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Serosal invasion in TNM staging of mass-forming intrahepatic cholangiocarcinoma

Takahiro Uenishi[1,3], Osamu Yamazaki[2], Takatsugu Yamamoto[3], Kazuhiro Hirohashi[1], Hiromu Tanaka[1], Shogo Tanaka[1], Seikan Hai[1], and Shoji Kubo[1]

[1]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
[2]Department of Gastrointestinal Surgery, Osaka City General Hospital, Osaka, Japan
[3]Department of Surgery, Ishikiri Seiki Hospital, Osaka, Japan

Abstract
Background/Purpose. The Liver Cancer Study Group of Japan established a tumor-nodule-metastasis (TNM) staging system for mass-forming intrahepatic cholangiocarcinoma, with T determined by tumor number and size and vascular or serosal invasion. Serosal invasion is not considered in the designation established by the International Union Against Cancer.
Methods. Sixty-three patients who underwent hepatic resection for mass-forming intrahepatic cholangiocarcinoma were investigated retrospectively, with the investigation including univariate and multivariate analyses of potential prognostic factors.
Results. By log-rank test, tumor size more than 3.0 cm, vascular invasion, lymph node metastasis, intrahepatic metastasis, and involved resection margin, but not serosal invasion, were associated significantly with poor prognosis. Even in patients with serosal invasion, the postoperative outcome was much better in those without than in those with vascular invasion. Multivariate analysis identified vascular invasion, lymph node metastasis, and an involved resection margin as independent prognostic factors. When serosal invasion was excluded from tumor staging, the 5-year survival rates became more clearly stratified: 100% in those with stage I disease, 62% in those with stage II, 25% in those with stage III, and 7% for patients with stage IV.
Conclusions. Serosal invasion showed no survival impact after hepatic resection for mass-forming intrahepatic cholangiocarcinoma. When serosal invasion was omitted from the TNM staging proposed by the Liver Cancer Study Group of Japan, stratification of postoperative survival between stages was more effective.

Key words Mass-forming intrahepatic cholangiocarcinoma · Serosal invasion · Tumor-nodule-metastasis classification · Prognosis

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Introduction

Distinct differences have been shown in the mechanisms of carcinogenesis and biologic behavior between hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC).[1–5] However, the TNM staging system defined by the International Union Against Cancer (UICC), developed solely from clinical experience in treating HCC, is used widely for both HCC and ICC.[6] Although ICC is the second most common primary hepatic cancer after HCC, it accounts for only 5% to 10% of hepatic cancer.[4,5] Because of the rarity and low resectability rates of ICC, few studies have reported postoperative outcomes from large numbers of patients.[7–13] However, current developments in diagnostic procedures, operative techniques, and perioperative management have made hepatic resection for ICC more frequent.[7–17] Recently, the Liver Cancer Study Group of Japan proposed a new TNM staging system for the mass-forming (MF) type of ICC.[18] In this system, the T factor is determined by three conditions: number of tumors, tumor size, and the presence of either vascular invasion or serosal invasion. On the other hand, serosal invasion is not a T-factor component in the International Union Against Cancer (UICC) tumor staging.[6] The relationship between the presence of serosal invasion and patient survival after surgery for ICC remains unclear, because few studies have analyzed serosal invasion as a prognostic factor in patients with ICC.[10,12,19] The objective of the present investigation was to clarify whether serosal invasion influenced postoperative survival and whether this component of the new TNM classification improved the prediction of postoperative survival in patients with MF-type ICC.

Patients and methods

Between January 1983 and December 2003, hepatic resection was performed in 81 patients with ICC. Hilar

cholangiocarcinoma, eponymically termed Klatskin tumor, was excluded from this study. The 81 ICCs were classified into three types according to the macroscopic classification proposed by the Liver Cancer Study Group of Japan.[18] The MF type ($n = 63$) showed a nodular mass with a distinct border separating it from the liver parenchyma. The periductal infiltrating (PI) type ($n = 15$) was diffuse, extending along bile ducts. The intraductal-growth (IG) type ($n = 3$) showed papillary growth within a bile duct lumen. When an ICC tumor included more than one component of these three macroscopic types, the tumor was categorized according to the predominant component. The 63 MF tumors included 34 MF+PI-type ICC. The histologic diagnoses in the 63 patients with MF tumors were reviewed to identify significant prognostic factors, using the histologic classification of the Liver Cancer Study Group of Japan.[18] When multiple lesions were demonstrated, the largest nodule was identified as the primary tumor, while the others were defined as intrahepatic metastasis. The tumor-free margin was defined as no histologic evidence of tumor cells on the surgical cut surface. Tumor stage was defined according to the TNM classification for MF-type ICC proposed by the Liver Cancer Study Group of Japan (Table 1).[18]

All patients were followed up after surgery until either death or the end of the study (December 31, 2004). Patient characteristics and histologic features, including components of tumor-staging schemes, were analyzed as variables possibly affecting prognosis. Cumulative survival rates were calculated by the Kaplan-Meier method, and these rates are reported with 95% confidence intervals. Survival differences were tested in a univariate manner, using the log-rank test. Multivariate analysis was performed using a Cox regression model with forward stepwise selection; multivariate risk ratios are presented with 95% confidence intervals.

