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Prognostic Factors After Hepatic Resection for Hepatocellular Carcinoma Associated With Child-Turcotte Class B and C Cirrhosis

Naofumi Nagasue, MD, Hitoshi Kohno, MD, Mitsuo Tachibana, MD, Akira Yamanoi, MD, Haruki Ohmori, MD, and Osama Nazmy El-Assal, MD

From the Second Department of Surgery, Shimane Medical University, Izumo, Japan

Objective

To evaluate prognostic factors after resection of hepatocellular carcinoma (HCC) in patients with Child-Turcotte class B and C cirrhosis.

Summary Background Data

Although hepatic resection remains the mainstay in the treatment of HCC and can be performed with low morbidity and mortality rates in patients without cirrhosis, its role is poorly defined for patients with severe cirrhosis.

Methods

From 1986 to 1996, partial hepatectomy was performed for HCC in 63 patients with Child-Turcotte class B (n = 46) and C (n = 17) cirrhosis. There were 46 men and 17 women, with an average age of 61.2 years (range 35 to 79 years). Associated conditions were diabetes mellitus in 45, esophageal varices in 32, severe hypersplenism in 26, cholelithiasis in 13, gastroduodenal ulcer in 6, and hiatal hernia, gastric lymphoma, splenic abscess, and pancreatic cyst each in 1. Concomitant surgical procedures were performed for most of these conditions.

Results

Major complications occurred in 17 patients (27%), six (9.5%) of whom died within 1 month after surgery. The overall in-hospital death rate was 14.3%. Liver failure and intraabdominal sepsis were mostly fatal complications. The overall and disease-free survival rates, respectively, were 70.2% and 64.5% at 1 year, 43.5% and 23.8% at 3 years, and 21.4% and 14.9% at 5 years. Multivariate analysis with the Cox regression model revealed that favorable factors for survival were Child class B, no transcatheter arterial embolization before surgery, young age, and low alanine aminotransferase (ALT) level before surgery.

Conclusions

Hepatic resection can provide a favorable result in young patients with HCC complicating Child class B cirrhosis with low hepatitis activity, but transcatheter arterial embolization before surgery should be avoided in such patients.

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors, accounting for >1 million deaths each year worldwide. The natural history of HCC is usually short, and even small HCCs have a poor prognosis if untreated: the 3-year survival rate is only 12.8%.[1] However, the prognosis of such tumors depends more on the grade of underlying cirrhosis than on tumor size; the survival rate is poor in Child class B and C patients.[2] Recently, various treatment modalities have been proposed for this tumor, but complete tumor resection offers the only realistic prospect of cure.[3]

In the absence of cirrhosis, hepatic resection is obviously the treatment of choice and can be undertaken with low morbidity and mortality rates.[4–10] Hepatic resection provides a 5-year survival rate of 40% to 55% in patients with HCC who do not have cirrhosis.[6–10] However, the surgical approach in patients with cirrhosis is less clearly defined. Resection of the cirrhotic liver is challenging and remains controversial in the treatment of HCC. In the United States, only a few centers have performed such resections, mostly with poor results.[4–6,9] Most data of resection of the cirrhotic liver have been reported from Europe[6,11–17] and Asia.[8,18–20] However, resection rates are low in patients with advanced

Address reprint requests to Naofumi Nagasue, MD, Second Department of Surgery, Shimane Medical University, Izumo 693-8501, Japan.
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cirrhosis (Child class B or C) because of the increased risk of such complications as hemorrhage, infection, and hepatic decompensation. Previous series have included only a few cases of Child class C cirrhosis.[4,5,11,13–15,17] Hepatic resection, transcatheter arterial chemoembolization (TAE), ethanol or acetic acid injection, and liver transplantation have extended the range of options in the treatment of HCC associated with cirrhosis.

The aims of this retrospective analysis were to elucidate the prognostic factors after hepatic resection in patients with HCC complicating Child class B and C cirrhosis and to delineate proper candidates for such resection and for other types of treatment, including liver transplantation.

