cancer recurrence. To our knowledge, there has been no detailed analysis of a large series of HCC patients with more than 10 years disease-free survival after curative hepatic resection. In the current series, 74 patients (8 %) survived for 10 years without disease recurrence after the initial hepatectomy. Fourteen of these patients (19 %) had later disease recurrence and received treatment with one or more treatment modalities. Generally, surgeons think that if there is no recurrence of cancer for 10 years after the initial operation, it should be thought that there will be little likelihood of recurrence of cancer long afterward. Should clinical follow-up then be terminated? From the results of this study, we believe that clinical follow-up after resection of HCC is very important and should continue for the remainder of the patient's life. Intrahepatic recurrence has been suggested to arise from three causes [28]: (1) the continued growth of residual tumor after incomplete excision may cause recurrence near the cut margin and may be responsible for early recurrence; (2) a metachronous and unrecognized synchronous multifocal primary tumor may cause recurrence far from the original site of the lesion and may be responsible for a late recurrence; and (3) a new primary tumor may develop. Because the median disease-free interval between the first operation and recurrence was 11.0 years in this series, and based on the higher incidence of dysplasia in patients with cirrhosis, it might be possible that there was new development of the cancer in these patients.

In multivariate analysis, the preoperative and 10-year platelet counts were identified as favorable independent factors for survival after 10 years of recurrence-free survival after curative hepatic resection of HCC. The platelet count is a simple test, and results can be determined easily by a routine laboratory procedure. In the present study, there was a significantly higher incidence of esophageal and/or gastric varices and serum type IV collagen 7S at 10 years after surgery in the recurrence group. In four patients with repeat hepatectomy for recurrent HCC, histological fibrosis of the underlying liver at the second operation was more advanced than at the first operation. Type IV collagen 7S is known to be useful for quantitative evaluation of liver fibrosis, and is employed for indirect testing of serum samples [17]. A low platelet count at 10 years after surgery, with a higher incidence of varices, higher levels of type IV collagen 7S, and more advanced fibrosis in patients with repeat hepatectomy, reflects the severity of portal hypertension, and indicates development of liver fibrosis in the recurrence group. Moriyama et al. [29] reported that monitoring of platelet counts is useful for determining the development of liver fibrosis in HCV-associated chronic liver diseases and for the determination of a highly carcinogenic state in the liver after interferon therapy. The importance of fibrosis in hepatocarcinogenesis has been described in patients with chronic viral hepatitis [30–32]. The annual incidence of development of HCC increased with the progression of liver fibrosis during long-term follow-up in patients with hepatitis B and C [31, 32]. Fibrosis of the liver develops through repeated necroinflammation and regeneration in the liver of patients with chronic hepatitis, and eventually progresses to liver cirrhosis [33]. Because this process requires vigorous mitosis of the hepatocytes in response to cell destruction, increased fibrosis is associated with a large amount of mitotic activity, which may allow accumulation of genetic transformations [34, 35].

The mechanisms involved in thrombocytopenia, which is observed in patients with chronic hepatitis, have not been fully elucidated. Increased sequestration and destruction of platelets in the enlarged spleen, which is an important mechanism involved in liver cirrhosis and portal hypertension, may not contribute to thrombocytopenia in chronic hepatitis C [36]. Possible mechanisms for thrombocytopenia have been proposed in chronic hepatitis, including decreased production of liver-derived thrombopoietin [37, 38], and increased destruction of platelets by antiplatelet antibodies [39]. Recent accumulated evidence indicates that the thrombocytopenia is caused by an autoimmune mechanism as a result of HCV infection. Nagamine et al. [40] found HCV-RNA in the platelets obtained from HCV-positive patients, indicating the possibility that an association of HCV/anti-HCV antibody immune complexes with the platelet surface can result in platelet antibody immunoglobulin) G (IgG) expression. They also demonstrated that platelet-associated IgG levels increased with the degree of histological progression in patients with chronic hepatitis C. In any case, thrombocytopenia is related to hepatocarcinogenesis through the development of liver fibrosis in patients with chronic hepatitis. It seems likely that a low platelet count is a risk factor for carcinogenesis from chronic hepatitis and for recurrence and survival of HCC after treatment, including liver resection [41–44]. The platelet count may be useful as a marker of late recurrence in HCC patients who survived in the long term.

Our first choice of treatment for recurrence of HCC is principally repeat hepatectomy because this procedure has been accepted as the most effective treatment [45]. However, repeat hepatectomy is limited to patients with resectable intrahepatic recurrence and well-preserved liver function. Our study indicated that nonsurgical treatments, such as RFA or TACE, could contribute to prolongation of survival when repeat hepatectomy is not indicated. Therefore, it is important to select appropriate treatment according to the pattern of recurrence, location of the tumor, and preserved liver function.

In conclusion, our data demonstrated that for patients with higher preoperative and 10-year platelet counts who

underwent curative resection of HCC, long-term survival after resection could be expected. However, because tumor recurrence is common even after 10 years, postoperative follow-up is important and should continue for the remainder of the patient's life. The platelet count is a useful, inexpensive, and convenient marker of late recurrence (later than 10 years following curative resection) of HCC. Finally, aggressive therapy for recurrence, including a second resection when necessary, is recommended.

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ORIGINAL ARTICLE

Predictors and outcome of early recurrence after resection of hepatic metastases from colorectal cancer

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Abstract
Purpose This study aimed to investigate the risk factors for early recurrence in patients who had undergone curative resection of colorectal liver metastases (CRLM) and to evaluate the outcome after recurrence.
Methods A total of 119 patients were divided into 2 groups: an early recurrence group (n=54) who had recurrence within 2 years of curative resection of CRLM and a 2-year recurrence-free group (n=65) who remained disease-free for at least 2 years following surgery.
Results During the initial 5-year period after surgery, 4 out of 65 patients (6%) in the 2-year recurrence-free group and 29 out of 54 patients (54%) in the early recurrence group died. Multivariate analysis showed that postoperative morbidity was an independent predictor of early recurrence after curative resection of CRLM.
Conclusions Early recurrence is the leading cause of death within 5 years after curative resection of CRLM. Postoperative morbidity increases the risk of early recurrence in these patients. A reduction in perioperative morbidity may, therefore, improve the outcome of curative resection, as well as reducing medical costs.

Keywords Colorectal cancer liver metastases · Hepatic resection · Early recurrence · Risk factor

Synopsis for table of contents Early recurrence is the leading cause of death within 5 years after curative resection of liver metastases from colorectal cancer. Postoperative morbidity influences early recurrence in patients with colorectal liver metastases.

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Introduction

Hepatic resection is currently the only potentially curative treatment for colorectal liver metastases (CRLM). Results from various specialist hepatobiliary centers have shown that surgical resection can potentially achieve a 5-year survival rate of 20–46% [1–7]. However, recurrence is a major problem after surgery, since it occurs in 80–85% of patients [1, 8, 9]. Reducing the recurrence rate is, therefore, necessary to improve the prognosis after resection of CRLM. A shorter interval until recurrence after resection of the primary tumor is correlated with a poorer prognosis in patients with colorectal cancer [8, 10], breast cancer [11], hepatocellular carcinoma [12], and renal cell carcinoma [13]. However, the relationship between the time to recurrence after resection of CRLM and prognosis is still unclear. After complete resection of CRLM, early recurrence (defined as intrahepatic, regional, or systemic recurrence within 2 years) is reported to be one of the most important factors determining prognosis. Tumor characteristics that have been reported to show an association with early recurrence include a high level of carcinoembryonic antigen (CEA), multiple metastases, a positive surgical margin, and a high clinical risk score [1, 8, 10, 14–19], but the relative importance of each of these factors is unclear.

The present study aimed to identify risk factors for early recurrence following curative resection of CRLM and to evaluate the prognosis after recurrence.

Materials and methods

Patients

Between February 1993 and March 2007, a total of 119 patients with CRLM underwent curative resection at our institution. Curative resection was defined as macroscopic removal of all hepatic tumors. None of the patients died in the hospital, and follow-up data were available until death or for more than 2 years in all cases. This study was performed by retrospective review of the medical records. Based on their status at 2 years after resection, the subjects were divided into an early recurrence group ($n=54$) composed of patients who suffered recurrence within 2 years after surgery and a 2-year recurrence-free group ($n=65$) composed of patients with no evidence of recurrence after 2 years of follow-up.

