Early cancer-related death after resection of hepatocellular carcinoma

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Early cancer-related death after resection of hepatocellular carcinoma

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Background. *Surgeons have attempted to prevent early cancer-related death after resection of hepatocellular carcinoma to identify risk factors associated with early death from hepatocellular carcinoma recurrence after liver resection.*
Methods. *The study group comprised 350 patients who had undergone liver resection for hepatocellular carcinoma between 1997 and 2007. The preoperative risk factors for early death from intrahepatic recurrence (within 1 year after resection) were evaluated.*
Results. *Fourteen (4%) patients died of intrahepatic recurrence in the first year after resection. Multivariate analyses identified the following risk factors for early cancer-related death: multiple tumors (odds ratio 10.4; 95% confidence interval, 2.42–44.3;* P = *.002), vascular invasion (odds ratio 10.1; 95% confidence interval 2.07–50;* P = *.004), serum alpha-fetoprotein level >20 ng/mL (odds ratio 9.52; 95% confidence interval 1.0—84.2;* P = *.043), and tumor size ≥50 mm (odds ratio 4.80; 95% confidence interval 1.06–21.9;* P = *.042). Each of these factors was assigned a score of 1 point, and an algorithm was developed to predict the risk of early death. Outcomes did not differ significantly between patients with 3 or 4 points (*P = *.48) or between those with 1 or 2 points (*P = *.49). Patients who underwent liver resection could be stratified into the following distinct groups according to the point score and the associated 1-year survival rate and median survival (shown respectively): 0 points, 99%, and not yet; 1 or 2 points, 96%, and 68 months; and 3 or 4 points, 50%, and 12 months) (*P < *.0001).*
Conclusion. *Even if hepatocellular carcinoma is resectable, patients with a score of 3 or 4 points may not be good candidates for liver resection. (Surgery 2012;151:232-7.)*

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HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common type of cancer, and its incidence is increasing worldwide.[1] One curative treatment for HCC is surgical resection, which is now a safe option with a low surgical mortality.[2] Improved diagnostic procedures, surgical techniques, and perioperative management have contributed to better outcomes of liver resection, even in patients with more advanced, resectable HCC; however, the high rate of recurrence even after curative resection (70–80% at 5 years[3]) remains an important problem. Disease frequently recurs (20–40%) within 1 year after liver resection,[2] and the rate of cancer-related death within 1 year is 9.7%.[4] Advanced HCC is associated with particularly bleak outcomes after resection.[5]

Several studies have proposed indications and selection criteria for liver resection.[6,7] Liver resection has been preferred because it is associated with longer survival than that obtained with palliative treatments. Treatments such as radiofrequency ablation (RFA) and endovascular therapy, however, including transcatheter arterial chemoembolization (TACE) and hepatic arterial infusion (HAI), recently have extended survival.[8-10]

Indications for hepatic resection also should be reconsidered if an appreciable proportion of patients, including those with resectable tumors, die in the early term after liver resection.

The aim of this cohort study was to identify preoperative risk factors for early cancer-related death (≤1 year after liver resection) from intrahepatic recurrence in Japanese patients who underwent liver resection for HCC.

METHODS

Study population. From January 1997 through December 2007, 472 patients underwent a first

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liver resection for HCC. Patients with any of the following conditions were excluded: extrahepatic tumor extension or metastasis, nodal metastasis, both conditions, or advanced cancer in another organ (n = 29); ruptured HCC (n = 4); loss to follow-up within 1 year (n = 53); refusal of treatment (n = 25); death from unknown causes within 1 year (n = 4); or death within 30 days after operation (n = 7). We retrospectively analyzed 350 adult patients who underwent curative liver resection.

Study design. The following factors were assessed on preoperative imaging studies: extensive portal vein invasion (invasion of second- or first-order branches of the portal vein), the number of tumors, and the size of the largest tumor. Liver function was assessed based on Child–Pugh class, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, and indocyanine green retention at 15 minutes (%). In addition, the serum AFP level was measured.

Liver resection. Curative liver resection was defined as no evidence of residual tumor in the remnant liver on intraoperative ultrasonography (US), with a pathologically proven negative surgical margin. Anatomical resection of Couinaud's segment on intraoperative US[7] was the preferred operative procedure, if permitted by the patient's liver functional reserve. All other types of resection, such as limited resection and tumor enucleation, were classified as nonanatomical resection.[11]

The decision to perform liver resection for HCC was based on the following criteria: liver function and tumor status. Liver function was classified according to Makuuchi's criteria.[12] As for tumor status, liver resection was indicated if all 3 of the following conditions were met: (1) no more than 3 tumors, (2) no distant metastasis, and (3) the portal trunk was not occluded by tumor thrombus.

Statistical analysis. The endpoint of this study was the time to death, defined as the period from the date of initial liver resection to the date of death from intrahepatic recurrence. Patients who died for reasons unrelated to intrahepatic recurrence were excluded from the early death group.

We examined factors contributing to early death (ie, death within 1 year after initial liver resection) and nonearly death (ie, death after 1 year or longer). Fisher's exact probability tests and χ^2 analysis were used to compare categorical variables. Logistic regression analysis was used for multivariate analysis of risk factors. Survival was calculated according to the Kaplan–Meier method. Differences in survival were assessed with the log-rank test. All statistical analyses were performed using SPSS statistical software (SPSS Inc., Chicago, IL), version 17.0. P values of <.05 were considered to indicate statistical significance. All follow-up data were summarized as of the end of August 2009. This study was deemed exempt from review by the Nihon University School of Medicine Institutional Review Board.

RESULTS

Baseline characteristics of patients. The baseline characteristics of the patients are summarized in Table I. The mean age of the patients was 66 years. The median size of the largest tumor was 31 mm (range, 4–160); 26% of the tumors were ≥50 mm in diameter. Most patients (78%) had solitary tumors, and nearly all (95%) had no vascular invasion on preoperative imaging. The disease stage according to the tumor-node-metastasis classification was stage I in 264 patients (75%), stage II in 62 patients (18%), and stage IIIA in 24 patients (7%). Median follow-up time was 38 months (range, 2.2–140). The median serum alpha-fetoprotein (AFP) level was 17 ng/mL (range, 1–320,800).

Postoperative early death. Twenty-one patients died within 1 year postoperatively. The cause of death was intrahepatic recurrence in 14 patients, and the median period from liver resection to intrahepatic recurrence was 3 months (range, 1–7).

The causes of death in the other 7 patients were liver failure (3 patients), upper gastrointestinal bleeding (1 patient), acute hepatitis (1 patient), and other illnesses (2 patients).

