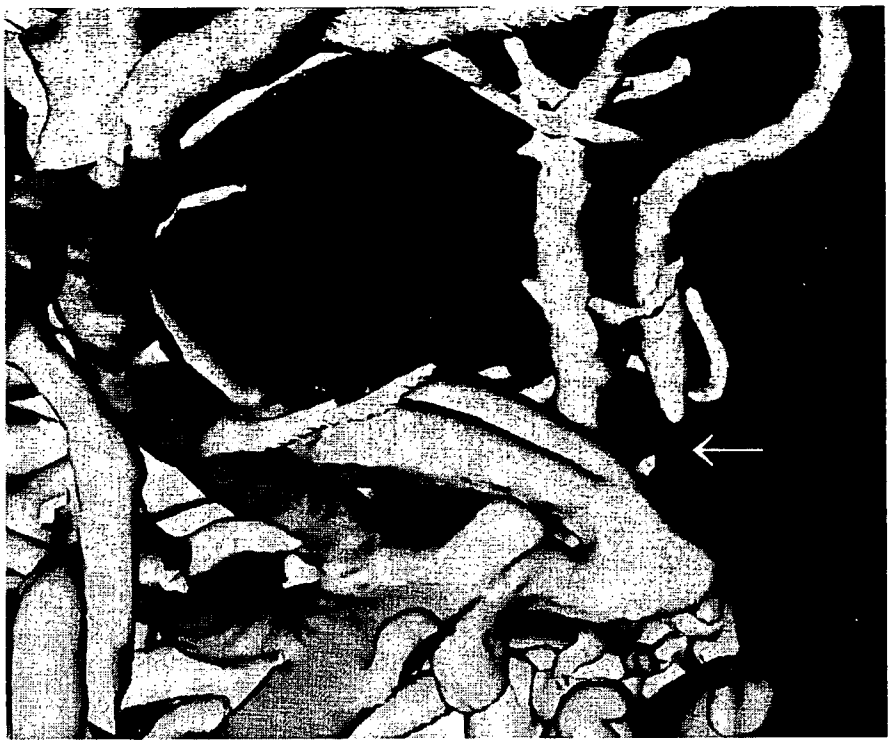

図9 3次元胆管像
矢印は尾状葉胆管(paracaval portion)の狭窄.

はないと考えている．しかし，左右肝管合流部への浸潤を認める場合には尾状葉胆管への浸潤を伴う可能性が高く，尾状葉全切除を伴う拡大肝切除術が必要となることが多い．著者らは3次元胆管画像を用いて(**図9**)，胆管浸潤および尾状葉胆管への浸潤を検討している[11]．

d. リンパ節郭清

肝内胆管癌切除例におけるリンパ節転移の頻度は高い．そしてリンパ節転移を認める肝内胆管癌の予後は極めて不良である．当センターでは，肝内胆管癌切除43例中16例(37%)にリンパ節転移を認めた．肝門浸潤型と末梢型を比較すると，肝門浸潤型23例中13例(57%)にリンパ節転移を認め，末梢型では20例中3例(15%)に認め，肝門浸潤型でのリンパ節転移頻度が高かった．リンパ節転移を認めた16例の予後は，1年生存率20%，3年生存率7%，5年生存率0%と極めて不良であり，当センターでは長期生存例は存在しなかった．Inoueらも，リンパ節転移を認める腫瘤形成型肝内胆管癌の予後は極めて不良であると報告している[2]．Shimadaらは肝内胆管癌術後の再発は肝転移が多く，リンパ節郭清は予後の向上には寄与していないようであると報告している[12]．しかし，Nakagawaらは3個以上のリンパ節転移を認めた肝内胆管癌の予後は不良だったが，2個以内のリンパ節転移例では比較的良好な予後が得られたので，こうした症例に関してはリンパ節郭清を伴う肝切除の意義はあると報告している[13]．しかし，これらの報告はすべて少数例での検討であり，リンパ節郭清の効果については更に多施設での検討が必要と思われる．

おわりに

肝内胆管癌は局所浸潤傾向が強く，肝外胆管および肝門部の門脈・肝動脈に高頻度に直接浸潤を認めるので，血管合併切除および肝外胆管切除を伴う拡大肝切除が必要となることが多い．肝内胆管癌に対してR0の治癒切除が達成できれば，比較的良好な予後が期待できる．しかし，R1の姑息切除に終わった場合には，肝内胆管癌の予後は極めて不良である．