MATERIALS AND METHODS

During the past 11 years (1986 to 1996), 292 patients were admitted to our clinic for the treatment of primary HCC. Curative hepatic resection was performed in 210 patients (71.9%). All the patients had underlying chronic liver disease—chronic hepatitis in 64 (30.5%) and liver cirrhosis in 146 (69.5%). Among the 146 patients with cirrhosis, 63 had Child-Turcotte class B or C disease.[21] Clinical data of these 63 patients are shown in Table 1. There were 46 men and 17 women. Age ranged from 35 to 79 years, averaging 61.2 ± 9.5. Eight patients in whom the cause of cirrhosis was unknown were admitted before hepatitis C virus antibody could be estimated; they tested negative for hepatitis B surface antigen. Twenty-four patients had received Lipiodol injections into the hepatic artery with or without chemotherapeutic agents before referral to us. Chemotherapy, mainly with epirubicin and 5-fluorouracil, was administered after surgery to 24 patients in the process of randomized studies. During the same period, there were 30 HCC patients with Child class B or C cirrhosis on whom treatments other than curative hepatic resection or no treatment were carried out. These patients served as controls.

Table 1. CLINICAL DATA OF 63 HCC PATIENTS WITH CHILD'S CLASS B AND C CIRRHOSIS

Data	No. of Cases	%
Age (yr)		
Younger than 50	8	12.7
50–65	30	47.6
Older than 65	25	39.7
Sex		
Male	46	73.0
Female	17	27.0
Alcohol abuse		
Yes	22	34.9
No	41	65.1
History of liver disease (yr)		
Less than 10	37	58.7
10–20	17	27.0
More than 20	9	14.3
Child's class		
B	46	73.0
C	17	27.0
Cause of cirrhosis		
HBV	16	25.4
HCV	29	46.0
HBV + HCV	3	4.8
Non B, non C	7	11.1
Unknown	8	12.7
Preoperative TAE		
Yes	24	38.1
No	39	61.9
Postoperative chemotherapy		
Yes	24	38.1
No	39	61.9

HBV = hepatitis B virus; HCV = hepatitis C virus; TAE = transcatheter arterial chemoembolization.

Presurgical Study

Detailed liver function studies, including indocyanine green and bromosulphalein tests, were routinely estimated (Table 2). Radioimmunoassay or enzyme immunoassay methods were used for detection of hepatitis B virus markers. Hepatitis C virus antibody was measured using enzyme immunoassay methods (Ortho HCV-Ab ELISA Tests, Ortho Pharmaceuticals, New Jersey); the first generation from April 1990 to September 1992, the second generation from October 1992 to March 1995, and the third generation thereafter. All patients underwent an oral glucose tolerance test to measure blood sugar and serum insulin concentrations. The diagnosis of diabetes mellitus was made on the basis of a fasting venous glucose level >140 mg/dl or a blood sugar concentration >200 mg/dl 2 hours after ingestion of 75 g glucose. Ultrasonography, computed tomography, and angiography were performed in all cases. Upper gastrointestinal series and fiberoptic examination of the esophagus and stomach were routinely performed.

Associated Conditions

In addition to HCC and cirrhosis, various associated conditions were seen: diabetes mellitus in 45, esophageal varices in 32, severe hypersplenism in 26, gallstones in 13, hypertension in 8, gastroduodenal ulcer in 6, heart disease in 5, and hyperthyroidism, hiatal hernia, gastric lymphoma, splenic abscess (complication of TAE), and pancreatic cyst in 1 patient each. The grade of esophageal varices was slight to moderate in 31 patients, but 1 with a history of variceal bleeding had received endoscopic injection sclerotherapy before referral.