Risk factors for early cancer-related death. The overall median survival was 75 months. Survival rates at 1, 3, and 5 years were 94%, 83%, and 64%, respectively. Fourteen (4%) patients died of intrahepatic recurrence within 1 year. The prognostic relevance of 11 baseline variables was examined by univariate analysis (Table I). The following factors were associated with an increased probability of death from intrahepatic recurrence within 1 year after resection: multiple tumors (P < .0001), vascular invasion (P < .0001), serum AFP level >20 ng/mL (P < .001), and tumor size ≥50 mm (P = .001). Multivariate logistic regression analysis identified the same 4 factors, including the following: multiple tumors (odds ratio [OR] 10.4; 95% confidence interval [95% CI] 2.42–44.3; P = .002), vascular invasion (OR 10.1; 95% CI 2.07–50; P = .004), serum AFP level >20 ng/mL (OR 9.52; 95% CI 1.08–84.2; P = .043), and tumor size ≥50 mm (OR 4.80; 95% CI 1.06–21.9; P = .042) (Table II). Descriptive survival statistics and Kaplan–Meier curves suggested that multiple tumors, vascular invasion, serum AFP level,

Table I. Patient characteristics

Variable	*Early death*	*Nonearly death (n = 336)*	P *value*
Sex (male/female)	11/3	266/70	.957
Age (years)			.174
<65	8	131	
≥65	6	205	
Etiology			.142
HCV	5	211	
HBV	6	68	
Non B non C	3	51	
Other	0	6	
Child–Pugh class			.366
A	13	326	
B	1	10	
Tumor number			<.0001
Single	3	269	
Multiple	11	67	
Largest tumor size (mm)			<.0001
<50	3	255	
≥50	11	81	
Vascular invasion			<.0001
Negative	7	325	
Positive	7	11	
α-fetoprotein (ng/mL)			<.0001
≤20	1	183	
≥20	13	153	
ICG15R (%)			.088
<10	8	117	
≥10	6	219	
ALT (IU/L)			.277
<40	4	153	
≥40	10	183	
AST (IU/L)			.586
<40	5	151	
≥40	9	175	

ALT, Alanine aminotransferase; *AST*, aspratate aminotransferase; *ICG15R*, indocyanine green retention at 15 min.

and tumor size had prognostic significance, even within this relatively selective cohort. Multiple tumors, vascular invasion, serum AFP level >20 ng/mL, and tumor size ≥50 mm were associated with a decrease in the 1-year survival rate from 97% to 82% (Fig 1, *A*), 96% to 56% (Fig 1, *B*), 98% to 90% (Fig 1, *C*), and 97% to 87% (Fig 1, *D*), respectively (Table III).

Grouping by number of risk factors. An algorithm then was developed to stratify patients with HCC according to the risk of death from early recurrence after liver resection. Given that multiple tumors, vascular invasion, serum AFP level >20 ng/mL, and tumor size ≥50 mm had similar effects on early cancer-related death, 1 point was allotted for each of these risk factors. Only 7 patients had a score of 4 points, and the outcomes of patients with scores of 3 (n = 15) or 4 points were similar (P = .48), as were the outcomes of patients with 1 (n = 131) or 2 points (n = 73) (P = .49). Patients with scores of 1 or 2 points and those with scores of 3 or 4 points were, therefore, combined into single groups. The 3 resulting groups (0 points, 1 or 2 points, and 3 or 4 points) had the following distinct 1-year survival rates (95% CI) and median survival (95% CI): 0 points (n = 124), 99% (range, 97–100%) and not yet; 1 or 2 points (n = 204), 96% (range, 93–99%), and 68 months (range, 60–77 months); and 3 or 4 points (n = 22), 50% (29–71%), and 12 months (range, 7–16 months) (Fig 2, *A* and *B*).

Table II. Multivariate analysis

Variable	*Odds ratio*	*95% CI*	P *value*
Multiple tumor	10.4	2.42–44.3	.002
Vascular invasion (+)	10.2	2.07–50.0	.004
AFP >20 ng/mL	9.52	1.08–84.2	.043
Tumor size ≥50 mm	4.80	1.06–21.9	.042

Patients with 3 or 4 risk factors who survived for longer than 1 year. Eleven patients with 3 or 4 points survived for longer than 1 year. Nine patients had recurrence in the remnant liver. Five of these patients died of recurrence within 3 years. At the time of this writing, 2 patients are still alive, 15 and 27 months after liver resection, respectively. Only 2 patients who received reliver resection and TACE survived for 5 years or longer. The other 2 patients have survived without recurrence for 13 and 23 months, respectively.

DISCUSSION

In this study, we identified 4 risk factors (multiple tumors, vascular invasion, tumor size ≥50 mm, and serum AFP level >20 ng/mL) for early death from intrahepatic recurrence after curative resection of HCC.

Regimbeau et al reported that a tumor size of greater than 5 cm, multiple tumors, and more than 5 mitoses per 10 high-power fields were associated with an increased risk of early death because of recurrence.[4] Kondo et al showed that microscopic vascular invasion was a significant risk factor for death within 2 years after operative therapy in patients with solitary HCC.[13] These previous studies, however, considered only factors that could be assessed intraoperatively or postoperatively. Such factors are not useful for selecting the best treatment. We therefore evaluated the relation of only preoperative factors to early cancer-related death.

Multiple tumors are classified as multicentric tumors and intrahepatic metastasis according to their origin. Intrahepatic recurrence within 1 year

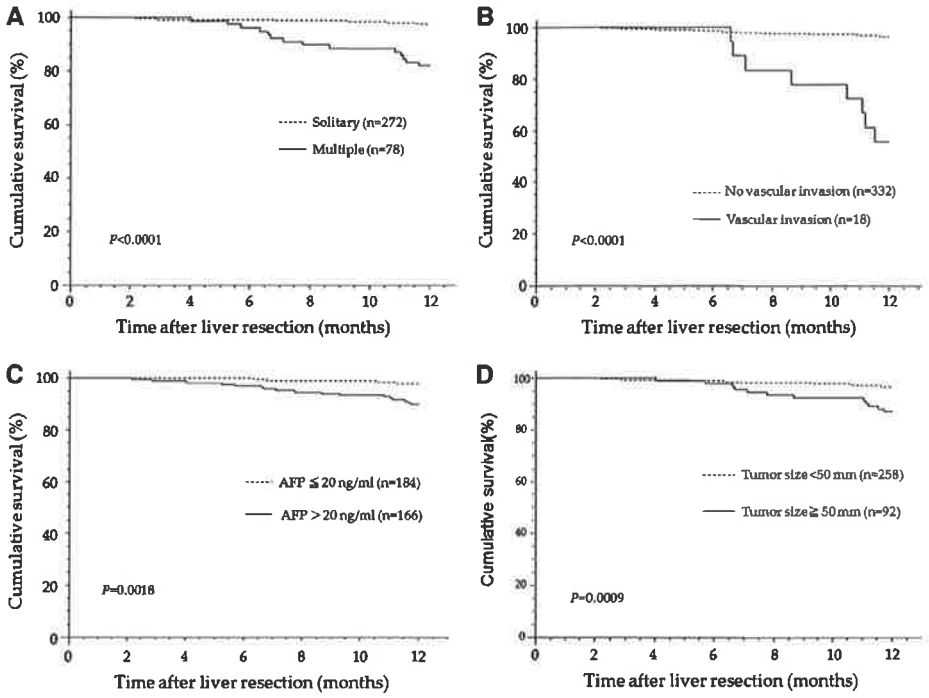

Fig 1. Kaplan-Meier survival estimates within 1 year after resection. (*A*) Stratified according to solitary or multiple tumors. (*B*) Stratified according to the presence of absence of vascular invasion. (*C*) Stratified according to the serum AFP level. (*D*) Stratified according to tumor size.