最近では，肝門部での門脈および肝動脈合併切除を伴う拡大肝切除術は比較的安全に施行可能となった．しかし，その有効性に関する明確なエビデンスがあるとはいえないのが実状である．したがって，肝内胆管癌に対する血行再建を伴う拡大肝切除術は，R0の治癒切除となる可能性が高い場合に限って施行すべきである．

■文　献

1) Nakagohri T, et al: Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma. World J Surg **27**(3): 289-293, 2003.
2) Inoue K, et al: Long-term survival and prognostic factors in the surgical treatment of mass-forming type cholangiocarcinoma. Surgery **127**(5): 498-505, 2000.
3) Uenishi T, et al: Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma. Br J Surg **88**(7): 969-974, 2001.
4) Nakeeb A, et al: Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg **224**(4): 463-473, 1996.
5) Okabayashi T, et al: A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer **92**(9): 2374-2383, 2001.
6) Ohtsuka M, et al: Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg **89**(12): 1525-1531, 2002.
7) Sobin LH, Wittekind CH: TNM Classification of Malignant Tumours, 6th ed, John Wiley & Sons Ltd, West Sussex, 2002.
8) Weber SM, et al: Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J Am Coll Surg **193**(4): 384-391, 2001.
9) Lang H, et al: Extended hepatectomy for intrahepatic cholangiocellular carcinoma (ICC): when is it worthwhile ? Single center experience with 27 resections in 50 patients over a 5-year period. Ann Surg **241**(1): 134-143, 2005.
10) Nakagohri T, et al: Extended right hepatic lobectomy with resection of inferior vena cava and portal vein for intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg **7**(6): 599-602, 2000.
11) 中郡聡夫ほか：胆道癌に対する仮想内視鏡と3次元胆管画像．臨床消化器内科 **20**(7): 971-975, 2005.
12) Shimada M, et al: Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma. Br J Surg **88**(11): 1463-1466, 2001.
13) Nakagawa T, et al: Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. World J Surg **29**: 728-733, 2005.

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ORIGINAL REPORT

Phase II Study of Radiotherapy Employing Proton Beam for Hepatocellular Carcinoma

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ABSTRACT

Purpose
To evaluate the safety and efficacy of proton beam radiotherapy (PRT) for hepatocellular carcinoma.

Patients and Methods
Eligibility criteria for this study were: solitary hepatocellular carcinoma (HCC); no indication for surgery or local ablation therapy; no ascites; age ≥ 20 years; Zubrod performance status of 0 to 2; no serious comorbidities other than liver cirrhosis; written informed consent. PRT was administered in doses of 76 cobalt gray equivalent in 20 fractions for 5 weeks. No patients received transarterial chemoembolization or local ablation in combination with PRT.

Results
Thirty patients were enrolled between May 1999 and February 2003. There were 20 male and 10 female patients, with a median age of 70 years. Maximum tumor diameter ranged from 25 to 82 mm (median, 45 mm). All patients had liver cirrhosis, the degree of which was Child-Pugh class A in 20, and class B in 10 patients. Acute reactions of PRT were well tolerated, and PRT was completed as planned in all patients. Four patients died of hepatic insufficiency without tumor recurrence at 6 to 9 months. Three of these four patients had pretreatment indocyanine green retention rate at 15 minutes of more than 50%. After a median follow-up period of 31 months (16 to 54 months), only one patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96% (95% CI, 88% to 100%). Actuarial overall survival rate at 2 years was 66% (48% to 84%).

Conclusion
PRT showed excellent control of the primary tumor, with minimal acute toxicity. Further study is warranted to scrutinize adequate patient selection in order to maximize survival benefit of this promising modality.

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INTRODUCTION

Cirrhosis is found in more than 80% of patients with hepatocellular carcinoma (HCC). This precludes more than 70% of the patients from receiving potentially curative treatments, and also contributes eventually to fatal hepatic insufficiency and multifocal tumorigenesis.[1,2] Approximately 50% to 70% and 30% to 50% of 5-year overall survival was achieved with surgery including liver transplantation[3-6] and percutaneous local ablation,[7-9] respectively, for an adequately selected population of patients. However, no standard strategy has been established for patients with unresectable HCC at present.