Clinicopathologic variables and surgery

Before surgery, each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 min (ICGR15). The levels of CEA and cancer antigen 19-9 (CA19-19) were also measured in all patients. Preoperative radiological assessment always included computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Intraoperative ultrasound (US) was performed to confirm the preoperative imaging findings and to assist in planning the surgical procedure. According to the Brisbane terminology proposed by Strasberg et al. [20], anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory. Anatomic resection was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments [21]), or segmentectomy (resection of one Couinaud subsegment). All nonanatomic procedures were classified as limited resection, while anatomic plus limited resection was classified as combined resection. One senior pathologist reviewed each resected specimen for histologic confirmation of the diagnosis. The width of the surgical margin was measured as the distance from the tumor edge to the resection line. The clinical risk score [10] (possible range, 0 to 5 points) was calculated by assigning 1 point for each of the following: positive nodal status of the primary colorectal tumor, disease-free interval of <1 year from resection of the primary tumor to the detection of liver metastasis, preoperative CEA level >200 ng/ml, more than one liver tumor, and largest tumor >5 cm in diameter.

Follow-up

Postoperative complications were investigated to assess morbidity following hepatectomy and were classified according to the Clavien system [22]. Briefly, grade I is any deviation from the normal postoperative course not requiring special treatment. Grade II is an event requiring pharmacological treatment. Grade III is an event requiring surgical or radiological intervention, without (IIIa) or with (IIIb) general anesthesia. Grade IV is a life-threatening complication, involving single (IVa) or multiple (IVb) organ dysfunction. Grade V is death. After discharge from the hospital, patients were reviewed at least every 3 months to check for intrahepatic recurrence based on the results of physical examination, liver function tests, and abdominal US, CT, or MRI. Chest X-rays were undertaken every 3 months and chest CT scans were undertaken every 6 months to detect pulmonary metastases. In patients with bone pain, scintigraphy was undertaken to detect bone metastases.

If recurrence of liver metastases was detected by changes in tumor markers or by imaging, recurrence that was limited to the remnant liver was treated by repeat resection or by percutaneous local therapy such as radiofrequency ablation. If extrahepatic metastases were detected, active treatment was undertaken in patients with a good performance status (0 or 1). In patients with bone metastases, radiation therapy was undertaken to relieve symptoms. Surgical resection was undertaken in patients with a solitary extrahepatic metastasis and no evidence of intrahepatic recurrence.

Prognostic factors

We performed univariate and multivariate analyses of various clinicopathologic factors to identify independent variables that could predict early recurrence of CRLM. The patient factors studied were gender, age, body mass index (BMI), primary tumor site, primary tumor lymph node status, primary tumor histology, primary tumor stage, preoperative neoadjuvant chemotherapy, postoperative chemotherapy, timing of hepatic metastasis (synchronous or metachronous), and liver function (including albumin, prothrombin time, and ICGR15). The operative factors studied were blood loss, perioperative blood transfusion, surgical procedure, extent of liver resection, postoperative morbidity, postoperative hospital stay, and repeat resection.

The tumor factors studied were CEA, CA19-9, tumor size, number of metastases, distribution of metastases, extrahepatic nodal disease, surgical margin, coexisting liver disease, and clinical risk score. Variables that were shown to be significant by univariate analysis were re-examined using a univariate and multivariate logistic regression model to identify independent predictors of early recurrence after curative resection.

Statistical analysis

For continuous variables, subjects were categorized into two groups divided by the median values, and the significance of differences between each pair of groups was assessed by the chi-square test. Categorical data were compared with the chi-square test and Fisher's exact test where appropriate. Multivariate logistic regression analysis was performed by the backward elimination method using all variables. The variable with the highest p value for the estimated odds ratio was excluded if $p>0.2$, and this process was repeated until all p values were <0.2. By subsequently individually adding the excluded variables to the final model, it was confirmed that none of these variables had a p value <0.2.

The Kaplan–Meier method was employed to calculate the time to recurrence, median survival, recurrence-free survival, and overall survival as of March 2009, and differences in survival were assessed by the generalized log-rank test. In all analyses, $p<0.05$ was considered to indicate statistical significance.

Results

Preoperative characteristics

Table 1 summarizes the preoperative characteristics of the early recurrence and 2-year recurrence-free groups. No differences were detected between the two groups with respect to gender, age, BMI, primary tumor site, primary tumor lymph node status, primary tumor histology, primary tumor stage, timing of hepatic metastasis, CEA, CA19-9, or liver function. Neoadjuvant chemotherapy was administered to 20 patients (37%) for a median of 5 months (range, 1–22 months) in the early recurrence group and to 28 patients (43%) for a median of 7 months (range, 1–18 months) in the 2-year disease-free group. The neoadjuvant chemotherapy regimens administered before hepatectomy did not differ significantly between the two groups.

Perioperative parameters and pathologic findings

As shown in Table 2, the operative blood loss, blood transfusion rate, surgical procedures, and extent of liver resection did not differ significantly between the two groups.

Table 1 Preoperative clinical characteristics of the two groups

Variable	Early recurrence group (n=54)	2-year recurrence-free group (n=65)	p value
Gender (male/female)	32/22	38/27	0.9299
Age >64 years	28 (52%)	34 (52%)	0.9605
BMI >23 kg/m^2	27 (50%)	35 (54%)	0.6758
Primary tumor (colon/rectum)	38/16	48/17	0.6733
Primary tumor nodal status (negative/positive)	17/37	22/43	0.7844
Primary tumor histology (well or moderate/poor or mucinous)	51/3	56/9	0.1348
Primary tumor stage (T1 or T2/T3 or T4)	7/47	5/60	0.3418
Preoperative neoadjuvant chemotherapy (no/yes)	34/20	37/28	0.5037
5-FU/LV	10 (50%)	16 (57%)	0.8745
5-FU/LV with irinotecan (CPT-11)	7 (35%)	8 (29%)	
5-FU/LV with oxaliplatin	3 (15%)	4 (14%)	
Timing of hepatic metastasis (metachronous/synchronous)	17/37	28/37	0.1941
CEA >6 ng/ml	27 (50%)	25 (38%)	0.2065
CA19-9 >30 ng/dl[a]	19 (49%)	22 (41%)	0.4445
Albumin >4.0 mg/dl[a]	26 (49%)	33 (52%)	0.7213
Prothrombin time >100%[a]	28 (56%)	36 (57%)	0.9031
ICGR15 >9%[a]	25 (60%)	23 (48%)	0.2708

Data represent the number of patients

BMI body mass index, *5-FU* 5-fluorouracil, *LV* leucovorin, *CEA* carcinoembryonic antigen, *ICGR15* indocyanine green retention rate at 15 min

[a]Indicated data were not available for all patients

Table 2 Intraoperative and postoperative characteristics of the two groups

Variable	Early recurrence group (n=54)	2-year recurrence-free group (n=65)	p value
Operative blood loss >800 ml	29 (54%)	29 (45%)	0.3234
Blood transfusion	20 (37%)	25 (38%)	0.8732
Surgical procedure			0.2671
Anatomic resection	14 (26%)	23 (35%)	
Limited or combined resection	40 (74%)	42 (65%)	
Extent of liver resection			0.4712
Less than hemihepatectomy	34 (63%)	45 (69%)	
Hemihepatectomy or more	20 (37%)	20 (31%)	
Postoperative morbidity	20 (37%)	7 (11%)	0.0007
Bile leakage	5	3	
Intra-abdominal abscess	5	3	
Liver failure	5	0	
Pneumonia	2	0	
Colitis	1	1	
Pleural effusion	1	0	
Ileus	1	0	
Grade of surgical complications			0.6518
I	0	0	
II	0	0	
IIIa	9 (45%)	5 (71%)	
IIIb	4 (20%)	1 (14%)	
IVa	6 (30%)	1 (14%)	
IVb	1 (5%)	0	
V	0	0	
Postoperative hospital stay >20 days	34 (63%)	27 (42%)	0.0199
Postoperative chemotherapy (no/yes)	24/30	39/26	0.0905
5-FU/LV	6 (20%)	4 (15%)	0.7321
5-FU/LV with irinotecan (CPT-11)	3 (10%)	5 (19%)	
5-FU/LV with oxaliplatin	7 (23%)	7 (27%)	
Others	14 (47%)	10 (38%)	
Tumor size >3.5 cm	27 (50%)	32 (49%)	0.9334
No. of metastases ≥3	24(44%)	14 (22%)	0.0076
Distribution of metastases (unilobar/bilobar)	30/24	47/18	0.0569
Extrahepatic nodal disease	5 (9%)	4 (6%)	0.5236
Positive surgical margin	13 (24%)	9 (14%)	0.1525
Coexisting liver disease	11 (20%)	15 (23%)	0.7220
Repeat resection	9 (17%)	6 (9%)	0.2237
Clinical risk score >2	25 (46%)	19 (29%)	0.0549
Median time to recurrence (months)	10.0	30.0	<0.0001
Median survival (months)	21.5	38.0	<0.0001