Table III. Survival statistics

		1-year survival		*Median survival*		
Variable	n	*Percent*	*95% CI*	*Months*	*95% CI*	P *value*
Overall	350	94	91–97	75	66–84	
Multiple tumor						<.0001
Yes	78	82	91–74	53	50–65	
No	272	97	99–95	80	65–95	
Vascular invasion						<.0001
Yes	18	56	79–33	14	0–67	
No	332	96	98–94	75	65–85	
Serum AFP level						<.0001
≤20 ng/mL	184	98	100–96	80	61–99	
≥20 ng/mL	166	90	95–85	63	55–72	
Tumor size						.001
<50 mm	258	97	99–94	77	57–97	
≥50 mm	92	87	94–80	59	41–78	

after operative therapy may be caused by intrahepatic metastasis.[14] Clinically occult metastasis of HCC present at the time of operation probably become detectable during follow-up. Shimada et al confirmed the invasion of the portal venous system in 57 (71%) of 80 patients with multinodular HCC who were positive for hepatitis C virus and had intrahepatic metastasis. Moreover, patients with intrahepatic metastasis had poorer outcomes than those with multicentric tumors.[15] A pathological diagnosis, however, is needed to distinguish between intrahepatic metastasis and multicentric tumors, and preoperative assessment is currently not feasible. Some investigators have reported that a tumor size of >5 cm is of prognostic importance only in patients with multiple tumors.[16] Pawlik et al reported that vascular invasion increased in parallel with tumor size and that the presence of vascular invasion indicated a poor prognosis.[17] Intrahepatic metastasis, portal vein

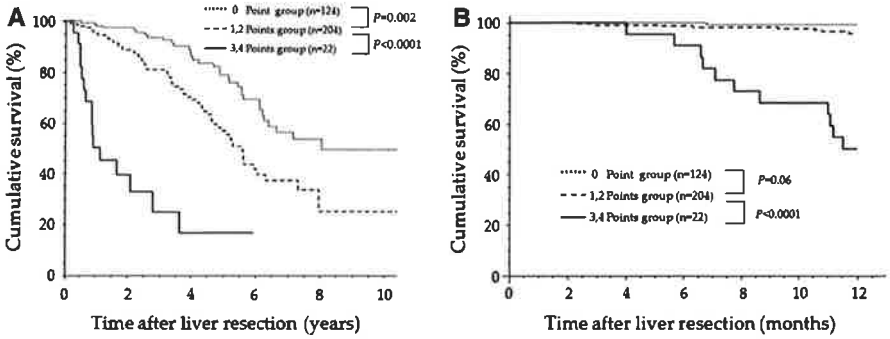

Fig 2. (*A*) Cumulative survival of patients according to the risk-factor score. The 3 groups (0 points, 1 or 2 points, and 3 or 4 points) had distinct 1-year survival rates and median survival (shown respectively): 0 points, 99% and not yet; 1 or 2 points, 96% and 68 months; and 3 or 4 points, 50% and 12 months. (*B*) Survival curve within 1 year after resection.

invasion, and tumor size thus may be interrelated. Farinati et al reported that the median survival of patients with HCC is related to serum AFP levels, with poorer survival in patients with higher AFP levels but with no clear prognostic impact in individual patients.[18] Among patients with 3 or 4 risk factors in our study, 11 patients (50%) survived longer than 1 year. Resection is not the treatment of first choice in patients with 3 or more risk factors; however, if other treatments are not effective, then resection should be reconsidered.

The question develops as to which treatments are best suited for patients with 3 or 4 factors. Apart from hepatic resection, treatment options include TACE, HAI, radiotherapy, and RFA. If survival after these less-invasive interventions were similar to that after liver resection, then use of the former probably would increase.

Major studies of TACE have yet to be performed in patients with 3 or 4 risk factors. Katumori et al reported a 1-year survival rate of 44% under the conditions that 8 of 9 patients (89%) had tumor thrombus in the first or second branch of the portal vein, the maximal tumor diameter was ≥50 mm, and 2 (22%) patients had multiple tumors.[19]

Intra-arterial 5-FU combined with subcutaneous interferon-alpha has been reported to be effective for advanced HCC. The 1-year survival rate was 34%, although all patients (n = 116) had portal venous invasion involving a major branch or the main trunk, the mean size of the intrahepatic HCC tumor was 8 cm in diameter, and 83% of patients had AFP levels of ≥20 ng/mL. Moreover, the 1-year survival rate was 43% in patients with a partial response (36%).[10]

Nakagawa et al obtained a 1-year survival rate of 45.1% in patients who received radiation therapy for portal venous invasion. Portal vein invasion was found in the first branch (24/52:46%) or main trunk (22/52:42%), tumor size was ≥50 mm in 19% of the patients, and multiple tumors were present in 75% of patients.[20]

RFA also has not been evaluated in major studies of patients with 3 or 4 risk factors; however, Hirooka et al obtained a 1-year survival rate of 89.7% in patients with large HCC who had portal vein thrombus (n = 20) and underwent RFA for mass reduction before HAI. Portal vein invasion was found in the major portal branch (14/20) or main portal trunk (6/20), the tumor size was 57.3 ± 20.9 mm, and AFP was elevated in that study.[21]

In the present study, patients with a score of 3 or 4 points were not good candidates for liver transplantation because disease was beyond the Milan criteria. Patients without vascular invasion, however, who fall within the up-to-7 criteria (HCC with 7 as the sum of the size of the largest tumor [in cm] and the number of tumors) have been shown to have good outcomes.[22] No patient who met the up-to-7 criteria had 3 or 4 risk factors.

In patients with 3 or 4 risk factors, there is no great difference in outcomes between liver resection and radiotherapy or RFA combined with TACE or HAI. Room exists for studying whether treatments other than liver resection can prolong long-term survival even in patients with 3 or 4 factors; however, given the risks and damage of resection, other treatments should be tried before resection in patients at risk for early cancer-related death. If such treatments are not effective, then liver resection can be performed. Because only 14 of the 350 patients studied had events, however, firm conclusions cannot be drawn. Our findings must be confirmed in larger, prospective studies.

In conclusion, even if HCC is resectable, whether to perform liver resection should be considered judiciously in patients who have 3 or

4 of the following factors: multiple tumors, vascular invasion, serum AFP level >20 ng/mL, and tumor size ≥50 mm.