Partial liver irradiation for HCC using 50 to 70 Gy of megavoltage x-ray with or without transarterial chemoembolizaztion (TACE) for 5 to 7 weeks has been widely applied during the last two decades. This resulted in response rates of 33% to 67%, with a median survival period of 13 to 19

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months and 10% to 25% overall survival at 3 years.[10-12] Since 1985, proton radiotherapy (PRT) administered at a median dose of 72 cobalt gray equivalent (Gy_E) in16 fractions during 3 weeks with or without TACE, had been applied in more than 160 patients with HCC at the University of Tsukuba, resulting in a more than 80% local progression-free survival rate with 45% and 25% overall survival at 3 and 5 years, respectively.[13,14] The excellent depth-dose profile of the proton beam enabled us to embark on an aggressive dose escalation while keeping a certain volume of the noncancerous portion of the liver free from receiving any dose of irradiation. This single-institutional, single-arm, prospective study was conducted to confirm encouraging retrospective results of PRT for HCC using our newly installed proton therapy equipment.

PATIENTS AND METHODS

Patient Population

Patients were required to have uni- or bidimensionally measurable solitary HCC of ≤ 10 cm in maximum diameter on computed tomography (CT) and/or magnetic resonance (MRI) imaging. In addition, the following eligibility criteria were required: no history of radiotherapy for the abdominal area; no previous treatment for HCC within 4 weeks of inclusion; no evidence of extrahepatic spread of HCC; age ≥ 20 years; Zubrod performance status (PS) of 0 to 2; WBC count ≥ 2,000/mm^3; hemoglobin level ≥ 7.5 g/dL; platelet count ≥ 25,000/mm^3; and adequate hepatic function (total bilirubin ≤ 3.0 mg/dL; AST and ALT < 5.0× upper limit of normal; no ascites). Patients who had multicentric HCCs were not considered as candidates for this study, except for those with the following two conditions: (1) multinodular aggregating HCC that could be encompassed by single clinical target volume; (2) lesions other than targeted tumor that were judged as controlled with prior surgery and/or local ablation therapy. Because a planned total dose would result in a significant likelihood of serious bowel complications, patients who had tumors abutting or invading the stomach or intestinal loop were excluded. The protocol was approved by our institutional ethics committee, and written informed consent was obtained from all patients.

Pretreatment Evaluation

All patients underwent indocyanine green clearance test, and the retention rate at 15 minutes (ICG R15) was measured for the purpose of quantitative assessment of hepatic functional reserve. CBC, biochemical profile including total protein, albumin, total cholesterol, electrolytes, kidney and liver function tests, and serological testing for hepatitis B surface antigen and antihepatitis C antibody were done. C-reactive protein and tumor markers including alpha feto-protein and carcinoembryonic antigen were also measured. Chest x-ray was required to exclude lung metastasis. All patients were judged as unresectable by expert hepatobiliary surgeons in our institution, based on their serum bilirubin level, ICG R15, and expected volume of resected liver.[15] Gastrointestinal endoscopy was done to exclude active ulcer and/or inflammatory disease located at the stomach and the duodenum. All patients underwent abdominal ultrasonography, triphasic CT or MRI, CT during arteriography and arterial portography.[16] Diagnosis of HCC was based on radiographic findings on triphasic CT/MRI. Radiologic criteria for HCC definition were as follows: tumor showing high attenuation during hepatic arterial and portal venous phase indicating hypervascular tumor; tumor showing low attenuation during delayed phase indicating rapid wash-out of contrast media. Confirmatory percutaneous fine-needle biopsies were required for all patients unless they had radiologically compatible, postsurgical recurrent HCC. Tumors that broadly abut on the vena cava, portal vein, or hepatic vein that were associated with caliber changes and/or filling defects of these vessels, were tentatively defined as positive for macroscopic vascular invasion. One patient had visible tumor on fluoroscopy because of residual iodized oil contrast medium used in previous TACE. For the other 29 patients, one or two metallic markers (inactive Au grain of which the diameter and length were 1.1 mm and 3.0 mm, respectively) were inserted percutaneously at the periphery of the target tumor.