Data represent the number of patients

However, patients in the early recurrence group had a higher perioperative morbidity rate and a longer postoperative hospital stay compared with those in the 2-year recurrence-free group. The grades of surgical complications according to the Clavien classification did not differ significantly between the two groups.

Postoperative chemotherapy was administered to 30 patients (56%) in the early recurrence group and to 26 patients (40%) in the 2-year disease-free group. The chemotherapy regimens administered after hepatectomy did not differ significantly between the two groups.

The pathologic findings obtained in the two groups are also listed in Table 2. Although the early recurrence group had a significantly higher number of metastases, the other pathologic characteristics did not differ significantly between the two groups.

Factors related to early recurrence

Variables in Table 3 with a p value <0.05 showed an association with early recurrence, and variables with p values ≥0.05 showed a possible association with recurrence. The other 21 variables were not associated with recurrence. Multivariate analysis showed that postoperative morbidity was the only independent predictor of early recurrence after curative resection of CRLM (odds ratio= 4.70; 95% CI=0.08 to 0.59; p=0.003) (Table 3).

Recurrence and survival

The median follow-up period was 31 months (range, 24–157 months). Early recurrence was detected as solitary or multifocal intrahepatic tumor in 38 patients and as metastasis to other sites in 16 patients (lung metastasis in 10, hepatoduodenal lymph node metastasis in 3, bone metastasis in 2, and intrahepatic plus lung metastasis in 1). In 36 of the 38 patients with intrahepatic recurrence, the new tumors arose further than 1 cm from the surgical margin, while the tumors were located at the margin in the remaining two patients. In the 2-year recurrence-free group, 10 out of 65 patients (15%) eventually developed recurrence after more than 2 years. Six of these patients had intrahepatic recurrence and four had lung metastases. Among all 119 patients with CRLM, 44 (37%) developed recurrence in the remnant liver. Late recurrence after resection was detected in 10 out of 119 (8%) of the patients in this series.

The disease-free survival rate and overall survival rate for all 119 patients were 38.7% and 67.8% at 3 years and 33.7% and 57.6% at 5 years, respectively. The median survival time and the time to recurrence after resection were 37 and 17 months, respectively. The median time to recurrence after resection in the 2-year recurrence-free group and early recurrence groups was 30.0 and 10.0 months, respectively (Table 2). The median survival time after resection in the 2-year recurrence-free and early recurrence groups was 38 and 21.5 months, respectively. Overall survival rates of the early recurrence and 2-year recurrence-free groups were 36.4% and 98.0% at 3 years, 24.2% and 87.8% at 5 years, and 18.2% and 87.8% at 7 years, respectively. There were significant differences in recurrence-free survival and overall survival between the early recurrence and 2-year recurrence-free groups (both p<0.0001). Of the 54 patients in the early recurrence group, 29 (54%) died within 5 years after curative resection. Of the 65 patients in the 2-year recurrence-free group, 4 (6%) died within 5 years of curative resection. All 33 deaths were directly attributable to metastatic colorectal cancer.

In the early recurrence group, 38 of the 54 patients (70%) underwent additional therapy after the detection of recurrence (9 underwent repeat resection of hepatic tumors, 1 received percutaneous microwave coagulation therapy, 1 received radiofrequency ablation, 6 received local chemotherapy via a reservoir, and 21 received systemic chemotherapy). In the 2-year recurrence-free group, 10 of the 65 patients (10%) eventually developed recurrence and underwent additional therapy (6 underwent repeat resection of hepatic tumors, 1 underwent resection of a solitary lung metastasis, and 3 received systemic chemotherapy).

Table 3 Multivariate analysis of factors predicting early recurrence after resection of liver metastases

Variable	Odds ratio	95% CI	p value
Poor clinical risk score	1.40	0.86–2.28	0.171
Bilobar metastases	1.94	0.78–4.80	0.152
Higher primary tumor stage	2.06	0.21–1.13	0.094
Postoperative morbidity	4.70	0.08–0.59	0.003

CI confidence interval

Perioperative characteristics and postoperative survival rates of patients with and without postoperative morbidity

Table 4 summarizes the perioperative characteristics of the patients with and without postoperative morbidity. No differences were detected between the two groups with respect to age, BMI, timing of hepatic metastasis, CEA, albumin, ICGR15, surgical procedure, extent of liver resection, tumor size, number of metastases, distribution of metastases, extrahepatic nodal disease, positive surgical margin, coexisting liver disease, repeat resection, or clinical risk score. Preoperative neoadjuvant chemotherapy was administered to 10 patients (37%) with morbidity and to 38 patients (41%) without morbidity. The neoadjuvant chemotherapy regimens administered before hepatectomy did not differ significantly between the two groups. Postoperative chemotherapy was administered to 10 patients (37%) with morbidity and to 46 patients (50%) without morbidity. The chemotherapy regimens administered after hepatectomy did not differ significantly between the two groups. Operative blood loss was greater among patients with postoperative morbidity than patients without, and the incidence of blood transfusion was also higher among patients with postoperative morbidity than patients without. Of the patients with postoperative morbidity, 20 out of 27 (74%) eventually developed recurrence.

The 5-year recurrence-free and overall survival rates among patients with postoperative morbidity were 17.5% and 42.4%, respectively, and among patients without morbidity were 38.8% and 63.4%, respectively (Fig. 1). There were significant differences in both recurrence-free survival (p=0.0009) and overall survival (p=0.001) between the groups with and without postoperative morbidity.

Table 4 Perioperative characteristics of the groups with and without postoperative morbidity

Variable	Morbidity (n=27)	No morbidity (n=92)	p value
Age >64 years	15 (56%)	47 (51%)	0.6828
BMI >23 kg/m^2	10 (37%)	52 (57%)	0.0747
Preoperative neoadjuvant chemotherapy (no/yes)	17/10	54/38	0.6911
5-FU/LV	7 (70%)	19 (50%)	0.2963
5-FU/LV with irinotecan (CPT-11)	3 (30%)	12 (32%)	
5-FU/LV with oxaliplatin	0 (0%)	7 (18%)	
Timing of hepatic metastasis (metachronous/synchronous)	8/19	37/55	0.3185
CEA >6 ng/ml	15 (56%)	37 (40%)	0.1577
Albumin >4.0 mg/dl[a]	9 (35%)	50 (56%)	0.0599
ICGR15 >9%[a]	10 (50%)	38 (54%)	0.7347
Operative blood loss >800 ml	19 (70%)	39 (42%)	0.0105
Blood transfusion	16 (59%)	29 (32%)	0.0090
Surgical procedure			
Anatomic resection	8 (30%)	29 (32%)	0.8518
Limited or combined resection	19 (70%)	63 (68%)	
Extent of liver resection			
Less than hemihepatectomy	21 (78%)	58 (63%)	0.1541
Hemihepatectomy or more	6 (22%)	34 (37%)	
Postoperative chemotherapy (no/yes)	17/10	46/46	0.2354
5-FU/LV	2 (20%)	8 (17%)	0.8252
5-FU/LV with irinotecan (CPT-11)	2 (20%)	6 (13%)	
5-FU/LV with oxaliplatin	3 (30%)	11 (24%)	
Others	3 (30%)	21 (46%)	
Tumor size >3.5 cm	16 (59%)	43 (47%)	0.2526
No. of metastases ≥3	10 (37%)	28 (30%)	0.5176
Distribution of metastases (unilobar/bilobar)	19/8	58/34	0.4836
Extrahepatic nodal disease	3 (11%)	6 (7%)	0.4278
Positive surgical margin	8 (30%)	14 (15%)	0.0898
Coexisting liver disease	4(15%)	22 (24%)	0.3144
Repeat resection	3 (11%)	12 (13%)	0.7902
Clinical risk score >2	14 (52%)	30 (33%)	0.0686
Recurrence within 2 years after surgery	20 (74%)	34 (37%)	0.0007