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背景

肝細胞癌は世界中で一般的に見られる癌腫である。根治的治療のひとつとして切除が挙げられ、安全であり手術死亡率も低い。手術技術や周術期の管理の進歩により、より進行したものにも施行されているようになった。しかし再発は高率（5年再発率70~80%）であり重要な問題である。一般的に切除後1年以内の再発率は20~40%とされ、肝癌関連死は9.7%と報告されている。特に進行肝癌では顕著である。そのため肝切除の適応について、いくつかの研究がなされている。肝切除において、もし切除が可能でも切除後早期死亡例が含まれているなら再考しなければならない。肝切除において切除範囲と肝予備能は密接に関係しており、各々の症例においてかなりの差がある。肝切除量は術前の肝予備能に元ずいて決定され、安全域が決められる。そのひとつが幕内基準（表-1）であり肝切除量について腹水、総ビリルビン値、ICG（インドシアニングリーン）R15値によって手術適応なし、核出、部分切除、亜区域切除、区域切除・左肝切除、右肝切除・左3区域切除の6種類に分類されている。現在過度の肝切除によって術後早期の肝不全により死亡する例は少ない。そのため本研究では肝癌関連死のみについて検討した。

肝癌における肝切除は姑息的治療より長期生存をうるために施行される。最近、RFA（ラジオ波焼灼治療）やTACE（肝動脈化学塞栓療法）、HAI（肝動注療法）等が生存期間を延長している。また肝癌の治療において本邦ではまだ少数ではあるが肝移植も重要なひとつである。肝移植においてミラノクライテリア（脈管侵襲がなく単発なら5cm以内、又は3cm、3個以内）は移植の適応において重要であり基準のひとつである。

目的

本研究の目的は、切除後早期肝癌関連死（切除後 1 年以内に肝内再発で死亡）について検討し、術前危険因子を探査することである。

対象

1997～2007 年　日本大学消化器外科で初回肝切除を施行された 472 名より、肝外転移、または肝外進展、リンパ節転移、多臓器進行癌合併：29 名、破裂肝癌：4 名、1 年以上経過観察が不可例：53 名、再発後治療拒否：25 名、死因不明 1 年以内死亡：4 名、術後 30 日以内死亡：7 名（肝癌死はなかった）。をのぞいた根治的切除例 350 名。

方法

対象の 350 名について、術前に知りうる 11 項目：性別、年齢、病因、Child-Pugh 分類（総ビリルビン値、プロトロンビン、血清アルブミン値、腹水、肝性脳症が含まれる。）腫瘍個数（単発 vs 多発）、最大腫瘍径（<50 vs ≧50mm）、画像上の門脈侵襲（1、2 次分枝　陽性 vs 陰性）、Table 1 -3 における vascular invasion はいずれも門脈侵襲をさしている。

AFP(≦20 vs >20ng/ml)、ICG15R(<10 vs ≧10%)、ALT(<40 vs ≧40IU/L)、AST(<40 vs ≧40IU/L)について早期死亡群とそれ以外の群で比較した。

術前ＣＴ画像については肝癌のほとんどが結節型であり、肝癌取り扱い規約の肉眼分類においても単結節型、単結節周囲増殖型、多結節癒合型を正確に分類することは難しいと思われたため本研究の術前因子に加えなかった。

肝切除

肝切除については、残肝に癌がのこっていないこと、切除断端陰性であること、を術中超

音波検査と病理学的検査で証明した。肝予備能が良好ならクイノーの区域での切除を行い、そうでなければ幕内基準にのっとり切除した。もし肝切除の適応があれば腫瘍数が 3 個以内、遠隔転移なし、門脈本幹が腫瘍栓で閉塞していなければ切除とした。

統計分析

本研究のエンドポイントは、初回肝切除例における肝内再発による早期死亡であり、肝内再発に関係ない早期死亡は除いた。

早期死亡群（初回肝切除例における肝内再発による 1 年以内死亡）とそれ以外（非早期死亡群）との 2 群間比較について、カテゴリー比較においては Fisher's exact test と χ 2 検定を用い、危険因子の多変量解析には Logistic regression 解析を用いた。

生存については Kaplan-Meier 法を用い log-rank 検定で評価した。統計分析には SPSS version17.0 を使用。$P<0.05$ を有意差ありとした。

結果

患者背景を Table 1 に示す。平均年齢 66 歳、腫瘍径の中央値は 31mm、26%が 50mm 以上であった。78%は単発であり 95%の患者は術前画像で門脈侵襲を認めなかった。血清 AFP 値は中央値 17ng/ml であった。執筆時の UICC 第 7 版（表-2）による病期ステージは I ：264 名(75%) II ：62 名(18%) IIIA:27 名 (7%)。現在は第 8 版（表-3）に改訂されている。

また本邦での原発性肝癌取り扱い規約（日本肝癌研究会編）においても執筆時第 2 版（表-4）が現在では第 3 版（表- 5 ）に改訂されている。観察中央値は 38 か月。なお Table 1 の α-フェトプロテインについて≧20 は誤りであり正しくは＞20 である。

21名が1年以内に死亡したが肝内再発で死亡したものは14名であった。再発までの期間は中央値で3か月であった。肝内再発死以外の7名の死亡原因は、肝不全死3名、消化管出血1名，急性肝炎1名、他病死2名であった。

全体の生存中央値は75か月。1、3、5年累積生存率は各々94、83、64%であり、肝内再発による1年以内死亡は14名(4%)であった。予後因子として、11因子での単変量解析では多発腫瘍（P<.0001)、門脈侵襲（P<.0001)、血清ＡＦＰ値>20ng/ml（P<.001)、腫瘍径≧50mm（P=.001）が有意差ありとなり（Table 1)、多変量解析でも同様の4因子が残った（Table 2)。4因子各々のKaplan-Meier法による1年以内生存曲線をFig 1のA、B、C、Dに示す。また1年生存低下率は多発腫瘍で97から82%、脈管侵襲では96から56%、血清AFP値>20ng/mlは98から90%、腫瘍径≧50mmで97から87%であった(Table 3)。またTable3では各々の因子別に生存中央値が示されており、Fig ２Ａにおいては因子数別の全生存曲線が示されている。

早期死亡のアルゴリズムを構築するため、4因子の重み付けを考慮した。4因子の重み付けにおいては、腫瘍径≧50mmのオッズ比がほかの3因子より小さいため多発、門脈侵襲、血清AFP値を各々2点とし腫瘍径を1点とした場合4因子すべて満たすものは7点となり、3因子を満たすものは6点か5点となる。3因子を満たすものは15名しかおらず6点と5点では有意差を見出せなかった。そのため各々同様の重みと判断し各1点とした。4点は7名しかいなかった。3点は15名であった。4点と3点では生存に有意差がなく（P=.48）ま

た1点（131名）と2点（73名）も同様に有意差を認めなかった（P=.49）。よって1・2点と3・4点は各々1つのグループとした。最終的に3グループ（0点、1・2点、3・4点）に分類し検討した。各々グループの1年生存率（95%CI）、生存中央値(95%CI)を示す。

0点（124名）99%(97-100) 到達せず。1・2点（204名）96%(93-99) 68か月（60-77）。3・4点（22名）50%(29-71) 12か月（7-16）であった。Fig 2A、2BにKaplan-Meier法による全体と1年以内の生存曲線を示す。全体の生存において3・4点は0点、1・2点のグループより有意差をもっておとっていた。また1年以内生存においても同様であった。危険因子3・4点でも1年以上生存したものは11名。このうち9名は残肝再発し5名は3年以内に死亡した。のこり4名のうち2名は生存（15、27か月）し、また2名は再肝切除、TACEにて5年以上生存している。2名は再発なく13、23か月生存している。