Treatment Planning

PRT was performed with the Proton Therapy System (Sumitomo Heavy Industries Ltd, Tokyo, Japan), and treatment planning, with the PT-PLAN/NDOSE System (Sumitomo Heavy Industries Ltd). In this system, the proton beam was generated with Cyclotron C235 with an energy of 235 MV at the exit. Gross tumor volume (GTV) was defined using a treatment planning CT scan using X Vision Real CT scanner (Toshiba Co Ltd, Tokyo, Japan), and clinical target volume (CTV) and planning target volume (PTV) were defined as follows: CTV = GTV + 5 mm, and PTV = CTV + 3 mm of lateral, craniocaudal, and anteroposterior margins. Proton beam was delivered with two-beam arrangement to minimize irradiated volume of noncancerous liver using our rotating gantry system. The beam energy and spread-out Bragg peak[13] were fine-tuned so that 90% isodose volume of prescribed dose encompassed PTV. To evaluate the risk of radiation-inducing hepatic insufficiency, dose-volume histogram (DVH) was calculated for all patients.[17]

Scanning of CT images for both treatment planning and irradiation of proton beam were done during the exhalation phase using a Respiration-Gated Irradiation System (ReGIS). Our ReGIS during this study period was composed in the following manner: strain gauge, which converts tension of the abdominal wall into electrical respiratory signal, was put on the abdominal skin of the patient; gating signal triggering CT scanning or proton beam was generated during the exhalation phase.

Treatment

The fractionation and dosage in this study were based on the results of a retrospective study at the University of Tsukuba. A total dose ranging from 50 Gy_E in 10 fractions to 87.5 Gy_E in 30 fractions (median, 72 Gy_E in16 fractions) was administered without serious acute and late adverse events. All patients received PRT to a total dose of 76 Gy_E for 5 weeks in 3.8-Gy_E once-daily fractions, four fractions in a week using 150 to 190 MV proton beam. Relative biologic effectiveness of our proton beam was defined as 1.1. No concomitant treatment (eg, TACE, local ablation, systemic chemotherapy) was allowed during and after the PRT, unless a treatment failure was detected. Verification of patient set-up was done in each fraction using a digital radiography subtraction system. In this system, fluoroscopic images obtained at daily set-up were subtracted by the original image that was taken at the time of treatment planning. Position of the patient couch was adjusted to overlap the diaphragm, inserted metallic markers, and bone landmarks on the original position at the end of the exhalation phase.

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PRT was administered 4 days a week, mainly Monday to Thursday, and Friday was reserved for maintenance of the PRT system. Predefined adverse reaction of PRT was dermatitis, pneumonitis, hepatic insufficiency, and gastrointestinal ulcer and/or bleeding. If one of these reactions of grade 3 or higher, or unexpected reactions of grade 4 or higher were observed in three patients, further accrual of patients was defined to be stopped. No further PRT was allowed when grade 4 hematologic toxicity or any of the toxicities of grade 3 or higher were observed at the digestive tract or lung. PRT was delayed up to 2 weeks until recovery when an acute nonhematologic toxicity of grade 3 or higher, other than that described above, was observed. However, when only an elevation of liver enzymes was observed without manifestation of clinically significant signs and symptoms, PRT was allowed to be continued according to the physician's judgment.

Outcomes

It has been reported that the tumor, although achieving a complete response, persisted over a long period, ranging from 3 weeks to 12+ months after the completion of PRT.[18] Therefore, a local progression-free survival rate at 4 weeks after the end of PRT was adopted as the primary end point of this study, where an event was defined as progression of the primary tumor with size increase of more than 25%, in order to facilitate an interim analysis as described in the Statistical Design section below. Assessment of primary tumor response using CT and/or MRI was performed 4 weeks after the completion of PRT. Overall survival and disease-free survival rates were also evaluated as secondary end points. Death of any cause was defined as an event in calculation of overall survival, whereas tumor recurrences at any sites or patient deaths were defined as events for disease-free survival. Adverse events were reviewed weekly during the PRT by means of physical examination, CBC, liver function test, and the other biochemical profiles as indicated. The severity of adverse events was assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. After completion of PRT, reviews monitoring disease status, including CT and/or MRI examinations and long-term toxicity were done at a minimum frequency of once every 3 months.