Methods of Hepatic Resection

The hepatic resections performed in this series were extended right lobectomy in 1 patient, right lobectomy in 2 patients, left lobectomy in 1 patient, left lateral segmentec-

Table 2. LABORATORY DATA OF 63 HCC PATIENTS WITH CHILD'S CLASS B AND C CIRRHOSIS

Data	No. of Cases	%
Hemoglobin (g/dl)		
Less than 10	6	9.5
10–13	36	57.2
More than 13	21	33.3
White blood cell		
Less than 3000	9	14.3
3000–4000	21	33.3
More than 4000	33	52.4
Platelet ($10^3/mm^3$)		
Less than 50	4	6.4
50–100	33	52.4
More than 100	26	41.3
Bilirubin (mg/dl)		
Less than 1	30	47.6
1–2	28	44.4
More than 2	5	8.0
Albumin (g/dl)		
Less than 3	16	25.4
3–3.5	44	69.8
More than 3.5	3	4.8
ICG R15 (%)		
Less than 20	16	25.4
20–40	25	39.7
More than 40	22	34.9
BSP R30 (%)		
Less than 20	3	4.8
20–40	33	52.4
More than 40	27	42.8

BSP = Bromsulphalein; ICG = indocyanine green.

tomy in 1 patient, Couinaud's one segmentectomy in 3 patients, and partial hepatic resections less than Couinaud's one segment in 55 patients.[22]

Concomitant Procedures

Splenectomy was performed in the treatment of hypersplenism in 26 patients and splenic abscess in 1 patient. In seven of them and another four patients, spontaneous portosystemic shunts were interrupted—splenorenal shunts in nine and patent umbilical vein (Cruveilheir-Baumgarten syndrome) in two. Cholecystectomy was performed in all 13 patients with gallstones. Other concomitant operations were cardia resection for gastric lymphoma, Nissen's fundoplication for hiatal hernia, and distal pancreatectomy for pancreatic cyst in one patient each.

Pathologic Study

Histopathologic features of the tumor and surrounding liver were examined macroscopically and microscopically (Table 3). Maximal diameter of the tumor was taken as the tumor size. In multiple HCCs, the size of the largest tumor was considered. Surgical margin <5 mm was defined as margin positive. The criteria proposed by Anthony et al[23] were used for the diagnosis of liver cirrhosis.

Follow-up

After discharge from the hospital, the patients were followed at 2-week intervals in the first 6 months and monthly thereafter. Imaging diagnosis with ultrasonography and computed tomography was repeated every 3 months. When tumor recurrence was suspected by such imaging studies, the patient was admitted for further evaluation by angiography. In equivocal cases, histologic diagnosis was performed by echo-guided needle biopsy. Treatment methods for recurrence were decided by the recurrence pattern, hepatic functional reserve, and the patient's desire.

Statistical Analysis

Endpoints were death and tumor recurrence. The cumulative overall and disease-free survival curves were obtained by the Kaplan–Meier method. The patient who died of an anesthetic accident during surgery was excluded from the former analysis. Six patients, including this patient, who died within 1 month after surgery were not included in the latter analysis. The statistical differences in survival in terms of various clinicopathologic variables were compared using the log-rank and generalized Wilcoxon tests. To identify prognostic factors for survival, univariate analysis was performed using the chi square test. Multivariate analysis

Table 3. HISTOPATHOLOGIC DATA OF 63 HCC PATIENTS WITH CHILD'S CLASS B AND C CIRRHOSIS

Data	No. of Cases	%
Number of tumor		
Solitary	52	82.5
Multiple	11	17.5
Tumor size (cm)		
Smaller than 3	25	39.7
3–5	24	38.1
Larger than 5	14	22.2
Capsule		
Present	48	76.2
Absent	15	23.8
Vascular invasion		
Present	25	39.7
Absent	26	41.3
Unknown	12	19.0
Surgical margin		
Positive	32	50.8
Negative	31	49.2
Type of cirrhosis		
Micronodular	18	28.6
Macronodular	25	39.7
Mixed type	20	31.7