考察

本研究にて肝癌治癒切除後の肝内再発による早期死亡について、多発腫瘍、門脈侵襲、腫瘍径≧50mm、血清AFP値>20ng/mlの4因子が危険因子として導きだされた。過去の研究においても腫瘍径≧50mm、多発、脈管侵襲核分裂像等が早期死亡の危険因子として報告されている。しかしこれらの因子のなかには術中、術後に明らかになるものが含まれ、最良の治療の選択に有用でない。我々は今回早期肝癌関連死において術前に知りえる因子のみを評価した。

多発腫瘍は多中心性と肝内転移に別けられる。肝切除後1年以内死亡においては肝内転移によるものと思われる。臨床的に手術時にはすでに存在したが目に見えなかった転移巣が

経過観察中に発見されると考えられる。

Shimada らは、HCV 陽性で肝内転移のある多発肝癌の 71%に門脈内侵潤が認められると報告している。肝内転移のある患者では多中心性のものより予後が悪いとされている。しかし肝内転移と多中心性病変の鑑別は病理学的診断が必要であり術前にはわからない。

多発腫瘍において、腫瘍径>5cm は予後に重要であるといういくつかの報告がある。Pawlik らは腫瘍径と脈管侵襲はパラレルであり予後不良であると報告しており、肝内転移、門脈侵襲、腫瘍径は関係しているのであろうと述べている。

Farinati らは血清 AFP 値が生存に関与していると報告している。AFP 高値は予後不良であるが、生存における影響は明らかでないとしている。

3・4 点の 11 名（50%）は 1 年以上生存したため、3 点以上の患者において、切除も治療の第一選択となりうる。しかしそれは他の治療の効果がない場合であり、そのとき再考されるべきである。それでは危険因子を 3 つ以上持った患者にとって最良の治療はなにか？

治療の選択枝として TACE、 HAI、放射線治療、RFA 等が挙げられる。低侵襲な治療が肝切除と同等の生存を可能とするならそのような治療が増えるであろう。TACE において危険因子が 3 つ以上のような症例での大規模研究はおこなわれていない。Katumori らは 9 人中 8 人（89%）が門脈 1 次、2 次分枝に腫瘍栓があり、最大腫瘍径≧50mm、くわえて 2 人（22%）は多発腫瘍であった症例において 1 年生存率は 44%と報告している。

5Fu の肝動注とインターフェロンαの皮下注の併用治療は進行肝癌に効果的であると報告

されている。門脈侵襲（本幹および1次分枝）全例、腫瘍径平均8cm、83%は血清AFP値≧20ng/mlでの116名の1年生存率は34%、PR例（36%)では43%であった。

Nakagawaらは門脈侵襲があるものに対し放射線治療をおこない1年生存率は45.1%としている。門脈侵襲については1次分枝（46%)、本幹（42%)。19%は腫瘍径≧50mm、75%の患者は多発腫瘍であった。

RFA治療について3・4点の症例を対照にした大規模研究は見当たらない。しかしHirookaらは門脈腫瘍栓をともなう大型肝癌20例に対し、肝動注前に腫瘍減量のためRFAを施行した患者の1年生存率は89.7%と報告している。門脈侵襲は1次分枝(14/20)本幹(6/20)、腫瘍径57.3±20.9mm、AFP値も上昇していた。

本研究における3・4点の症例は、ミラノクライテリア（脈管侵襲がなく単発なら5cm以内、又は3cm3個以内の肝癌）を逸脱しているため肝移植のよい適応とならなかった。

脈管侵襲がなく、up-to-7クライテリア（腫瘍径cmと腫瘍数をたしたものが7以下）を満たすものは、成績良好であるが本研究の3・4点では当てはまる症例が無かった。

以上より、本研究における3因子または4因子を満たす患者において肝切除、放射線治療、TACE、やHAIとRFAの併用治療は成績に大差を認めなかった。このような患者において、長期生存の可能性がある肝切除以外の治療が存在するなら、肝切除はリスクやダメージが大きいため別の治療を考慮しなければならない。もしそのような治療が効果なければ肝切除が考慮されるべきである。

本研究では350名のうち早期死亡例は14名に過ぎなかったため、結論を下すことはできない。大規模な前向き研究で結論を出すべきだろう。

また本研究における4因子を2013～2018年の症例にあわせてみたところ(本研究の対象は1997～2007年）全体351名において早期死亡は11名いた。また3因子以上に合致したのは24名であった。そのうち1年以内に死亡が確認できたものは6名にすぎなかった。理由については①研究の対象に約10年の差があり手術技術の向上もありより進行した肝癌を切除するようになった。②造影エコーやMRIの進歩により再発の早期発見技術の進歩。③RFA、DAA等の術後再発治療、C型肝炎治療の進歩。が考えられる。今後も新しい画像や検査を取り入れる必要があると思われる。

最近の早期再発死亡因子については、2019年にEuropean Radiology 29： 1231-1239において肝細胞癌のＣＴ画像におけるtexture analysis (Tex RADというソフトウエアー用いてCT画像よりその腫瘍のheterogeneityを解析する方法のひとつ)によりある程度予測がつけられると報告されている。

結論

もし切除が可能であっても多発、画像上の門脈侵襲、AFP>20ng/ml、腫瘍径≧50mmの4因子のうち3因子以上を満たしたものについて肝切除は慎重に判断しなければならない。