Statistical Design

The null hypothesis of a true local progression-free rate of 50% or lower was based on average results of photon radiotherapy reported from Japan, in which each study accumulated approximately 20 patients.[11,12] This was tested against the alternative hypothesis of a true rate of 80% or higher with an α level of 5% and a power of 80%, which required 30 patients according to the method by Makuch and Simon.[19] If fewer than five patients experienced local progression-free status within 4 weeks postirradiation at the end of first nine enrollments, the trial would be stopped. Otherwise, if more than 24 patients remained locally progression-free among the total of 30 patients, this would be sufficient to reject the null hypothesis and conclude that PRT warrants further study. Time-to-event analyses were done using Kaplan-Meier estimates, and 95% CIs were calculated. The difference of time-to-event curve was evaluated with the log-rank test. Multivariate analyses were performed with Cox's proportional hazards model.

RESULTS

Patients

Thirty patients were enrolled between May 1999 and February 2003. Patient characteristics at the start of PRT are

Table 1. Characteristics of 30 Enrolled Patients

Characteristic	Patients No.	Patients %
Age, years		
Median	70	
Range	48-87	
Sex		
Male	20	67
Female	10	33
ECOG performance status		
0-1	29	97
2	1	3
Clinical stage (2)		
I	9	30
II	19	63
III	2	7
Positive viral markers		
Hepatitis B virus	3	10
Hepatitis C virus	26	87
Both	1	3
Child-Pugh classification		
A	20	67
B	10	33
C	0	0
Pretreatment indocyanine green clearance at 15 minutes, %		
< 15	0	0
15-40	21	70
40-50	5	17
> 50	4	13
Tumor size, mm		
Median	45	
Range	25-82	
20-50	19*	63
> 50	11	37
Macroscopic vascular invasion		
Yes	12	40
No	18	60
Morphology of primary tumor		
Single nodular	26	87
Multinodular, aggregating	1	3
Diffuse	2	7
Portal vein tumor thrombosis	1*	3
Serum alpha-fetoprotein level, ng/mL		
< 300	21	70
≥ 300	9	30
Histology		
Well-differentiated	10	33
Moderately differentiated	14†	47
Poorly differentiated	2	7
Differentiation not specified	3	10
Negative (radiologic diagnosis only)	1	3
Prior treatment		
No	13	43
Recurrence	6	20
Local ablation/TACE	11	37

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.
*Includes one patient whose gross target volume was tumor thrombosis at the posterior branch of right portal vein as a result of postsurgical recurrence.
†Includes two patients with histological diagnoses that were defined in previous surgery.

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listed in Table 1. All patients had underlying liver cirrhosis with an initial ICG R15 value of ≥ 15%. Thirteen patients received PRT as a first treatment for their HCC. Six patients had postsurgical recurrences, and 11 received unsuccessful local ablation and/or TACE to the targeted tumor before PRT. Histologic confirmation was not obtained in one patient who had tumor with typical radiographic features compatible with HCC. Vascular invasion was diagnosed as positive in 12 patients. Three patients had HCC of ≤ 3 cm in diameter; however, they were not considered as candidates for local ablation therapy because of tumor locations that were in close proximity to the great vessels or the lung.

Adverse Events

All patients completed the treatment plan and received 76 Gy_E in 20 fractions of PRT with a median duration of 35 days (range, 30 to 64 days). Prolongation of overall treatment time of more than 1 week occurred in four patients: three were due to availability of the proton beam, and one because of fever associated with grade 3 elevation of total bilirubin that spontaneously resolved within 1 week. Adverse events within 90 days from commencement of PRT are listed in Table 2. Decrease of blood cell count was observed most frequently. A total of 10 patients experienced transient grade 3 leukopenia and/or thrombocytopenia without infection or bleeding necessitating treatment. Of note, eight of them already had leuko- and/or thrombocytopenia, which could be ascribable to portal hypertension, before commencement of PRT corresponding to grade 2 in terms of the NCI-CTC criteria. Because none of the five patients experiencing grade 3 elevation of transaminases showed clinical manifestation of hepatic insufficiency and maintained good performance status, PRT was not discontinued. Nevertheless, these events spontaneously resolved within 1 to 2 weeks.