Table 1. TNM staging system proposed by the Liver Cancer Study Group of Japan[18]

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	N1	M0
	Any T	Any N	M1

T category
T1, meets all three requirements below; T2, meets any two requirements below; T3, meets one requirement below; T4, meets no requirements
Requirements
Number of tumors: solitary
Size of tumor: diameter less than 2 cm
No invasion of portal vein, hepatic vein, or hepatic serosa
N category
N0, no metastasis to lymph nodes; N1, metastasis to any lymph node
M category
M0, absence of distant metastasis; M1, presence of distant metastasis

Results

Patients

The 63 patients with MF tumors consisted of 46 men and 17 women, with a mean age of 63.4 years (range, 35 to 84 years). Right upper-quadrant abdominal pain, the most common symptom, was present in 21 patients. Other symptoms were weight loss in 10 patients, fever in 5, and jaundice in 6. Thirty-four tumors were located in the left hepatic lobe, while 29 were in the right lobe. Twenty-six tumors invaded the hepatic hilus. Healey bisegmentectomy, or more extended hepatic resection, was performed in 45 patients. The remaining 18 resections included 11 segmentectomies, 2 subsegmentectomies, and 5 limited hepatic resections, with subsegments corresponding to segments in the classification of Couinaud.[20] Lymph node dissection, including the hepatoduodenal ligament, the area surrounding the common hepatic artery, and the retropancreatic region was performed in 30 patients. Of these 30 patients, 20 had tumors located in the left hepatic lobe, so their lymph node dissections also included nodes adjoining the cardiac portion and the lesser curvature of the stomach. Resection included the caudate lobe in 23 patients who had tumor invasion of the hepatic hilus. Tumor diameters ranged from 1.4 to 16.0 cm (mean, 7.0 cm). Microscopically, vascular and serosal invasion were present in 30 and 29 patients, respectively. Lymph node metastasis and intrahepatic metastasis were confirmed histologically in 21 and 23 patients, respectively. Of the 63 patients, 3 had stage I tumors, 15 had stage II tumors, 16 had stage III tumors, 8 had stage IVa tumors, and 21 had stage IVb tumors.

Univariate and multivariate analyses of prognostic factors

Median survival time after hepatic resection for MF-type ICC was 535 days. The survival rates of the 63 patients at 1, 3, and 5 years after surgery were 61%, 40%, and 33%, respectively. Six in -hospital deaths occurred (postoperative mortality rate, 9.5%).

A log-rank test indicated that tumor size of more than 3.0 cm ($P = 0.0473$), intrahepatic metastasis ($P = 0.0001$), tumors with vascular invasion ($P < 0.0001$), lymph node metastasis ($P < 0.0001$), and a microscopically involved resection margin ($P < 0.001$) were associated with a significantly lower survival rate (Table 2). Although the survival rate for patients with serosal invasion tended to be lower than that for those without serosal invasion (Fig. 1), no statistically significant difference was demonstrated ($P = 0.1687$; Table 2). In the patients with vascular invasion, the 5-year survival rates for patients with and without serosal invasion were 0% and 17%,

Table 2. Univariate analysis with respect to outcome

Factors	Number of patients	Survival rate, % (95% CI) 3 Years	5 Years	*P* value
Age, years				
<65	32	33 (17–50)	33 (17–50)	0.7387
≥65	31	47 (30–65)	30 (7–52)	
Sex				
Male	46	43 (28–57)	32 (15–49)	0.6810
Female	17	33 (10–56)	33 (10–56)	
Tumor size, cm				
<3.0	8	88 (65–100)	58 (9–100)	0.0473
≥3.0	55	33 (20–49)	29 (15–42)	
Intrahepatic metastasis				
Present	23	6 (0–16)	6 (0–16)	0.0001
Absent	40	59 (44–74)	48 (29–67)	
Vascular invasion				
Present	30	20 (6–34)	13 (0–28)	<0.0001
Absent	33	59 (44–74)	48 (29–67)	
Serosal invasion				
Present	29	32 (14–50)	24 (5–43)	0.1687
Absent	34	46 (29–63)	39 (21–58)	
Lymph node metastasis				
Present	21	5 (0–14)	5 (0–14)	<0.0001
Absent	42	58 (42–73)	47 (28–65)	
Resection margin				
Free of tumor	51	48 (34–62)	39 (24–55)	<0.0001
Involved by tumor	12	8 (0–24)	—	

