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Impact of Surgical Margin on Prognosis and Recurrence in Intrahepatic Cholangiocarcinoma

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Objective: This study investigated the impact of surgical margin (SM) on the prognosis and recurrence of intrahepatic cholangiocarcinoma (ICC).

Summary of background data: The impact of SM on the prognosis remains controversial.

Methods: We analyzed 58 ICC patients who underwent macroscopically curative surgery. The patients were classified into 5 categories according to the SM; microscopically positive (R1), 0 to <1 mm, 1 to <5 mm, 5 to <10 mm, and ≥10 mm. The overall survival (OS) rate was significantly different for SM <1 mm or SM ≥1 mm; therefore, the cutoff value was set at 1 mm.

Results: Twenty-five patients (43.1%) had an SM <1 mm, and 33 (56.9%) had an SM ≥1 mm. The multivariate analysis identified SM <1 mm ($P = 0.027$) as an independent predictor of OS. After the propensity score matching based on tumor-related factors, the OS rate of the SM <1 mm group was significantly lower than that of the SM ≥1 mm group ($P = 0.013$). Peritoneal dissemination was significantly increased in the SM <1 mm group ($P = 0.007$). The postrecurrence survival rate of the SM <1 mm group was significantly lower than that of the SM ≥1 mm group ($P = 0.012$).

Conclusions: This study suggests that an SM of at least 1 mm should be achieved regardless of tumor status during ICC resection. An SM < 1 mm may indicate a higher risk of peritoneal dissemination.

Key words: Intrahepatic cholangiocarcinoma – Surgical margin – Hepatic resection – Prognosis – Recurrence

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Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer arising from the second or higher divisions of the intrahepatic bile ducts.[1,2] The incidence of ICC has been increasing; however, the survival has not improved.[3–6] Despite surgical resection being the only potential curative treatment for ICC, the prognosis after surgical resection is not fully satisfactory. The 5-year survival rate only ranges from 30% to 35%.[7] Regarding liver resection, a previous study reported that ICC patients who underwent major hepatectomy had an overall survival (OS) and relapse-free survival (RFS) equivalent to those who underwent a minor hepatectomy. Furthermore, major hepatectomy was associated with increased perioperative mortality and morbidity.[8] However, the impact of the surgical margin (SM) on long-term survival remains controversial. Reportedly, SM was significantly associated with the survival of ICC patients.[9–14] In contrast, some studies have concluded that SM had a limited effect on long-term outcomes.[15–18] In the present study, we investigated the association of SM with prognosis and recurrence patterns in ICC patients.

Methods

Informed consent

This study was performed in line with the principles of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of Nara Medical University Hospital (no. 3109). Because this was a retrospective study and the data analyzed were anonymized, and informed consent from all patients was obtained through an opt-out method on our hospital website in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Patients and data

A total of 58 ICC patients who underwent macroscopically curative surgical resection at Nara Medical University Hospital between January 2003 and March 2021 were included. We excluded the cases of R2 resection: macroscopically residual tumor.

The following baseline characteristics of the patients were obtained from their medical records: age, sex, comorbidities (including cardiovascular disease and diabetes mellitus), liver function, tumor number, tumor size, tumor location, lymph node metastasis, microvascular invasion, morphologic type, surgical approach, surgical procedure, lymphadenectomy, operative time, amount of blood loss, and adjuvant chemotherapy. ICCs located on the liver surface (superficial ICCs) were defined as those that extended to a depth of <5 cm from the diaphragmatic plane of the liver surface. In addition, the stage of ICC was defined according to the eighth edition of the American Joint Committee on Cancer TNM classification system. Lastly, we collected the results of blood tests performed preoperatively, including the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9).