Development of hepatic insufficiency within 6 months after completion of PRT was defined as proton-inducing hepatic insufficiency (PHI), and this was observed in eight patients. Causal relationship between PHI and several factors are described separately below. One patient developed transient skin erosion at 4 months that spontaneously resolved within 2 months. Another patient developed painful subcutaneous fibrosis at 6 months that required nonsteroidal analgesics for approximately 12 months thereafter. Both of these skin changes developed at the area receiving ≥ 90% of the prescribed dose because the targeted tumors were located at the surface of the liver adjacent to the skin. However, they remained free from refractory ulcer, bleeding, or rib fracture.

Table 2. Adverse Events Within 90 Days From the Start of Proton Beam Radiotherapy

Grade	0	1	2	3	4
Leukopenia	7	2	13	8	0
Thrombocytopenia	2	6	15	7	0
Total bilirubin	20	2	7	1	0
Transaminases	4	8	13	5	0
Nausea/anorexia	23	7	0	0	0
Overall (maximum grade)	0	4	14	12	0

There were no observations made of gastrointestinal or pulmonary toxicity of grade 2 or greater in all patients. In addition, after percutaneous insertion of metallic markers, no serious adverse events, including bleeding or tumor seeding along the needle tracts, were observed.

Tumor Control and Survival

At the time of analysis on November 2003, 12 patients had already died because of intrahepatic recurrence of HCC in seven, distant metastasis in two, and hepatic insufficiency without recurrence in three. Eleven of these 12 patients had been free from local progression until death; the durations ranged from 6 to 41 months (median, 8 months). One patient who had a single nodular tumor of 4.2 cm in diameter experienced local recurrence at 5 months and subsequently died of multifocal intrahepatic HCC recurrence. Otherwise, 18 patients were alive at 16 to 54 months (median, 31 months) without local progression. A total of 24 patients achieved complete disappearance of the primary tumor at 5 to 20 months (median, 8 months) post-PRT. Five had residual tumor mass on CT and MRI images for 3 to 35 months (median, 12 months) until the time of death (n = 4) or until last follow-up at 16 months (n = 1). As a whole, 29 of 30 enrolled patients were free from local progression until death or last follow-up, and the local progression-free rate at 2 years was 96% (95% CI, 88% to 100%). Tumor regression was associated with gradual atrophy of the surrounding noncancerous portion of the liver that initially suffered from radiation hepatitis,[20] as shown in Figure 1.

A total of 18 patients developed intrahepatic tumor recurrences that were outside of the PTV at 3 to 35 months (median, 18 months) post-PRT. Five of these occurred within the same segment of the primary tumor. Eight patients received TACE, and four received radiofrequency ablation for recurrent tumors; however, six did not receive any further treatment because of poor general condition in three and refusal in three. Five died without intrahepatic recurrence. Seven patients remained recurrence-free at 16 to 39 months (median, 35 months). Actuarial overall survival rates were 77% (95% CI, 61% to 92%), 66% (95% CI, 48% to 84%), and 62% (95% CI, 44% to 80%), and disease-free survival rates were 60% (95% CI, 42% to 78%), 38% (95% CI, 20% to 56%), and 16% (95% CI, 1% to 31%) at 1, 2, and 3 years, respectively (Fig 2).

Correlation of Survival With Prognostic Factors

Overall survival was evaluated according to 10 factors as listed in Table 3. Univariate analyses revealed that factors

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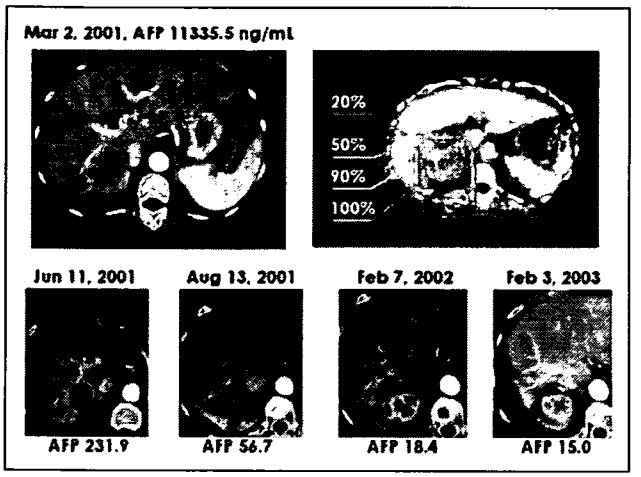