表-1 幕内基準

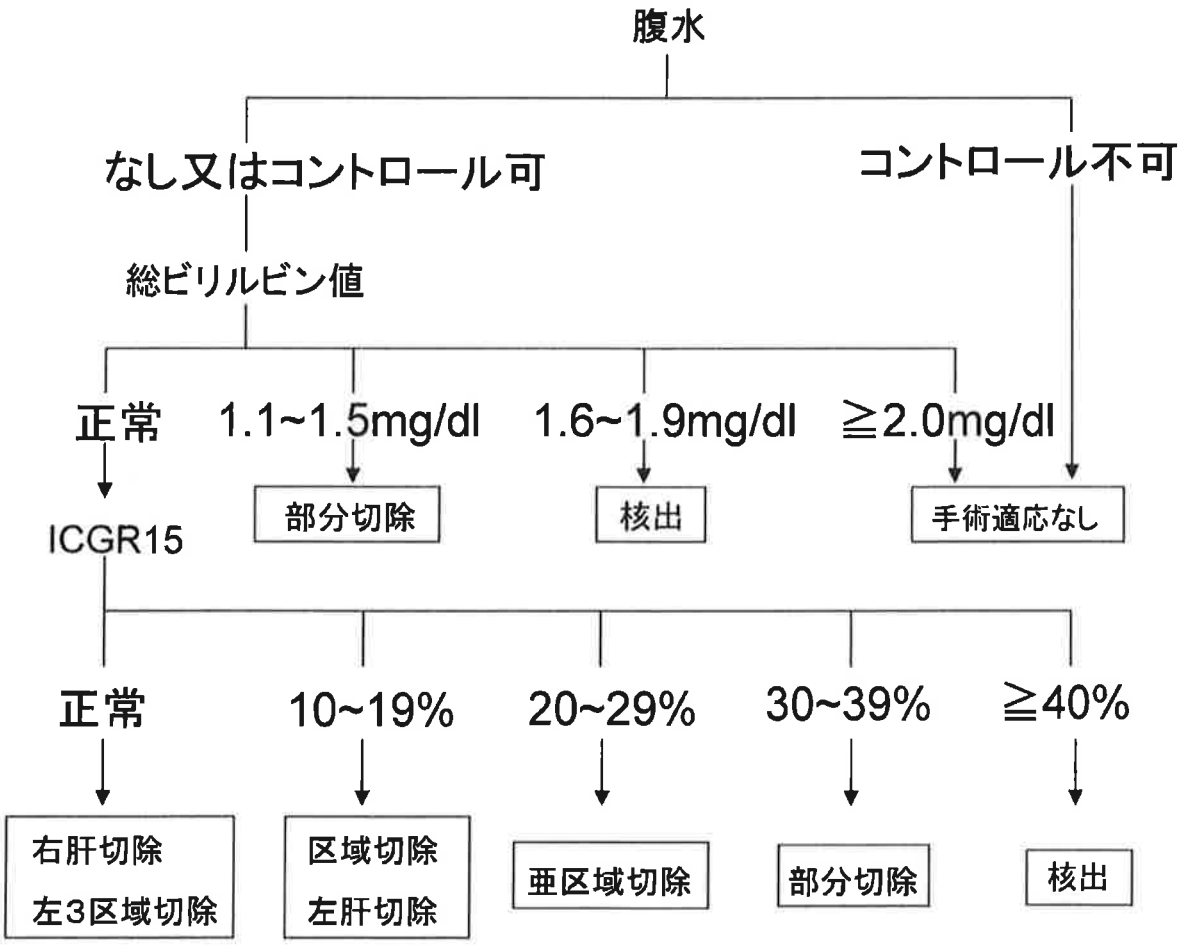

腹水
なし又はコントロール可
コントロール不可
総ビリルビン値
正常
1.1~1.5mg/dl
1.6~1.9mg/dl
≧2.0mg/dl
部分切除
核出
手術適応なし
ICGR15
正常
10~19%
20~29%
30~39%
≧40%
右肝切除
左3区域切除
区域切除
左肝切除
亜区域切除
部分切除
核出

表-2

Unio Internationalis Contra Cancrum:UICC 第7版

Ⅰ	T1	N0	M0
Ⅱ	T2	N0	M0
ⅢA	T3	N0	M0
ⅢB	T4	N0	M0
ⅢC	anyT	N1	M0
Ⅳ	anyT	anyN	M1

T1：単発、血管浸潤なし

T2：単発、血管浸潤あり　または　多発で5cm以下

T3:多発で＞5cm　または門脈（Vp3-4）、肝静脈（Vv2-3）、胆管（B2-4）に浸潤

T4：胆嚢以外の隣接臓器に直接浸潤あり

N1：肝門部、肝十二指腸間膜内

表-3

Unio Internationalis Contra Cancrum:UICC　第8版

ⅠA	T1a	N0	M0
ⅠB	T1b	N0	M0
Ⅱ	T2	N0	M0
ⅢA	T3	N0	M0
ⅢB	T4	N0	M0
ⅣA	anyT	N1	M0
ⅣB	anyT	N0,1	M1

T1a：単発、≦2cm

T1b：単発、2cm<　血管侵襲なし

T2: 単発で 血管侵襲(Vp1-2,またはVv1)あり　2cm< ／多発　≦5cm

T3: 多発　5cm<

T4: Vp3-4, Vv2-3 又は胆嚢以外の隣接臓器に直接浸潤。臓側腹膜を貫通。

N1：肝門部、肝臓(固有肝動脈に沿う)。傍門脈(門脈に沿う)。大静脈。

表-4

原発性肝癌取り扱い規約（日本肝癌研究会編）2003年第2版

Ⅰ	T1	N0	M0
Ⅱ	T2	N0	M0
Ⅲ	T3	N0	M0
ⅣA	T4	N0	M0
ⅣB	T1~4	N1	M0
		N0, N1	M1

T因子について

①単発　②大きさ2cm以下　③血管侵襲なし

T1　3因子すべてを満たす。

T2　2因子を満たす。

T3　1因子のみ満たす。

T4　すべて満たさない。

表-5

原発性肝癌取り扱い規約（日本肝癌研究会編）2010年第3版

Ⅰ	T1	N0	M0
Ⅱ	T2	N0	M0
Ⅲ	T3	N0	M0
ⅣA	T4	N0	M0
	T1~4	N1	M0
ⅣB	T1~4	N0,1	M1

T因子について

①単発　②大きさ2cm以下　③血管侵襲なし

T1　3因子すべてを満たす。

T2　2因子を満たす。

T3　1因子のみ満たす。

T4　すべて満たさない。

Table 1

Table 1. Patient characteristics

Variable	Early death (n=14)	Non-early death (n=336)	*P*
Sex (male/female)	11 / 3	266 / 70	0.957
Age (years)			0.174
＜65	8	131	
≧65	6	205	
Etiology			0.142
HCV	5	211	
HBV	6	68	
Non B non C	3	51	
Other	0	6	
Child-Pugh class			0.366
A	13	326	
B	1	10	
Tumor number			<0.0001
Single	3	269	
Multiple	11	67	
Largest tumor size (mm)			<0.0001
＜50	3	255	
≧50	11	81	
Vascular invasion			<0.0001
Negative	7	325	
Positive	7	11	
α-fetoprotein (ng/ml)			<0.0001
≦20	1	183	
＞20	13	153	
ICG15R(%)*			0.088
＜10	8	117	
≧10	6	219	
ALT(IU/L)†			0.277
＜40	4	153	
≧40	10	183	
AST(IU/L)‡			0.586
＜40	5	151	
≧40	9	175	

*indocyanine green retention at 15 minutes
† alanine aminotransferase ‡ aspartate aminotransferase

Table 2

Table 2. Multivariate analysis			
Variable	Odds ratio	95%CI	*P*
Multiple tumor	10.4	2.42 - 44.3	0.002
Vascular invasion (+)	10.2	2.07 - 50.0	0.004
AFP level >20 ng/ml	9.52	1.08 - 84.2	0.043
Tumor size≧50 mm	4.80	1.06 - 21.9	0.042
CI indicates confidence interval			