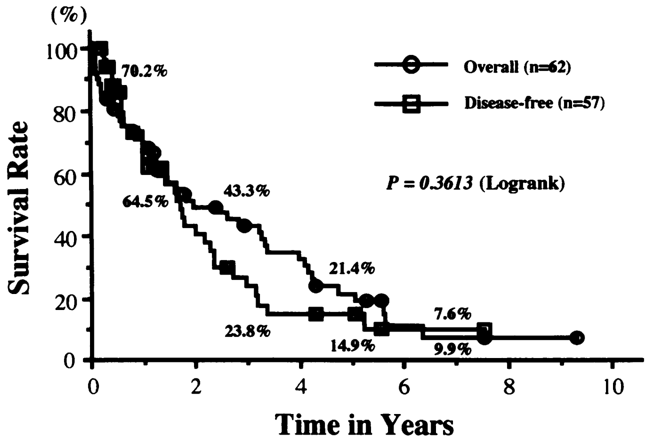

Figure 1. Overall and disease-free survival rates after hepatic resection in patients with hepatocellular carcinoma and Child class B or C cirrhosis. One patient who died of an anesthetic accident during surgery was excluded from the former analysis; another 5 deaths within 1 month after surgery were excluded from the latter analysis.

was performed using the stepwise forward Cox regression model using StatView 4.11 (Abacus Concepts, Inc., Berkeley, CA). In the multivariate analysis, the significance of the variable selected at each step was further evaluated by the Wald, score, and likelihood ratio tests. All the analyses were two-sided, and differences with probability values <0.05 were considered statistically significant.

RESULTS

Morbidity and Mortality

Seventeen patients (27%) had major complications during and after surgery: anesthetic accident (air injection) in 1 (1 death), bleeding after surgery in 4 (1 death), intraabdominal septic complications in 4 (3 deaths), liver failure in 2 (2 deaths), bile leakage in 2, pneumonia in 2 (1 death), cerebral infarction in 1, and bleeding from acute gastroduodenal ulcer in 1. The mortality rate was high once liver failure or intraabdominal septic complications occurred. In one of the deaths resulting from hemorrhage, bleeding occurred from the retroperitoneum 21 days after hepatic resection. The source of bleeding could not be identified, and the patient died of bleeding during a second surgical procedure. Thus, the surgical death rate within 1 month was 9.5% (6.5% for class B and 17.6% for class C), and the in-hospital death rate was 14.3% (10.9% for class B and 23.5% for class C).

Patient Survival and Cause of Late Death

Fifty-four patients (85.7%) could be discharged from the hospital. Seventeen patients were alive as of December 1997, but 1 patient was lost to follow-up 4 years after surgery. The overall and disease-free survival rates are shown in Figure 1. The death that resulted from the anesthetic accident was excluded from the former analysis, and the 6 patients who died within 1 month were excluded from the latter analysis. The 5-year overall and disease-free survival rates were 21.4% and 14.9%, respectively.

During the same period, 30 patients with HCC with Child class B or C cirrhosis were treated by other methods. Only two patients are currently alive. The 1-, 3-, and 5-year survival rates were 19.8%, 9.2%, and 0%, respectively. The difference between the two groups was significant (log-rank test, $p < 0.0001$).

The cause of late death in 36 patients was cancer recurrence in 24, liver failure in 8, variceal bleeding in 3, and bleeding from peptic ulcer in 2.

Prognostic Factors for Survival

Among eight clinical (sex, age, alcohol abuse, diabetes mellitus, Child class, esophageal varices, TAE before surgery, and chemotherapy after surgery), five liver functional (platelet count, prothrombin time, serum alanine aminotransferase (ALT), ICG-R15, and α-fetoprotein), three surgical (extent of liver resection, splenectomy, and blood loss during surgery), and five pathologic variables (number of tumors, tumor size, capsule, vascular invasion, and surgical margin), only age ($p = 0.0195$) and Child class ($p = 0.0070$) were prognostic factors for survival by the univariate analysis. The probability value for tumor size was 0.0504.