Fig 1. Case presentation: 70-year-old woman who received proton radiotherapy of 76 Gy in 20 fractions for 37 days from April 2, 2001, for her tumor located at the right posterior segment of the liver (left upper panel). Dose distribution was demonstrated in the right upper panel. Two portals from posterior and right lateral directions were used.

related to functional reserve of the liver and tumor size had significant influences on overall survival ($P < .05$). Liver function was the only independent and significant prognostic factor by multivariate analysis, as presented in Table 3. When clinical stage or Child-Pugh classification was substituted for ICG R15 as a covariate for liver function, the results of multivariate analyses were unchanged (data not shown). Overall survival according to pretreatment ICG R15 is shown in Figure 3.

Estimation of the Risk of Proton-Inducing Hepatic Insufficiency by Dose-Volume Histogram Analysis

Eight patients developed PHI and presented with ascites and/or asterixis at 1 to 4 months after completion of PRT, without elevation of serum bilirubin and transaminases in the range of more than 3× the upper limit of normal. Of these, four died without evidence of intrahepatic tumor recurrence at 6 to 9 months; three died with recurrences of HCC at 4, 8, and 22 months; and one was alive at 41 months without tumor recurrence. DVH for hepatic noncancerous portions (entire liver volume minus gross tumor volume) was drawn according to pretreatment ICG R15 values (Fig 4A to C). The results showed that all of the nine patients with ICG R15 less than 20% were free from PHI and alive at 14 to 54 months. Three of the four patients with pretreatment ICG R15 ≥ 50% experienced fatal PHI without evidence of HCC recurrence, and another patient died of PHI with intrahepatic and systemic dissemination of HCC at 4 months. Among patients whose ICG R15 values ranged from 20% to 50%, all of the four patients whose percentage of hepatic noncancerous portions receiving ≥ 30 Gy_E (V_{30}%) exceeded 25% developed PHI. On the other hand, none of the patients whose V_{30}% was less than 25% experienced PHI, as shown in Figure 4B ($P = .044$, Mann-Whitney U test). Three-year overall survival for patients with either the V_{30}% ≥ 25% or ICG R15 ≥ 50% (n = 9) was 22% (95% CI, 0% to 50%), whereas it was 79% (95% CI, 60% to 98%) for the remaining 21 patients with favorable risk ($P = .001$).

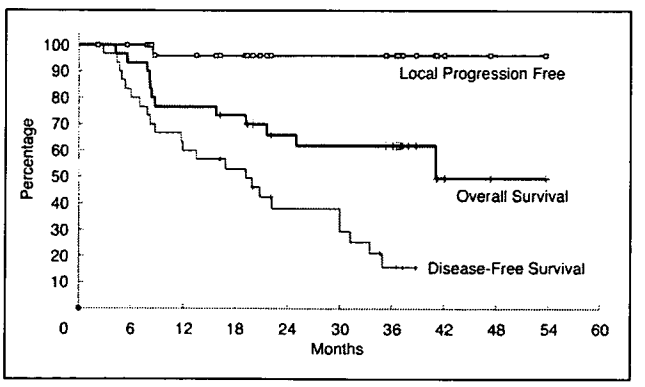

Fig 2. Kaplan-Meier estimate of local progression-free, overall, and disease-free survival rates for all 30 patients enrolled.

DISCUSSION

The principal advantage of PRT lies in its possibility of aggressive dose escalation without prolongation of treatment duration in order to improve local control rate. The liver will be the most appropriate organ for this approach because it has a unique characteristic of developing compensatory hypertrophy when a part of this organ suffers from permanent damage. This study showed that the local control rate of PRT alone for patients with advanced HCC was consistent, as previously reported.[14] Slow regression of tumor volumes associated with gradual atrophy of surrounding noncancerous liver tissue was also in agreement with a previous report.[20] No serious gastrointestinal toxicity occurred, with careful patient selection performed in order to exclude these structures from PTV receiving high PRT dose. Eligibility criteria as to blood cell count in this study were eased up considerably in order to test the safety of PRT for patients with cirrhosis associated with portal hypertension. Nevertheless, no patients experienced serious sequelae relating to leukopenia or thrombocytopenia, which were the most frequently observed adverse events during PRT. All patients were able to complete their PRT basically in an outpatient clinic. Therefore we submit that the safety, accuracy, and efficacy of PRT administering 76 Gy_E/5 weeks using our newly installed Proton Therapy System and ReGIS for selected patients with advanced HCC has been confirmed.