Fig 1A

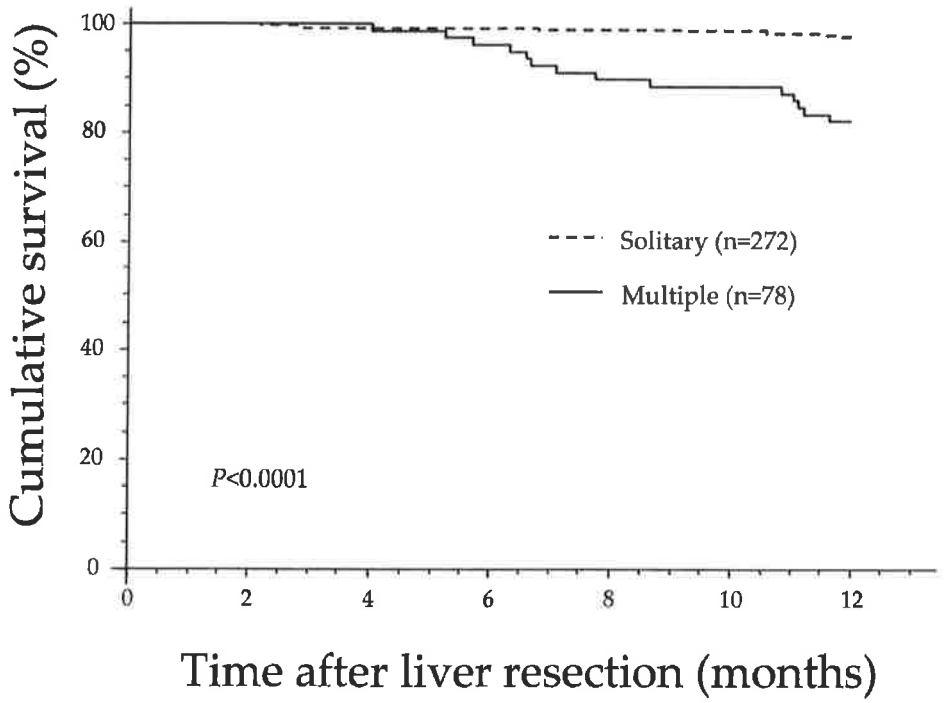

Cumulative survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Solitary (n=272)
Multiple (n=78)
P<0.0001
Time after liver resection (months)

Fig 1B

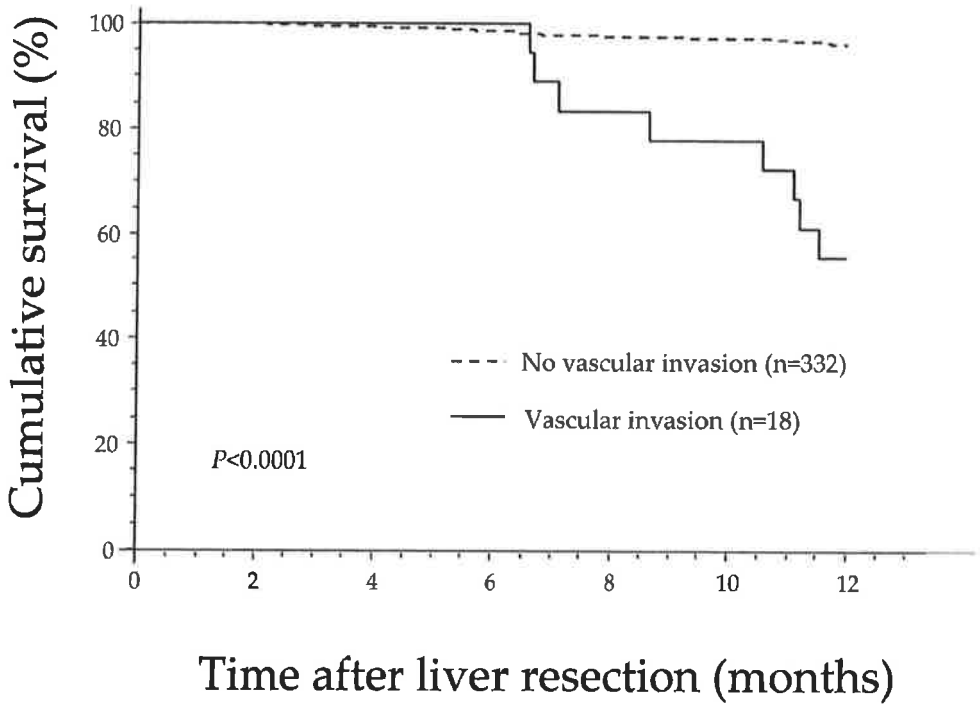

Cumulative survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
No vascular invasion (n=332)
Vascular invasion (n=18)
P<0.0001
Time after liver resection (months)

Fig 1C

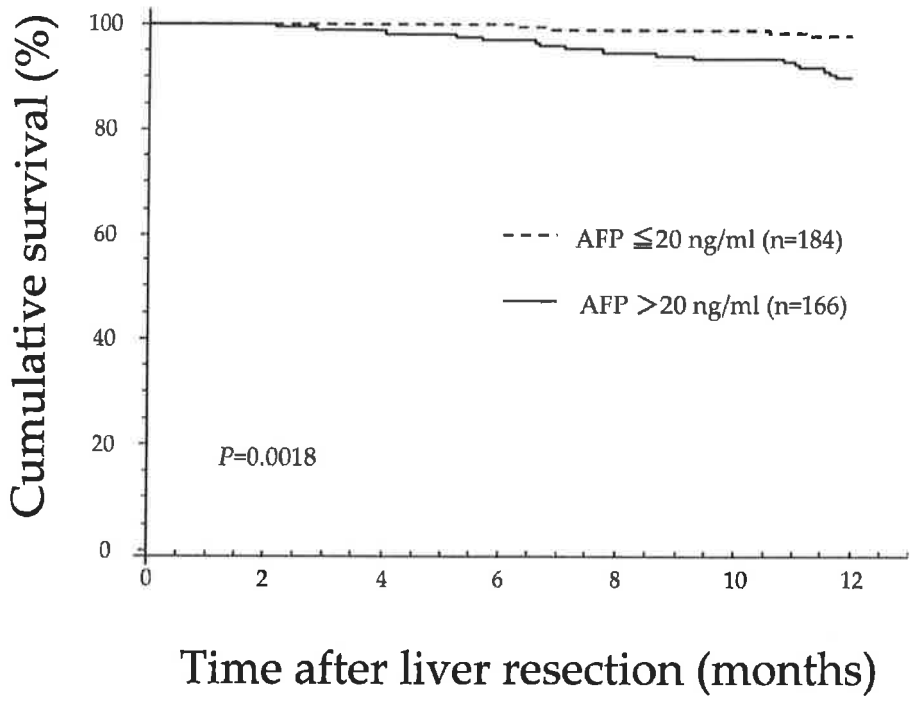

Cumulative survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
AFP ≦20 ng/ml (n=184)
AFP >20 ng/ml (n=166)
P=0.0018
Time after liver resection (months)

Fig 1D

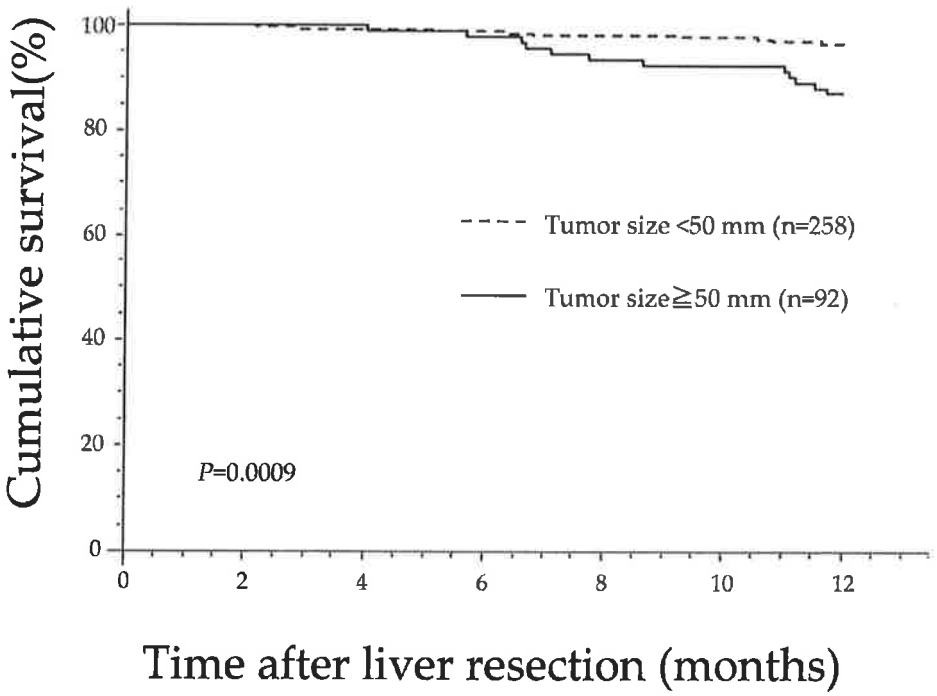

Cumulative survival(%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Tumor size <50 mm (n=258)
Tumor size≧50 mm (n=92)
P=0.0009
Time after liver resection (months)