Data represent the number of patients

BMI body mass index, *5-FU* 5-fluorouracil, *LV* leucovorin, *CEA* carcinoembryonic antigen, *ICGR15* indocyanine green retention rate at 15 min

[a]Indicated data were not available for all patients

Discussion

Surgical resection offers the only possibility of cure for patients with hepatic metastasis from colorectal cancer. Hepatectomy is currently associated with a perioperative mortality rate of <5% and morbidity rate of 15% to 35% and achieves a 5-year survival rate of 20% to 46% [1–7, 14, 23–26]. In the present series, we found a mortality rate of 0%, a morbidity rate of 23%, and a 5-year survival rate of 58%, which are generally in agreement with the reported data.

In this series, 45% of patients undergoing curative resection of CRLM developed recurrence within 2 years of surgery. Early recurrence of liver metastases is the leading cause of death during the initial 5-year period after curative resection. In the present study, 4 out of 65 patients (6%) in the 2-year disease-free group and 29 out of 54 patients (54%) in the early recurrence group died during the initial 5-year period after resection. Death was attributable to metastatic colorectal cancer in all 29 patients with early recurrence who died within 5 years after resection. Chok et al. also reported that the presence of postoperative complications is the leading cause of death during the early period after curative resection of hepatocellular carcinoma [27]. Early recurrence occurred in approximately 74% of patients with postoperative morbidity, and postoperative morbidity was the only factor shown to be significantly associated with recurrence by multivariate analysis. Although several other preoperative and intraoperative factors also appeared to be associated with early

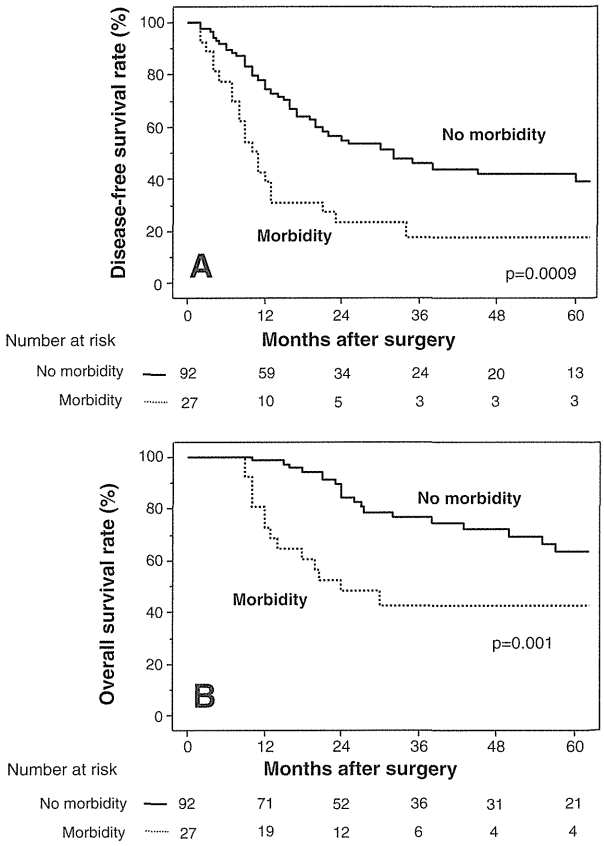

Fig. 1 Influence of postoperative morbidity on survival. Comparison of recurrence-free survival (**a**) and overall survival (**b**) after resection of liver metastases between patients with postoperative morbidity (*dotted lines*) and patients without morbidity (*unbroken lines*). The disease-free and overall survival rates of the two groups were significantly different (p=0.0009 and p=0.001, respectively). The number of patients at risk is shown below each graph

recurrence, our sample size was too small to confirm significance. Previously reported risk factors for early recurrence include tumor doubling time, CEA level, tumor size, multiple metastases, positive surgical margin, lymph node involvement, histology of the primary tumor, and clinical risk score [1, 8, 10, 14–19]. However, various studies have yielded conflicting results concerning the predictors of recurrence, and there is still debate about which factors are important. In the present series, the presence or absence of postoperative morbidity was found to be useful for predicting recurrence.

Postoperative morbidity after liver resection increases both the length of hospital stay and medical costs [28]. The impact of postoperative morbidity on the long-term outcome after cancer surgery has recently been investigated. A study analyzing data from the National Surgical Quality Improvement Program demonstrated that postoperative morbidity was associated with worse long-term survival after selected major operations [29], and a negative impact of postoperative morbidity on long-term outcome has also been documented after surgery for head and neck cancer [30], colorectal cancer [31, 32], esophageal cancer [33], and CRLM [34–37]. The precise mechanism by which postoperative morbidity influences the long-term outcome of cancer remains to be elucidated. Major surgery causes a systemic inflammatory response and immunosuppression [38], and it is possible that postoperative morbidity exacerbates this inflammatory response and/or immunosuppression. There has been speculation that prolonged systemic inflammation and immunosuppression associated with postoperative morbidity may promote the survival and subsequent growth of tumor micrometastases. The occurrence of infection, anastomotic leakage, and organ failure may, therefore, contribute to the survival of tumor cells after surgical resection [39–41]. In the present series, 10 out of 20 patients (50%) with postoperative morbidity in the early recurrence group had infection and 5 out of 20 patients (25%) had liver failure (Table 2). There have been four previous reports investigating the interactions between postoperative morbidity, postoperative recurrence of CRLM, and survival [34–37].

Nordlinger et al. [42] recently undertook a prospective randomized controlled trial of perioperative chemotherapy versus surgery alone for resectable CRLM and found increased postoperative morbidity together with better disease-free survival in the group receiving chemotherapy. However, the present study did not find any differences in the neoadjuvant or postoperative chemotherapy provided between the early recurrence and 2-year recurrence-free groups or between patients with and without postoperative morbidity (Tables 2 and 4). It is worth considering that postoperative morbidity presumably delays postoperative chemotherapy.

In Table 4, the lack of statistical differences between groups does not indicate equivalence. Patients with postoperative morbidity were more likely to have a clinical risk score >2 (52% vs. 33%), a positive surgical margin (30% vs. 15%), CEA >6 ng/ml (56% vs. 40%), and tumor size >3.5 cm (59% vs. 47%) than patients without morbidity, suggesting that the tumor burden was heavier in the high-morbidity group. The present study only evaluated a small group of patients, was retrospective in nature, and collected data from a long period of time.

Conclusion

Early recurrence is the leading cause of death during the initial 5-year period after curative resection of CRLM, and postoperative morbidity is a significant risk factor for early recurrence after curative resection. Efforts to further refine surgical techniques and perioperative management may, therefore, help to improve the long-term outcome of patients with metastatic colorectal cancer.

Conflicts of interest None.