Multivariate analysis suggested that the the functional reserve of the liver had significant influence on overall survival. Recent prospective series of untreated patients with

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Table 3. Factors Related to Overall Survival

Factor	No. of Patients	Overall Survival at 2 Years (%)	Univariate *P*	Multivariate *P*	Hazard Ratio	95% CI
Age, years			.263	.665	1.54	0.22 to 10.75
< 70	15	59				
≥ 70	15	71				
Sex			.829	.732	1.44	0.18 to 11.65
Male	20	67				
Female	10	60				
Tumor size, mm			.045	.159	0.34	0.08 to 1.52
20 to 50	19	71				
> 50	11	44				
Pretreatment ICG R15			.006	.026	0.19	0.05 to 0.82
≤ 40%	21	80				
> 40%	9	30				
Clinical stage			< .001			
I	9	73				
II	19	68				
III	2	0				
Child-Pugh classification			.006			
A	20	78				
B	10	38				
Vascular invasion			.930	.650	1.44	0.30 to 7.03
Yes	12	67				
No	18	66				
Serum AFP level, ng/mL			.313	.061	0.20	0.04 to 1.07
< 300	21	67				
≥ 300	9	60				
V_{30}%			.213	.141	0.25	0.04 to 1.58
≤ 25%	24	65				
> 25%	6	40				
Prior treatment			.455	.091	3.63	0.82 to 16.18
No	13	69				
Recurrence	17	60				

Abbreviations: ICG R15, percentage of indocyanine green clearance at 15 minutes; AFP, alpha-fetoprotein; V_{30}%, percentage of hepatic noncancerous portion receiving ≥ 30 cobalt gray equivalent.

advanced HCC and underlying cirrhosis showed that overall survival rate at 3 years ranged from 13% to 38%, and rarely exceeded 50% even for those with most favorable prognostic factors.[1] In this study, actuarial overall survival rate at 3 years for all 30 patients including those who had HCC with vascular invasion and/or severe cirrhosis was 62%. Furthermore, 21 patients with initial ICG R15 of ≤ 50% and V_{30}% of ≤ 25% achieved 79% of overall survival rate at 3 years. All of the eight patients with favorable liver functional reserve (ICG R15, 15% to 20%) were alive at 20 to 54 months as shown in Figure 3. This suggests that adequate local control with PRT provides survival benefit for selected patients with HCC and moderate cirrhosis. On the other hand, prognoses of aggressive PRT were disappointing for patients, with poor functional liver reserve showing an ICG R15 of 50% or worse, and, therefore, indication of PRT for such patients was thought to be extremely limited.

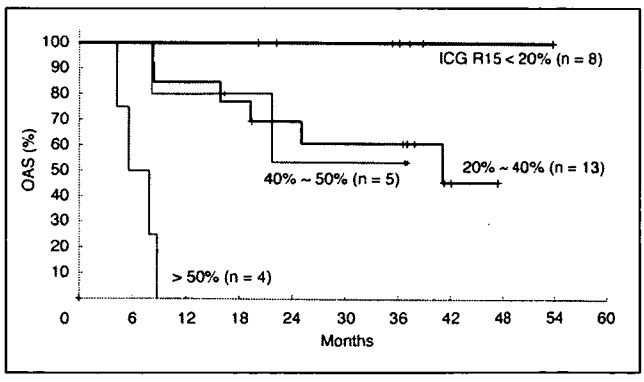

Fig 3. Overall survival (OAS) rates according to pretreatment indocyanine green clearance at 15 minutes (ICG R15).

A part of noncancerous liver suffering from PRT-inducing hepatitis gradually developed dense fibrosis and resulted in almost complete atrophy,[20] whereas the absorbed dose in a large proportion of the remaining liver was 0 Gy_E, as shown in Figures 1 and 4. This change is similar to

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