Table 3

Table 3. Survival statistics

		1-year survival		Median survival		
Variable	n	Percent	95%CI	Months	95%CI	*P*
Overall	350	94	91-97	75	66-84	
Multiple tumor						<0.0001
Yes	78	82	91-74	53	50-65	
No	272	97	99-95	80	65-95	
Vascular invasion						<0.0001
Yes	18	56	79-33	14	0-67	
No	332	96	98-94	75	65-85	
Serum AFP level						<0.0001
≦20 ng/ml	184	98	100-96	80	61-99	
>20 ng/ml	166	90	95-85	63	55-72	
Tumor size						0.001
< 50mm	258	97	99-94	77	57-97	
≧50 mm	92	87	94-80	59	41-78	

CI indicates confidence interval

Fig 2A

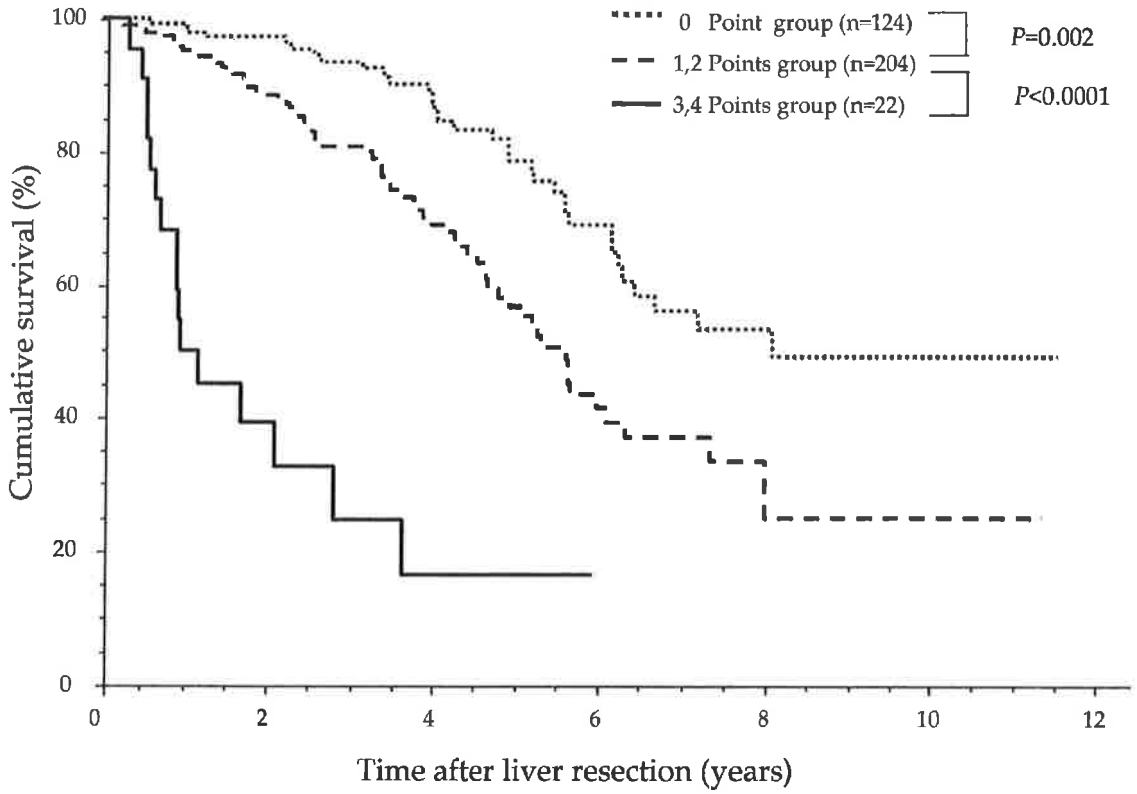
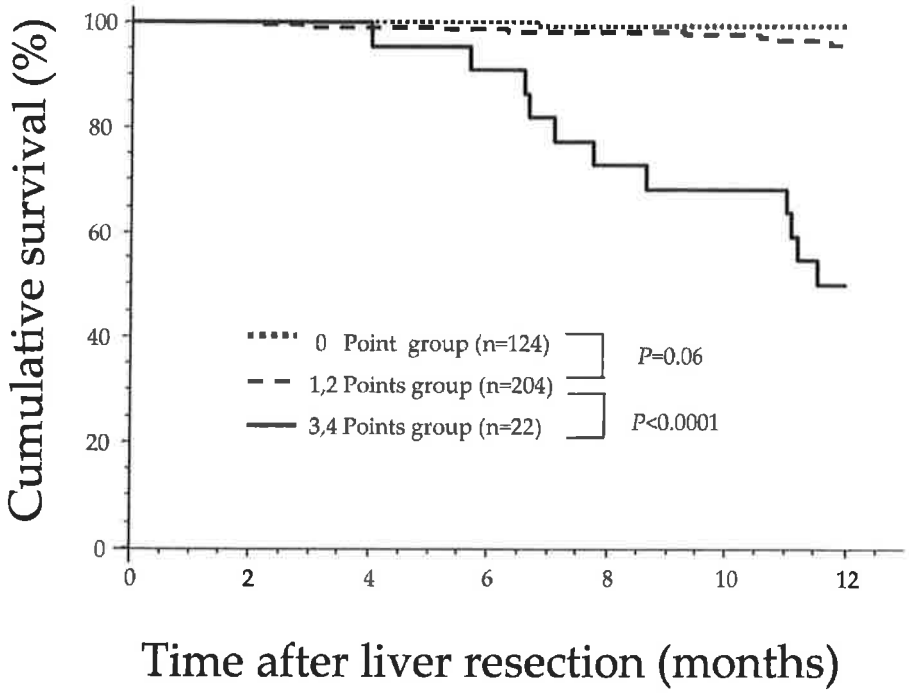

0 Point group (n=124)
1,2 Points group (n=204)
3,4 Points group (n=22)
P=0.002
P<0.0001
Cumulative survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Time after liver resection (years)

Fig 2B


Cumulative survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
0 Point group (n=124)
1,2 Points group (n=204)
3,4 Points group (n=22)
P=0.06
P<0.0001
Time after liver resection (months)