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ORIGINAL ARTICLE

A Prospective Randomized Controlled Trial of Preoperative Whole-Liver Chemolipiodolization for Hepatocellular Carcinoma

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Abstract
Background We previously reported that preoperative chemolipiodolization of the whole liver is effective for reducing the incidence of postoperative recurrence and prolonging survival in patients with resectable hepatocellular carcinoma (HCC). The present randomized controlled trial was performed to evaluate the influence of preoperative transcatheter arterial chemoembolization (TACE) on survival after the resection of HCC.
Methods Operative results and long-term outcome were prospectively compared among 42 patients who received only selective TACE targeting the tumor (selective group), 39 patients who received TACE targeting the tumor plus chemolipiodolization of the whole liver (whole-liver group), and 43 patients without preoperative TACE or chemolipiodolization (control group).
Results There were no serious side effects of TACE or chemolipiodolization and the operative outcomes did not differ among the three groups. Even though preoperative TACE induced complete tumor necrosis, there were no significant differences in the pattern of intrahepatic recurrence or the time until recurrence among the three groups. There were also no significant differences in disease-free survival or overall survival among the three groups, even among patients with larger tumor size.
Conclusion These results indicate that preoperative selective TACE and whole-liver chemolipiodolization plus TACE do not reduce the incidence of postoperative recurrence or prolong survival in patients with resectable HCC.

Keywords Hepatocellular carcinoma · Preoperative chemolipiodolization · Whole liver · Hepatectomy · Randomized controlled trial

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide [1]. Although the majority of patients are still found in Asia and Africa, recent studies have shown that the incidence and mortality rate of HCC are rising in North America and Europe [2, 3]. There has been an increase in reports of non-surgical therapeutic options for small HCC, such as percutaneous ethanol injection therapy [4], microwave coagulation therapy [5], and percutaneous radiofrequency ablation (RFA) [6], but there is ongoing controversy regarding the best method of treating small tumors. In Japan, liver transplantation is not a practical option for most HCC patients, because the national health insurance scheme only covers transplantation for patients with decompensated cirrhosis whose tumors fit the Milan criteria. Resection is, therefore, generally the first-line treatment for patients with small tumors and underlying chronic liver disease, but the long-term survival rate after

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potentially curative resection of HCC is still unsatisfactory because of the high rate of recurrence [7]. To improve prognosis, it is important to prevent the recurrence of HCC after its initial resection, but standard therapy for intrahepatic metastasis has not yet been developed.

With various improvements in interventional radiology, transcatheter arterial chemoembolization (TACE) has become an increasingly important palliative treatment for HCC. Initially, TACE was only performed for unresectable HCC, as well as for some early tumors that were extremely difficult to resect. More recently, TACE has been used as preoperative adjuvant therapy in patients who have resectable HCC with the hope that it may improve survival [8–13]. Based on the current evidence, however, preoperative TACE is not routinely recommended for patients undergoing hepatectomy to treat resectable HCC [14–16], and TACE may be contraindicated in patients with cirrhosis because it can lead to the progressive deterioration of liver function [14]. Whether preoperative TACE can improve the long-term survival of HCC patients is still unclear, and there have been only three randomized controlled trials evaluating the influence of preoperative TACE on survival [15, 17, 18]. We previously reported that preoperative chemolipiodolization of the entire liver is effective for reducing the incidence of postoperative recurrence and for prolonging survival in patients with resectable HCC [19]. Accordingly, the present randomized controlled trial was conducted to better assess the influence of preoperative TACE combined with whole-liver chemolipiodolization on survival after the resection of HCC.

Patients and Methods

Patients

Between January 2004 and June 2007, 124 patients with HCC underwent curative hepatic resection at our institution. A curative operation was defined as the resection of all detectable tumors. The eligibility criteria for inclusion in this study were as follows: (1) age 20–80 years; (2) a preoperative diagnosis of HCC with no previous treatment; (3) no other malignancies; (4) Child–Pugh score A or B; (5) leukocyte count $\geq$3,000/mm^3; (6) hemoglobin level $\geq$9.5 g/dl; (7) platelet count $\geq$50,000/mm^3; (8) serum creatinine level <1.2 mg/dl; (9) total bilirubin <2.0 mg/dl; (10) local nodular disease without extrahepatic metastasis; and (11) Eastern Cooperative Oncology Group (ECOG) performance status 0–1 [20]. The etiology of HCC (HCV-related or other [HBV-related or non-B, non-C-related]) and the size of the tumor on imaging were taken into consideration when dividing patients into the three groups. The sample size was estimated based on our previously reported 3-year disease-free survival rates in selective and whole-liver groups, being 25 and 60%, respectively [19]. We needed 37 patients in each group for a type I error rate of 5% and a type II error rate of 20% with a two-tailed test. Among the 124 patients, TACE was performed preoperatively in 81. Patients were randomized to receive chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization without gelatin sponge for the non-cancerous liver (whole-liver group, $n = 39$), or no preoperative TACE (control group, $n = 43$). The study protocol was explained to all patients, and they understood that they would be randomly selected for one of the above three groups. All patients gave written informed consent to participation in the trial. They were randomized by the envelope method and were informed of the result of the randomization before angiography. All operations were performed by the same surgeon, who had experience of over 700 hepatic resections. The protocol for this study was approved by the ethics committee of Kansai Medical University. The primary outcome measures were disease-free survival rate and overall survival rate. Secondary outcome measures included procedure-related complications and hospital mortality (Fig. 1).

Chemolipiodolization

A catheter was selectively inserted into the right or left hepatic artery, a segmental artery, or a subsegmental artery by Seldinger's method. In the selective group, TACE was performed via the right hepatic artery in 16 patients, the left hepatic artery in 10 patients, a segmental artery in 9 patients, and a subsegmental artery in 7 patients. In the whole-liver group, TACE (i.e., chemolipiodolization with gelatin sponge) was performed via the right hepatic artery in 18 patients and the left hepatic artery in 13 patients to target the tumor, while chemolipiodolization alone was performed on the non-cancerous side via the left or right hepatic artery. In a further 8 patients, TACE was performed via a right or left subsegmental artery to target the tumor and chemolipiodolization of the non-cancerous liver was performed via the right and left hepatic arteries as the catheter was withdrawn. The selective group was treated with epirubicin (Farmorubicin) at a mean ($\pm$ standard deviation [SD]) dose of 47.0 $\pm$ 17.8 mg, iodized oil (Lipiodol) at a mean volume of 3.8 $\pm$ 2.1 ml, and gelatin sponge particles. In the whole-liver group, epirubicin (28.1 $\pm$ 5.5 mg), Lipiodol (2.9 $\pm$ 1.4 ml), and gelatin sponge particles were used to treat the tumor, while only epirubicin (22.2 $\pm$ 6.2 mg) and Lipiodol (1.9 $\pm$ 0.8 ml) were infused into the non-cancerous liver. In the control group, only angiography was performed.

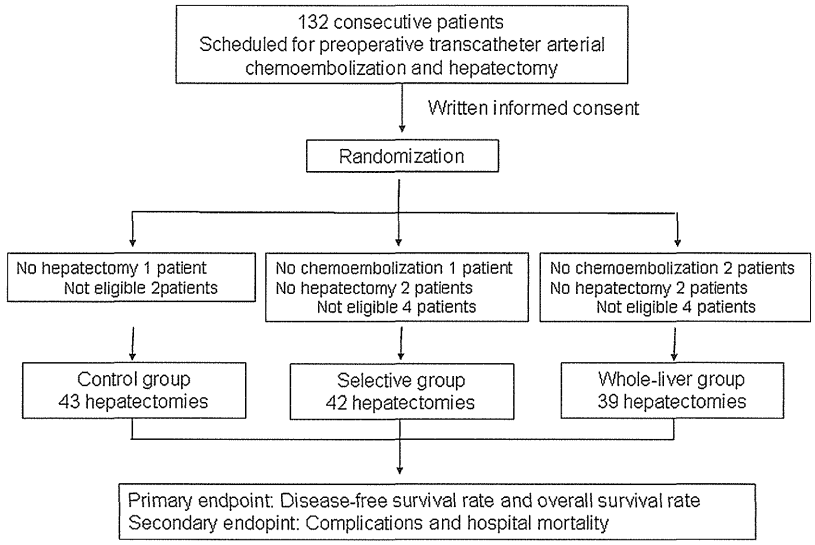

Fig. 1 Study design. We randomly divided patients into three groups: chemolipiodolization with gelatin sponge (equal to transcatheter arterial chemoembolization [TACE]) targeting the tumor (selective group, $n = 42$), chemolipiodolization with gelatin sponge (equal to TACE) targeting the tumor plus chemolipiodolization without gelatin sponge for the non-cancerous liver (whole-liver group, $n = 39$), or no preoperative TACE (control group, $n = 43$)