CI, confidence interval

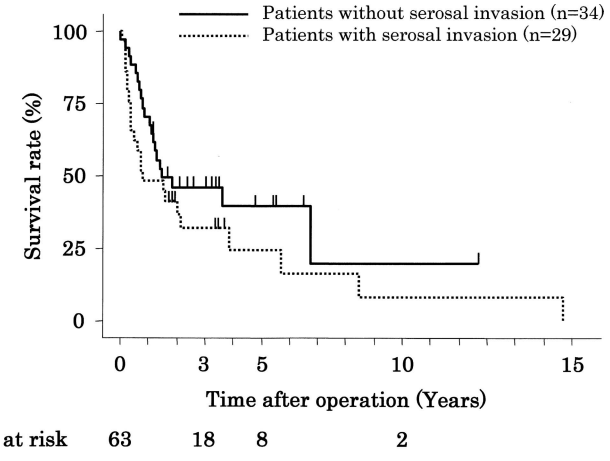

Fig. 1. Survival of 63 patients after hepatic resection for mass-forming intrahepatic cholangiocarcinoma, according to serosal invasion

respectively. These survival rates in the patients with vascular invasion did not differ according to serosal invasion. On the other hand, the 5-year survival rates for patients without vascular invasion were approximately 50%, even in the patients with serosal invasion. Despite the presence of serosal invasion, the postoperative outcome in patients without vascular invasion was much better than that in those with vascular invasion.

Table 3. Multivariate analysis of factors predicting postoperative outcome

Variable	Multivariate risk ratio (95% CI)	*P* value
Vascular invasion		
Absent	1	
Present	2.1 (1.0–4.1)	0.0478
Lymph node metastasis		
Absent	1	
Present	3.0 (1.4–6.0)	0.0030
Resection margin		
Free of tumor	1	
Involved by tumor	3.5 (1.6–7.9)	0.0025

CI, confidence interval

By multivariate analysis, the presence of vascular invasion (risk ratio, 2.1; $P = 0.0478$), the presence of lymph node metastasis (risk ratio, 3.0; $P = 0.0030$), and a microscopically involved resection margin (risk ratio, 3.5; $P = 0.0025$) were independent factors associated with poor postoperative outcome (Table 3).

Survival stratification by staging of MF-type ICC

When the cumulative survival rate was calculated for each subgroup classified by the TNM staging system proposed by the Liver Cancer Study Group of Japan,[18]

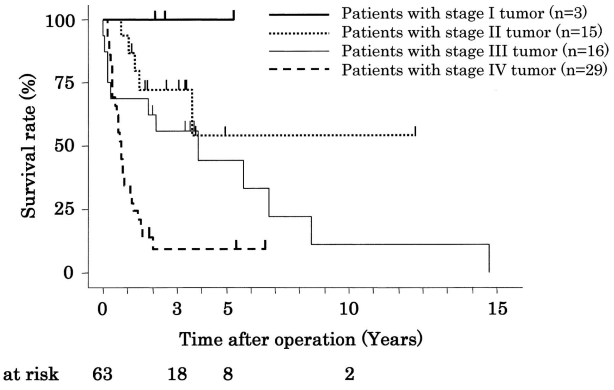

Fig. 2. Survival of 63 patients after hepatic resection for mass-forming intrahepatic cholangiocarcinoma, according to tumor staging

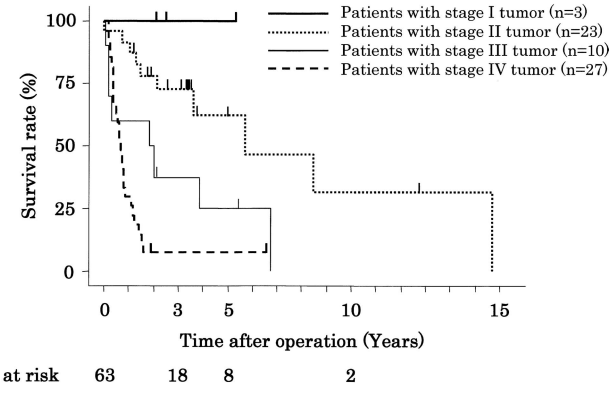

Fig. 3. Survival of 63 patients after hepatic resection for mass-forming intrahepatic cholangiocarcinoma, according to current Japanese tumor staging,[18] with omission of serosal invasion from the staging