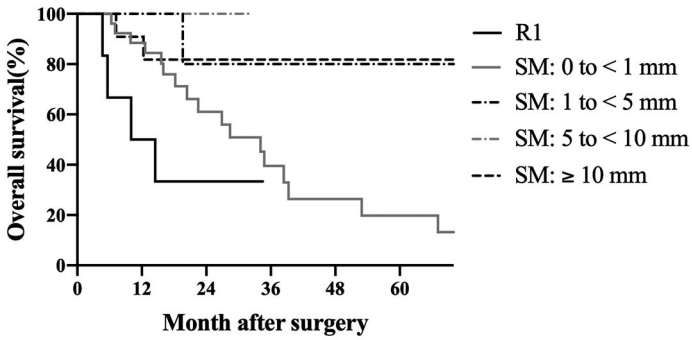
SM was defined as the shortest distance between the edge of the liver tumor and the transection line. In the event of multiple lesions, the shortest margin was recorded. In the present study, the patients were classified into 5 groups according to the margin width: microscopically positive (R1); SM microscopically negative (R0) and 0 to <1 mm; SM 1 to <5 mm; SM 5 to <10 mm; and SM ≥10 mm. Furthermore, we evaluated the OS of these 5 groups. Figure 1 summarizes the prognosis of each group. The OS rate was significantly different for SM <1 mm or SM ≥1 mm. There were no significant differences in the OS rates among the SM 1 to <5 mm, the SM 5 to <10 mm, and the SM ≥10 mm groups. Therefore, the cutoff value was set at 1 mm, and we categorized the patients into 2 groups.

Surgical procedure

The decision to perform partial resection or anatomical resection was determined by the location of the tumor and the historical background of the introduction of laparoscopic liver resection. Anatomic resection included segmentectomy, sectionectomy, hemihepatectomy, and trisectionectomy. Partial resection was defined as the resection of the tumor without regard to segmental, sectional, or lobar anatomy. Hilar lymph node dissection was performed for the central type of ICC: close to the left or right Glisson pedicle.

Follow-up

The patients were followed up every 4 months for up to 5 years after the initial operation and then every 6 months thereafter. During the follow-up, blood tests (including CEA and CA 19-9) and computed tomography were routinely performed. Adjuvant chemotherapy with TS-1, gemcitabine, or gemcitabine/cisplatin was performed for 6 months depending on performance status. Recurrence was defined as the appearance of a new lesion having radiologic features compatible with ICC.



No. at risk						
R1	6	4	2	1	1	1
SM: 0 to < 1 mm	27	23	13	8	5	4
SM: 1 to < 5 mm	10	9	5	5	4	4
SM: 5 to < 10 mm	3	2	2	1	1	1
SM: ≥ 10 mm	12	11	10	10	9	7

Fig. 1 OS of ICC patients according to the SM.

Statistical analyses

Continuous variables were expressed as mean and SD. The means were compared using Student *t* test. Categoric variables were presented as numbers and percentages, and the groups were compared using the χ^2 test or Fisher exact test. At the time of the final follow-up (August 2021), the median follow-up period was 20.2 months. The OS was defined as the period from the operation to death or final follow-up. RFS was defined as the duration from the operation to the recurrence of ICC. Survival curves were generated by the Kaplan-Meier method. The differences between curves were analyzed by the log-rank test. Cox regression analyses were used to determine hazard ratios. The variables with $P < 0.05$ on the univariate analysis were further assessed with the multivariate analysis. One-to-one propensity score matching was performed using logistic regression analysis. *P* values of <0.05 were considered statistically significant, and 95% confidence intervals were calculated. All statistical analyses were performed using SPSS (version 22.0, SPSS, Chicago, Illinois).

Results

Postoperative survival

Twenty-five patients (43.1%) were classified into the SM <1 mm group, and 33 patients (56.9%) were classified into the SM ≥1 mm group. Both the OS and RFS rates of the SM <1 mm group were significantly lower than those of the SM ≥1 mm group ($P < 0.001$ and $P < 0.001$, respectively). The 1-, 3-, and 5-year OS rates of the SM ≥1 mm group were 95.5%, 84.4%, and 84.4%, respectively, whereas those of the SM <1 mm group were 81.3%, 37.1%, and 18.5%, respectively (Fig. 2A). The 1-, 3-, and 5-year RFS rates of the SM ≥1 mm group were 82.3%, 55.1%, and 49.6%, respectively, whereas those of the SM <1 mm group were 40.1%, 17.5%, and 17.5%, respectively (Fig. 2B).