Clinicopathologic Variables and Surgery

Before randomization, each patient underwent conventional liver function tests, measurement of the indocyanine green retention rate at 15 min (ICGR15), and technetium-99m-diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy [21]. Hepatitis screening was undertaken by testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb). The levels of α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were also measured. Surgical procedures were classified according to the Brisbane terminology proposed by Strasberg et al. [22]. In brief, anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory, and was classified as hemihepatectomy (resection of half of the liver), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of two Couinaud subsegments [23]), or segmentectomy (resection of one Couinaud subsegment). All of the other procedures were non-anatomic and were classified as limited resection. Peripheral tumors and those with extrahepatic growth were managed by limited resection because this achieved adequate surgical margins. Central tumors located near the hepatic hilum or major vessels were treated by enucleation because it was too difficult or dangerous to remove enough of the liver to obtain an adequate margin. One senior pathologist reviewed all the specimens for histologic confirmation of the diagnosis. The width of the surgical margin was measured from the tumor border to the resection line. We evaluated the extent of necrosis on the largest tumor at its greatest diameter, even in cases with multiple tumors. The tumor stage was defined according to the TNM classification [24].

Follow-Up

Patients who survived were followed up after discharge, with physical examination, liver function tests, and ultrasound, computed tomography (CT), or magnetic resonance imaging being performed at least every 3 months to detect intrahepatic recurrence. Chest radiographs were also obtained to detect pulmonary metastases and chest CT was performed if the plain radiograph showed any abnormalities. Bone metastases were diagnosed by bone scintigraphy.

If the recurrence of HCC was detected by changes in the levels of tumor markers or by imaging, recurrence limited to the remnant liver was treated by TACE, lipiodolization, re-resection, or percutaneous local ablation therapy, such as RFA. If extrahepatic metastases were detected, active treatment was undertaken in patients with good hepatic functional reserve (Child–Pugh class A or B) and good performance status (0 or 1) who had a solitary extrahepatic metastasis and no evidence of intrahepatic recurrence, while other patients were treated only with radiation therapy to control symptoms caused by bone metastases.

Statistical Analysis

The results were expressed as the mean ± SD. Continuous variables were evaluated with the Mann–Whitney *U*-test or the Kruskal–Wallis test, as appropriate. Categorical data were compared with the Chi-square test or Fisher's exact test. The Kaplan–Meier method was used to calculate the

disease-free survival rate and the overall survival rate as of June 2010, and the significance of differences in survival rates was assessed with the generalized log-rank test. In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

There were no serious side effects of selective TACE or whole-liver chemolipiodolization. The interval between selective TACE, whole-liver chemolipiodolization, or angiography and hepatic resection was 21.2 ± 10.8, 23.0 ± 13.2, and 20.0 ± 13.2 days, respectively. Table 1 shows the preoperative characteristics of the patients in the three groups. There were no significant differences among the groups with respect to gender, age, Child–Pugh class, etiology of hepatitis or cirrhosis, alcohol abuse, preoperative liver function, or serum AFP and PIVKA-II levels. The operative results and pathologic findings in each group are listed in Table 2. The operating time, blood loss, requirement for transfusion, and operative procedures did not differ significantly among the three groups, nor did the rates of postoperative complications and hospital deaths. There were no significant differences in tumor size or the number of tumors detected on imaging before randomization among the groups. Although the tumor sizes measured in the surgical specimens were smaller in the selective group and the whole-liver group compared with the control group, the differences were not significant. In the selective, whole-liver, and control groups, complete tumor necrosis was confirmed in 9/42 patients (21%), 8/39 patients (21%), and 0/43 patients (0%), respectively. The other pathological characteristics of the tumors were comparable among the three groups.

Recurrence and Survival

The pattern of recurrence and time to recurrence in the three groups are shown in Table 3. A total of 27 patients in the selective group, 28 patients in the whole-liver group, and 26 patients in the control group developed recurrence of HCC. Extrahepatic recurrence was significantly less common in the selective and whole-liver groups compared with the control group. However, the percentage of intrahepatic recurrences due to multinodular/diffuse tumors and the incidence of recurrence within 6 months or 1 year following curative resection were not significantly different among the three groups.

The disease-free survival rates of the entire TACE group (selective and whole-liver groups) and the control group were 65 and 53% at 1 year, and 27 and 32% at 3 years, respectively (Fig. 2a). The overall survival rates of the entire TACE group and the control group were 88 and 83% at 1 year, 75 and 60% at 3 years, and 47 and 56% at 5 years, respectively (Fig. 2b). There were no significant

Table 1 Preoperative clinical characteristics of the three groups

	Control group ($n = 43$)	Selective group ($n = 42$)	Whole-liver group ($n = 39$)	*P*-value
Sex (male/female)	32/11	35/7	30/9	0.5921
Age (years)	66.1 ± 10.6	68.1 ± 5.7	66.8 ± 5.4	0.5122
Child–Pugh class (A/B)	39/4	37/5	34/5	0.8708
Etiology (HBV/HCV/NBC)	11/23/9	4/30/8	6/29/4	0.1663
Alcohol abuse (+/−)	17/26	19/23	19/20	0.6981
Platelet count (10^4/μl)	18.9 ± 10.6	15.2 ± 7.5	15.1 ± 6.9	0.2448
Total bilirubin (mg/dl)	0.89 ± 0.87	0.86 ± 0.32	0.89 ± 0.41	0.3861
Albumin (g/dl)	3.64 ± 0.57	3.67 ± 0.39	3.50 ± 0.47	0.2804
AST (IU/l)	47 ± 34	46 ± 23	47 ± 21	0.5452
ALT (IU/l)	44 ± 37	40 ± 25	45 ± 23	0.3158
Prothrombin time (%)	89 ± 14	86 ± 13	84 ± 14	0.3568
ALP (U/l)	353 ± 162	346 ± 165	365 ± 144	0.6605
γ-GTP (U/l)	99 ± 69	87 ± 95	101 ± 96	0.1859
ICGR15 (%)	15.5 ± 8.3	19.0 ± 9.5	19.2 ± 9.5	0.1384
GSA Rmax (mg/min)	0.554 ± 0.211	0.505 ± 0.194	0.584 ± 0.277	0.3985
Hyaluronic acid (ng/ml)	175 ± 165	199 ± 226	289 ± 385	0.3140
AFP (ng/ml)	858 ± 5,269	2,432 ± 11,638	1,791 ± 9,898	0.2750
PIVKA-II (mAU/ml)	2,385 ± 9,481	4,845 ± 17,126	1,124 ± 3,970	0.8634

The data represent the mean ± standard deviation (SD) or the number of patients

HBV hepatitis B virus, *HCV* hepatitis C virus, *NBC*, non-hepatitis B or C virus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyltransferase, *ICGR15* indocyanine green retention rate at 15 min, *GSA Rmax* maximum removal rate of technetium-99m-diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA), *AFP* α-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II

Table 2 Intraoperative and postoperative characteristics of the three groups

	Control group ($n = 43$)	Selective group ($n = 42$)	Whole-liver group ($n = 39$)	P-value
Operating time (min)	321 ± 124	300 ± 100	318 ± 135	0.8368
Operative blood loss (ml)	1,875 ± 1,841	1,418 ± 1,324	1,309 ± 1,218	0.3953
Blood transfusion (+/−)	20/23	15/27	13/26	0.4195
Operative procedure (limited/anatomic resection)	33/10	30/12	29/10	0.8545
No. of patients with complications	8 (19%)	3 (7%)	5 (13%)	0.2888
Hospital death	1 (2%)	1 (2%)	0 (0%)	0.6272
Postoperative hospital stay (days)	20 ± 18	16 ± 5	18 ± 12	0.1685
Tumor size on imaging before TACE (cm)	4.86 ± 4.12	4.30 ± 2.13	4.02 ± 3.88	0.7668
Tumor size in specimen (cm)	4.94 ± 3.52	3.66 ± 1.95	3.45 ± 2.15	0.1610
No. of tumors on imaging before TACE (single/multiple)	34/9	33/9	32/7	0.9156
No. of tumors in specimen (single/multiple)	32/11	32/10	31/8	0.8609
Histology (well/moderately/poorly/complete necrosis)	3/34/6/0	3/30/0/9	1/29/1/8	0.0052
Microscopic capsule (+/−)	38/5	38/4	38/1	0.2940
Microvascular invasion (+/−)	28/15	31/11	24/15	0.4785
Microscopic surgical margin (+/−)	5/38	4/38	2/37	0.5763
Associated liver disease (normal/hepatitis/cirrhosis)	4/28/11	1/27/14	2/24/13	0.6581
Tumor stage (I + II/III + IV)	31/12	31/11	30/9	0.8807