the survival rates for patients with stage II tumor and stage III tumor, respectively, were 72% and 56% at 3 years; and 54% and 44% at 5 years (Fig. 2); thus, patients with a stage II tumor showed survival comparable to that in patients with a stage III tumor. In contrast, when serosal invasion was omitted from the tumor-staging scheme, 3- and 5-year survival rates, respectively, were 100% and 100% for patients with stage I disease, 73% and 62% for patients with stage II disease, 38% and 25% for patients with stage III disease, and 7% and 7% for patients with stage IV disease (Fig. 3). Thus, when serosal invasion was not considered, a significant difference in survival became evident between patients with stage II and those with stage III tumors ($P = 0.026$).

Discussion

Although surgical resection offers the only chance for long-term survival in patients with ICC, the postoperative prognosis for ICC is still unsatisfactory because of the invasive characteristics of the disease.[7–17,21–27] The overall 5-year survival of patients with ICC has been reported to range from 16% to 42%.[7–12,16,17,21–26] Macroscopically, ICCs are classified into three tumor-growth patterns: MF, PI, and IG types.[18] Because differences in biologic behavior between macroscopic ICC types affect postoperative outcome,[9,10,13,16,21,28] the surgical strategy should be individualized according to macroscopic type.

Recently, the Liver Cancer Study Group of Japan proposed a new TNM staging scheme for MF-type ICC.[18] The staging system was based on an analysis of prognostic factors in 136 patients with MF-type ICC.[19] In that study,[19] a tumor size of 2 cm or more, lymph node metastasis, multiple tumors, serosal invasion, portal vein invasion, and hepatic vein invasion were judged to be statistically significant predictors of poor outcome. Among these factors, the presence of lymph node metastasis was reported to have the strongest prognostic influence in MF-type ICC. Therefore, in the Japanese system, a case with any lymph node metastasis (N category), accordingly, is assigned to stage IVb regardless of T category,[18] indicating that lymph node metastasis influences postoperative outcome to the same extent as distant metastasis (M category). In the present study, despite receiving lymph node dissection, 20 of 21 patients with nodal metastasis died within 2 years after surgery, and the presence of lymph node metastasis was identified as an independent predictor of poor postoperative outcome.

The T-category in the new Japanese staging system is determined according to the number of tumors, tumor diameter, and vascular and/or serosal invasion,[18] although serosal invasion is not a component of the UICC staging system.[6] Several previous studies have implicated various factors, including tumor size, intrahepatic metastasis, and vascular invasion as significant prognostic factors in ICC.[7–12,17,22–24] In the present study, the postoperative survival rates of patients who had a tumor size of more than 3.0 cm, vascular invasion, or intrahepatic metastasis were also significantly lower than those of other patients. Furthermore, vascular invasion was identified as an independent factor associated with poor postoperative outcome. In contrast, no difference in postoperative survival was noted between patients with and without serosal invasion. Indeed, the significance of serosal invasion for survival has been unclear, because few previous studies have addressed the issue.[10,12,19] Among these, Okabayashi et al.[12] reported that serosal invasion was not associated with poor prognosis, while another group of authors reported serosal invasion to be a negative prognostic factor on univariate analysis but not on multivariate analysis.[10] In our present study, the postoperative survival rate in patients with vascular

invasion was extremely poor, irrespective of the presence of serosal invasion. On the other hand, the postoperative outcome in patients without vascular invasion was much better than that in those with vascular invasion, even in the patients with serosal invasion. These findings suggest that serosal invasion alone has little value in predicting the survival of patients after hepatic resection for MF-type ICC.

Using the TNM staging system, including serosal invasion, proposed by the Liver Cancer Study Group of Japan,[18] we obtained a survival curve for patients with stage II tumors similar to that for patients with stage III tumors. In contrast, the exclusion of serosal invasion enabled us to note a significant difference in survival between patients with stage II and those with stage III tumors. Thus, the TNM staging system proposed by the Liver Cancer Study Group of Japan reliably defines differences in the postoperative survival of patients with ICC, particularly when serosal invasion is disregarded. However, a review of postoperative outcomes in a much larger number of patients with MF-type ICC will be needed to definitively resolve this issue.

In conclusion, serosal invasion alone had no impact on the survival of patients who underwent hepatic resection for MF-type ICC. When serosal invasion was omitted from the TNM staging components proposed by the Liver Cancer Study Group of Japan, postoperative survival was clearly stratified between stages.

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