Predictive factors for OS

Table 1 shows the univariate and multivariate analysis of the factors associated with OS. In the univariate analysis, the following factors were significantly associated with OS; SM <1 mm ($P = 0.002$), female sex ($P = 0.017$), tumor size ≥3 cm ($P = 0.001$), multiple tumors ($P = 0.020$), CA 19-9 level ≥37 ng/mL ($P = 0.017$), microvascular invasion ($P < 0.001$), and lymph node metastasis ($P = 0.003$). The multivariate Cox regression analysis identified SM <1 mm ($P = 0.027$) and microvascular invasion ($P = 0.026$) as independent predictors of OS.

Predictive factors for RFS

Table 2 shows the univariate and multivariate analysis of the factors associated with RFS. In the univariate analysis, the following factors were significantly associated with RFS; SM <1 mm ($P = 0.005$), multiple tumors ($P = 0.007$), microvascular invasion ($P < 0.001$), and lymph node metastasis ($P = 0.015$). The multivariate Cox regression analysis identified microvascular invasion ($P = 0.002$) and multiple tumors ($P = 0.026$) as independent predictors of RFS.

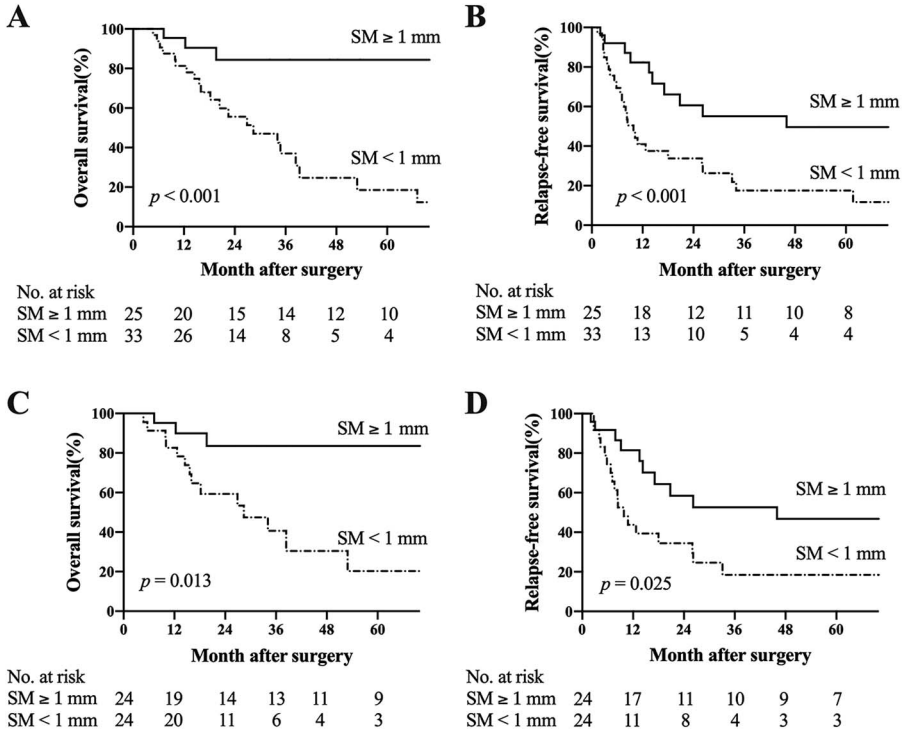


Fig. 2 (A) OS and RFS according to SM <1 mm or SM ≥1 mm ($P < 0.001$). (B) RFS according to SM <1 mm or SM ≥1 mm ($P < 0.001$). (C) OS according to SM <1 mm or SM ≥1 mm in the one-to-one propensity score matching ($P = 0.013$). (D) RFS according to SM <1 mm or SM ≥1 mm in the one-to-one propensity score matching ($P = 0.025$).