The data represent the mean ± standard deviation (SD) or the number of patients

Table 3 Patterns and timing of recurrence

	Control group ($n = 26$)	Selective group ($n = 27$)	Whole-liver group ($n = 28$)	P-value
Extrahepatic recurrence	7/26 (27%)	3/27 (11%)	1/28 (4%)	0.0393
Intrahepatic recurrence				0.8829
Nodular recurrence	6/19 (32%)	6/24 (25%)	8/27 (30%)	
Multinodular/diffuse recurrence	13/19 (68%)	18/24 (75%)	19/27 (70%)	
Timing of recurrence				
≤6 months	7/26 (27%)	6/27 (22%)	4/28 (14%)	0.5128
≤12 months	18/26 (69%)	13/27 (48%)	14/28 (50%)	0.2323

The data represent the number (percentage) of patients

differences in disease-free survival ($P = 0.6603$) or overall survival ($P = 0.4115$) between the two groups. Comparing the three groups, the disease-free survival rates of the selective group, whole-liver group, and control group were 67, 63, and 53% at 1 year, and 29, 27, and 32% at 3 years, respectively (Fig. 3a). The overall survival rates of the selective, whole-liver, and control groups were 91, 84, and 83% at 1 year, and 80, 70, and 60% at 3 years, respectively (Fig. 3b). There were no significant differences in disease-free survival ($P = 0.8303$) or overall survival ($P = 0.7126$) among the three groups.

When only patients with a solitary tumor measuring ≥5 cm in the greatest diameter were analyzed, the disease-free survival rates of the selective, whole-liver, and control groups were 50, 34, and 44% at 1 year, and 10, 11, and 9% at 3 years, respectively ($P = 0.8650$) (Fig. 4a). Among these patients, there were also no differences in the overall survival rate between the selective, whole-liver, and control groups, with survival rates of 82, 79, and 67% at 1 year, and 53, 68, and 47% at 3 years, respectively ($P = 0.7264$) (Fig. 4b).

Discussion

In our previous retrospective study, we found that preoperative chemolipiodolization of the whole liver achieved significant prolongation of both disease-free survival and overall survival for HCC patients [19]. The precise mechanism remains unclear, but some possible explanations are: (1) subclinical micrometastases due to portal vein dissemination or multicentric primary tumors are eliminated by whole-liver therapy and (2) reducing the tumor burden before surgery may lessen the chance of developing resistance to chemotherapy. TACE is a well-recognized treatment for HCC, either as adjuvant therapy or as a

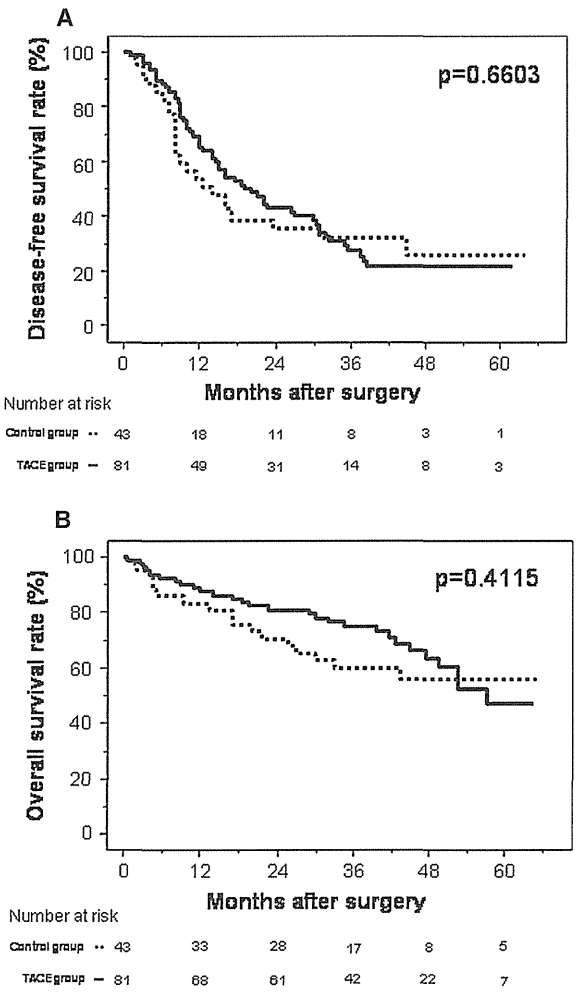

Fig. 2 **a** Comparison of disease-free survival after the resection of hepatocellular carcinoma (HCC) between patients receiving preoperative selective TACE and patients receiving preoperative TACE plus whole-liver chemolipiodolization (entire TACE group, $n = 81$, *solid line*) and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in disease-free survival between the two groups ($P = 0.6603$). **b** Comparison of overall survival after the resection of HCC between patients receiving preoperative selective TACE and patients receiving preoperative TACE plus whole-liver chemolipiodolization (entire TACE group, $n = 81$, *solid line*) and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in overall survival between the two groups ($P = 0.4115$)

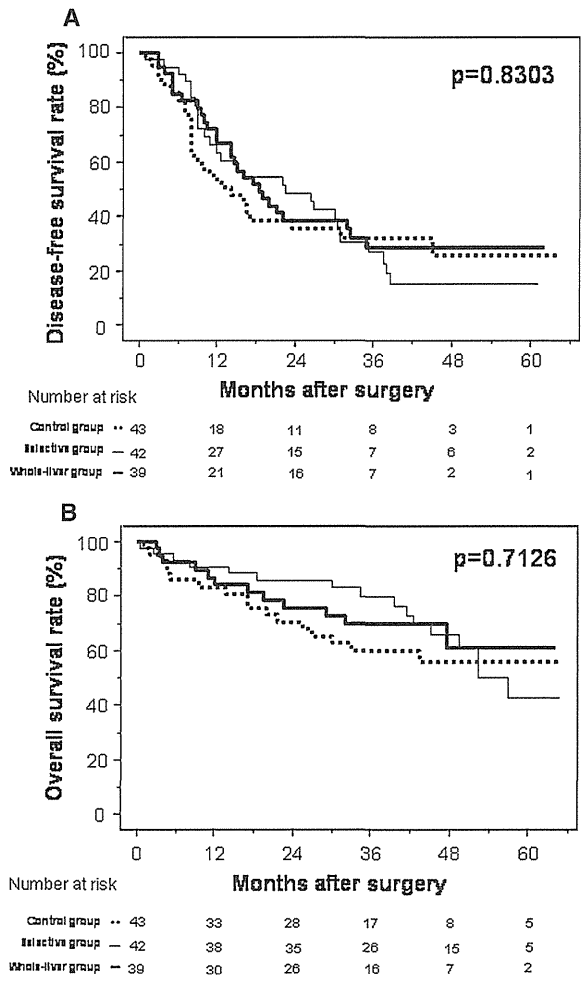

Fig. 3 **a** Comparison of disease-free survival after the resection of HCC among patients receiving preoperative selective TACE (selective group, $n = 42$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver group, $n = 39$, *thick solid line*), and patients not receiving preoperative TACE (control group, $n = 43$, *dotted line*). There were no significant differences in disease-free survival among the three groups ($P = 0.8303$). **b** Comparison of overall survival after the resection of HCC among the selective group ($n = 42$, *thin solid line*), the whole-liver group ($n = 39$, *thick solid line*), and the control group ($n = 43$, *dotted line*). There were no significant differences in overall survival among the three groups ($P = 0.7126$)

definitive procedure in patients whose tumors are considered to be unresectable [25, 26]. Preoperative TACE is not only intended to prevent recurrence by controlling intrahepatic spread via the portal system, but also to facilitate surgery by reducing tumor bulk. In particular, minimizing resection of the non-tumorous liver is vital in patients with cirrhosis to avoid postoperative hepatic failure. Uchida et al. [14] reported a lower survival rate among cirrhosis patients who underwent TACE prior to the resection of HCC compared with patients who did not undergo TACE, and they recommended against preoperative TACE for patients with cirrhosis because the procedure could accelerate the deterioration of liver function. Lu et al. [11] performed a retrospective analysis of 120 HCC patients and concluded that preoperative TACE might benefit those with tumors >8 cm in diameter, but not those with tumors