Multivariate analysis using the stepwise regression model showed that independent factors for survival were Child

Table 4. INDEPENDENT PROGNOSTIC FACTORS FOR SURVIVAL VERIFIED BY MULTIVARIATE ANALYSIS (COX HAZARDS MODEL)

Variable	Coefficient	SEM	χ^2	p value	Risk Ratio	95% Confidence Interval
Child's class	1.159	0.391	8.785	0.0030	3.187	1.481–6.861
Preoperative TAE	0.988	0.359	7.594	0.0059	2.686	1.330–5.423
Age	0.056	0.019	8.160	0.0043	1.057	1.018–1.098
ALT	0.011	0.005	5.502	0.0190	1.011	1.002–1.020

ALT = alanine transaminase; SEM = standard error of mean; TAE = transcatheter arterial chemoembolization.

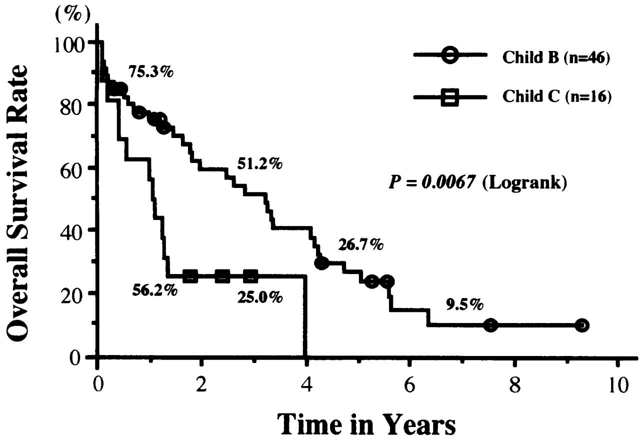

Figure 2. Overall survival rates after hepatic resection in Child class B and C patients. The risk ratio was 3.187 (p = 0.0030) by multivariate analysis. The accidental death during surgery was not included in this and the following analyses.

class, TAE before surgery, age, and serum ALT level before surgery (Table 4). The cumulative survival curves in Child class B and C patients are shown in Figure 2. The difference was significant by the log-rank test (p = 0.0067). Although TAE performed before surgery was a significant adverse factor for survival by multivariate analysis, no difference was found by the log-rank test (Fig. 3). The probability value at 4 years was 0.0695 by the Wilcoxon test. Figure 4 shows the survival curves in terms of age (younger than 60 *vs.* 60 or older). Although neither univariate nor multivariate analyses showed tumor size to be a significant prognostic factor, the survival rate was different by the log-rank test (p = 0.0003) when the size was divided at 3 cm (Fig. 5). Figure 6 shows the survival curves of 13 patients who were younger than 60 years old and had Child class B cirrhosis

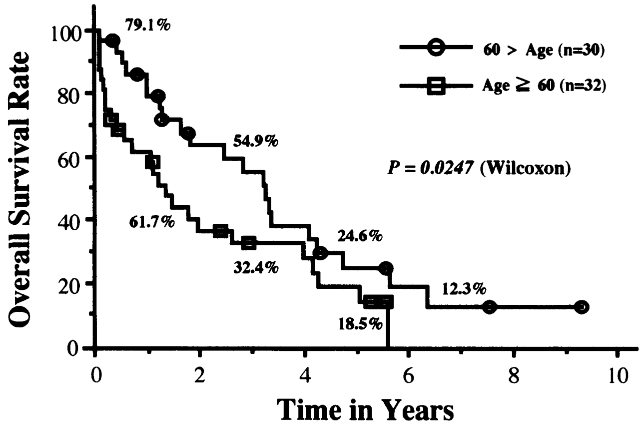

Figure 4. Overall survival rates after hepatic resection in patients younger than 60 years and those 60 or older. The risk ratio was 1.057 (p = 0.0043) by multivariate analysis.

and tumors ≤3 cm, and the remaining 49 patients. The difference was highly significant (p= 0.0018 by the log-rank test).