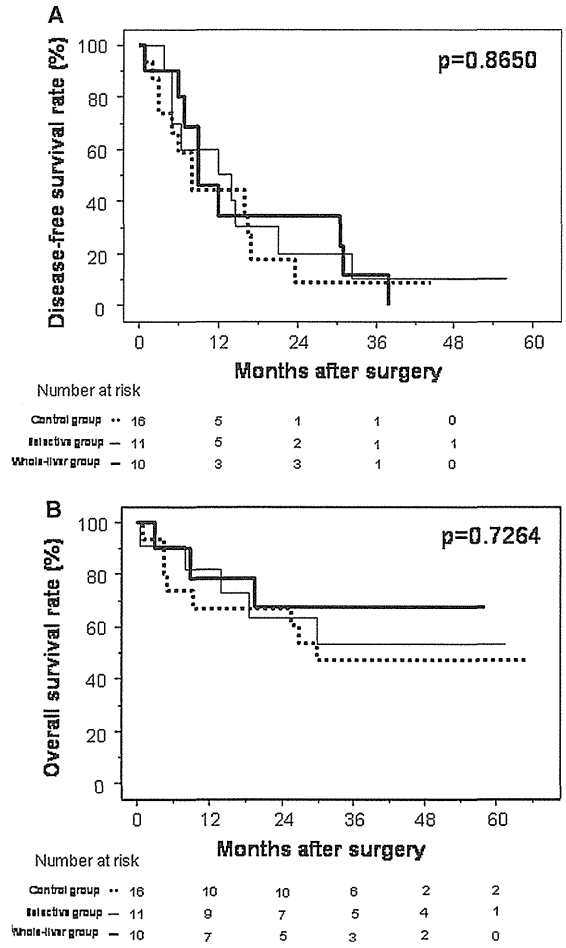

Fig. 4 **a** Comparison of disease-free survival after resection of a solitary HCC ≥5 cm in the greatest diameter among patients receiving preoperative selective TACE (selective group, $n = 11$, *thin solid line*), patients receiving preoperative TACE plus whole-liver chemolipiodolization (whole-liver group, $n = 10$, *thick solid line*), and patients without preoperative TACE (control group, $n = 16$, *dotted line*). There were no significant differences in disease-free survival among the three groups ($P = 0.8650$). **b** Comparison of overall survival after resection of a solitary HCC ≥5 cm in the greatest diameter among the selective group ($n = 11$, *thin solid line*), the whole-liver group ($n = 10$, *thick solid line*), and the control group ($n = 16$, *dotted line*). There were no significant differences in overall survival among the three groups ($P = 0.7264$)

2–8 cm in diameter. In contrast, it was reported that downstaging or total necrosis of the tumor was achieved by preoperative TACE in 62% of 103 HCC patients with cirrhosis, leading to an improvement of disease-free survival after liver resection and liver transplantation [13]. Thus, the value of preoperative TACE is still controversial.

A meta-analysis including seven randomized clinical trials was undertaken in the late 1990s to investigate the usefulness of TACE for treating unresectable HCC, which demonstrated an improvement in 2-year survival (odds ratio 0.53, $P = 0.017$) compared with control patients who were treated conservatively or received suboptimal management [27]. This established the role of TACE as the standard care for unresectable HCC, whether as palliative therapy or to improve resectability [27]. Subsequent investigations were directed towards the preoperative use of TACE as neoadjuvant therapy to prevent recurrence. To assess the clinical efficacy of preoperative TACE for resectable HCC, two randomized trials were conducted in 1995 and 1996 [15, 17] (Table 4). Both of these trials found no improvement in disease-free survival following neoadjuvant TACE, and Wu et al. [17] reported worse overall survival in the TACE group. In 2009, a randomized trial of neoadjuvant TACE for large resectable HCC was reported [18]. The results were similar, with no difference in disease-free survival or overall survival between the groups with or without TACE (Table 4). The present study is the fourth randomized trial to compare the long-term prognosis after the resection of HCC in patients with or without preoperative TACE. However, it is difficult to simply compare these trials. Zhou et al. [18] and Wu et al. [17] enrolled patients with large HCCs, whereas Yamasaki et al. [15] and the current trial enrolled patients with smaller HCCs. In the trial reported by Wu et al. [17], patients who received TACE underwent surgery a mean of 17.9 weeks after the detection of HCC, which was significantly longer than those not receiving TACE, who underwent resection 2.3 weeks after the detection of HCC ($P = 0.009$). In this study, patients in all groups underwent surgery in 20–23 days. Differences in the conclusions of the different trials could be attributed to the differences in the study designs or background characteristics.

We found no significant differences in disease-free survival or overall survival between the entire TACE group (selective and whole-liver groups) and the control group, or among the whole-liver, selective, and control groups, even among patients with tumor size >5 cm (Figs. 2, 3, and 4). The extrahepatic recurrence rate was significantly lower in the selective and whole-liver groups compared with the control group. However, even though preoperative TACE induced complete tumor necrosis, there were no significant differences in the pattern of intrahepatic recurrence or the time until recurrence among the three groups.

In conclusion, preoperative selective TACE or TACE plus whole-liver chemolipiodolization neither reduced the incidence of postoperative recurrence nor prolonged survival in patients with resectable HCC. Thus, despite its safety and feasibility, we cannot recommend preoperative TACE as a routine procedure before hepatectomy in patients with resectable HCC.

Table 4 Results of randomized controlled trials on neoadjuvant transarterial chemoembolization and non-transarterial chemoembolization before hepatectomy for resectable hepatocellular carcinoma (HCC)

Study	Year	Total patients (*n*)	(TACE/non-TACE) patients (*n*)	Percentage of HBV (TACE/non-TACE)	Percentage of HCV (TACE/non-TACE)	Percentage of Child–Pugh class A (TACE/non-TACE)
This study		124	81/43	12/26	73/53	88/91
Zhou et al. [18]	2009	108	52/56	98/98	0/0	84/89
Yamasaki et al. [15]	1996	97	50/47	NR	NR	NR
Wu et al. [17]	1995	52	24/28	75/68	NR	92/86

Study	Mean preoperative tumor size (cm) (TACE/non-TACE)	Cytotoxic agent	TACE sessions per patient (*n*)	Complete necrosis (%) (TACE/non-TACE)
This study	4.1/5.0	EPI	1	**21/0**
Zhou et al. [18]	9.0/9.5	5FU, CDDP	1.5	**15/0**
Yamasaki et al. [15]	3.1/3.3	DOX	1	**16/NR**
Wu et al. [17]	14.3/14.5	DOX	3	NR/NR

Study	Morbidity (%) (TACE/non-TACE)	Mortality (%) (TACE/non-TACE)	3-year disease-free survival (%)	3-year overall survival (%) (TACE/non-TACE)
This study	10/19	1/2	28/32	75/60
Zhou et al. [18]	**Adhesions and longer operating time in TACE group**	0/0	26/21	40/32
Yamasaki et al. [15]	NR	6/9	54/42	91/88
Wu et al. [17]	NR	4/7	40/50	**33/60**

Significant differences are shown in **bold**. The number of patients receiving TACE in this study was 81 (42 patients in the selective group and 39 patients in the whole-liver group)

TACE transcatheter arterial chemoembolization, *NR* not reported, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *EPI* epirubicin, *5FU* 5-fluorouracil, *CDDP* cisplatin, *DOX* doxorubicin

Conflict of interest None.

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