DISCUSSION

Cirrhosis of the liver is a major cause of death in many parts of the world. The Child-Turcotte classification was first reported to assess the hepatic functional reserve and surgical risk of portacaval shunts in patients with portal hypertension.[21] This classification is simple, rational, and prognostically reliable for not only surgical but also medical patients.[24,25] So far, the natural history of cirrhosis has been studied extensively. The 5-year survival rate is approximately 70% in compensated cirrhosis (Child class A) but only 20% in Child class B and C cirrhosis.[26–28] The mortality rate from hepatic causes such as liver failure, gastrointestinal bleeding, and HCC increases significantly as the Child class advances.[25–27]

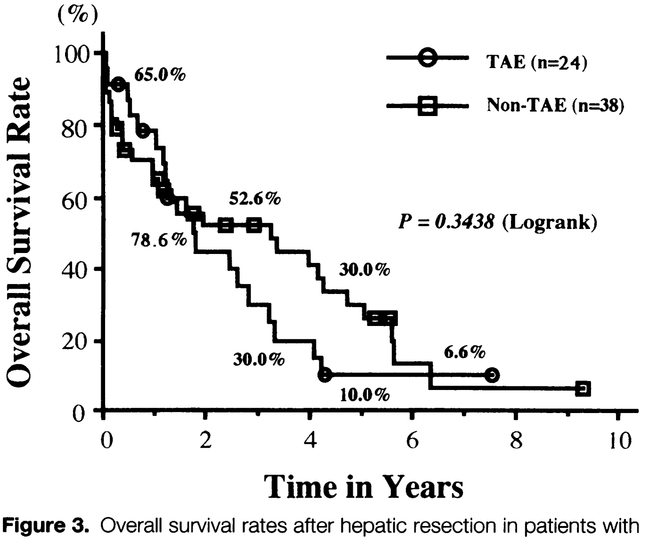

Figure 3. Overall survival rates after hepatic resection in patients with and without transcatheter arterial embolization. The probability value at 4 years was 0.0695 by the Wilcoxon test. The risk ratio was 2.686 (p = 0.0059) by multivariate analysis.

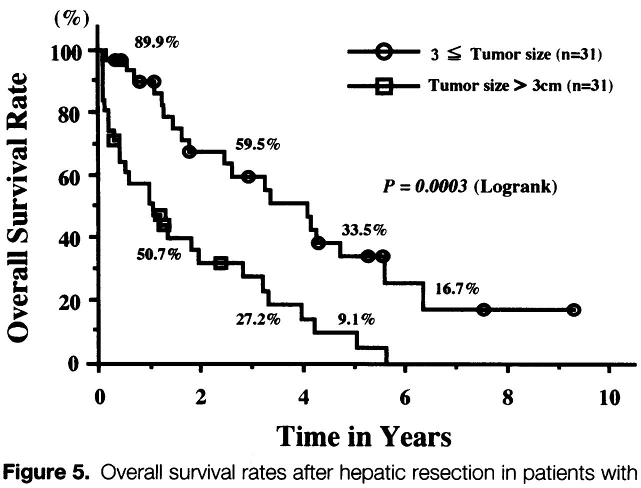

Figure 5. Overall survival rates after hepatic resection in patients with hepatocellular carcinoma ≤3 cm and patients with tumors >3 cm. The difference was highly significant by the logrank test, but tumor size was not an independent factor for survival by multivariate analysis.

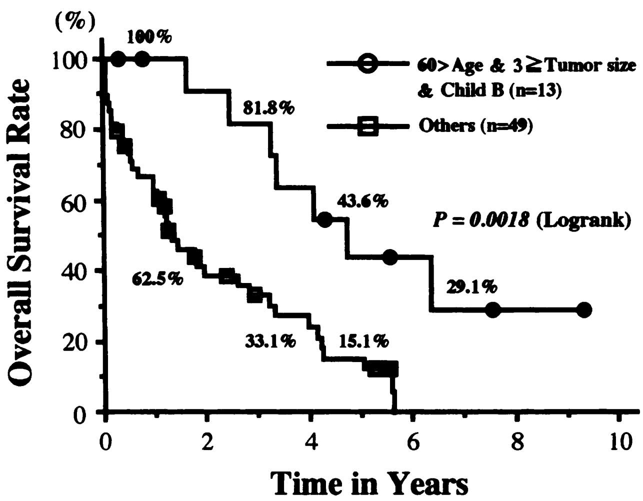

Figure 6. Overall survival rates after hepatic resection in patients who were younger than 60 years old and had Child class B cirrhosis and tumors ≤3 cm, and the remaining patients.

What is the most appropriate treatment method once HCC has developed in the liver with Child B or C cirrhosis? In the present study, we analyzed the result of hepatic resection in such patients and compared it with the results of other treatment methods reported in the literature.

Resection of the cirrhotic liver carries high morbidity and mortality rates. The mortality rate is significantly high in Child class B and C patients. Bismuth et al[11] reported a 50% mortality rate in class B and C patients, whereas all 25 class A patients tolerated hepatic resection. A slightly lower mortality rate has been reported by other authors.[8,13,15] In the present series, major complications occurred in 27% of our patients. The death rate within 1 month of surgery was 9.5%, and the overall in-hospital death rate was 14.3%. Intraabdominal septic complications and hepatic failure were mostly fatal. Four patients had bleeding, from the surgical site in three and the retroperitoneum of unknown origin in one. The last patient died of bleeding during a second surgical procedure. Although it is well known that the surgical risk is high in the presence of advanced cirrhosis,[29,30] concomitant procedures such as cholecystectomy or splenectomy did not increase the surgical risk in the present study.

The multivariate analysis revealed that Child class, TAE performed before surgery, age, and serum ALT level were independent prognostic factors for survival. The former two showed especially high risk ratios. Among 16 Child class C patients, only 3 are alive; the 3-year survival rate was 25%, with no 5-year survivors. These results are in agreement with other studies.[5,13,15,17] However, the 1-, 3-, and 5-year survival rates in Child class B patients were 75.3%, 51.2%, and 26.7%, respectively. According to the recent study from Paul Brousse Hospital, TAE before surgery with Lipiodol and chemotherapeutic agents does not improve the overall disease-free survival rate in patients with compensated cirrhosis and resectable HCC.[31] We have previously shown that such therapy decreases the survival rate if patients with severe cirrhosis (Child class B and C) are included.[32,33] This could be because although TAE suppresses tumor recurrence in the remnant liver, it increases later deaths from liver failure and gastrointestinal tract hemorrhage. The present study again suggests that TAE before surgery should be avoided in Child class B and C patients.

Long-term results of TAE for HCC in the presence of cirrhosis are far from satisfactory, particularly in patients with advanced cirrhosis (Child class B or C).[34–37] However, ethanol injection produces a 5-year survival rate of 44% to 55% in patients with small HCCs complicating Child class A cirrhosis,[38–40] but the survival rate in class C patients is poor.[40] Since the report of Iwatsuki et al,[41] patients with incidental small HCCs complicating severe liver disease have been considered the best candidates for liver transplantation among various hepatic malignancies.[42–44] If the tumor is <5 cm, liver transplantation can produce a 5-year survival rate of >70% with a low tumor recurrence rate, irrespective of Child class.[45,46]

The overall results of our current patients with advanced cirrhosis were apparently inferior to those obtained by liver transplantation, although our series contained 14 patients with HCC <5 cm. An acceptable survival rate was obtained in a subgroup of patients who were younger than 60 years old and had HCCs ≤3 cm and Child class B cirrhosis: the 1-, 3-, 5-year survival rates were 100%, 81.8%, and 43.6%, respectively. This result is still inferior to that with liver transplantation.[42,45,46] Because of the relative shortage of donors, however, hepatic resection should be considered first for patients who are young and have relatively small HCCs complicating Child class B cirrhosis. TAE should be avoided before surgery in these patients. Liver transplantation is best indicated for similar patients but with Child class C cirrhosis. The best treatment in elderly patients with small HCCs and class B or C cirrhosis may be ethanol or acetic acid injection.[47] Superselective TAE may be the treatment of choice in patients with HCCs >5 cm and class B cirrhosis. Only conservative treatments should be considered for patients with HCCs >5 cm and Child class C cirrhosis.

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