Table 1 Univariate and multivariate analysis of the factors associated with OS

		Univariate		Multivariate	
Variables	No. (%)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)		1.005 (0.959–1.053)	0.841		
Sex, female	21 (36.2)	2.703 (1.192–6.135)	0.017	1.712 (0.651–4.505)	0.276
Cardiovascular disease, present	32 (55.2)	1.189 (0.552–2.558)	0.658		
Diabetes mellitus, present	6 (10.3)	1.061 (0.248–4.527)	0.937		
Liver function, chronic hepatitis	22 (37.9)	0.723 (0.315–1.663)	0.446		
Tumor number, multiple	10 (17.2)	2.829 (1.175–6.813)	0.020	2.547 (0.945–6.863)	0.064
Tumor size ≥3 cm	39 (67.2)	3.657 (1.100–12.162)	0.034	1.433 (0.391–5.248)	0.587
Tumor location, nonsuperficial	23 (39.7)	1.173 (0.541–2.546)	0.686		
Lymph node metastasis, positive	9 (15.5)	3.897 (1.571–9.667)	0.003	1.775 (0.581–5.424)	0.314
Microvascular invasion, positive	38 (65.5)	6.798 (2.313–19.979)	<0.001	5.185 (1.219–22.044)	0.026
Morphologic type, mass forming	48 (82.8)	0.941 (0.377–2.346)	0.896		
CEA, ≥5 ng/mL	14 (24.1)	1.173 (0.492–2.799)	0.719		
CA 19-9, ≥37 ng/mL	26 (44.8)	2.637 (1.188–5.853)	0.017	1.686 (0.621–4.573)	0.305
Surgical approach, laparoscopic	15 (25.9)	0.934 (0.310–2.814)	0.903		
Surgical procedure, anatomic	48 (82.8)	1.738 (0.522–5.785)	0.368		
Lymphadenectomy, present	27 (46.6)	1.058 (0.494–2.266)	0.885		
Operative time (min)		1.000 (0.997–1.003)	0.889		
Blood loss (mL)		1.000 (1.000–1.001)	0.066		
Adjuvant chemotherapy, present	34 (58.6)	1.065 (0.490–2.313)	0.873		
SM, < 1 mm	33 (56.9)	4.394 (1.726–11.181)	0.002	3.518 (1.158–10.688)	0.027

CI, confidence interval.

Table 2 Univariate and multivariate analysis of the factors associated with RFS

Variables	Univariate			Multivariate	
	No. (%)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (y)		1.020 (0.980–1.062)	0.326		
Sex, female	21 (36.2%)	1.695 (0.873–3.289)	0.119		
Cardiovascular disease, present	32 (55.2%)	1.088 (0.569–2.078)	0.799		
Diabetes mellitus, present	6 (10.3%)	0.629 (0.151–2.621)	0.524		
Liver function, chronic hepatitis	22 (37.9%)	1.057 (0.536–2.083)	0.874		
Tumor number, nultiple	10 (17.2%)	3.065 (1.365–6.880)	0.007	2.680 (1.127–6.370)	0.026
Tumor size, ≥3 cm	39 (67.2%)	1.848 (0.869–3.927)	0110		
Tumor location, nonsuperficial	23 (39.7%)	1.022 (0.532–1.962)	0.948		
Lymph node metastasis, positive	9 (15.5%)	2.732 (1.219–6.122)	0.015	1.188 (0.500–2.821)	0.697
Microvascular invasion, positive	38 (65.5%)	5.262 (2.181–12.694)	<0.001	4.349 (1.700–11.126)	0.002
Morphologic type, mass forming	48 (82.8%)	1.201 (0.524–2.754)	0.665		
CEA, ≥5 ng/mL	14 (24.1%)	0.785 (0.357–1.723)	0.545		
CA 19-9, ≥37 ng/mL	26 (44.8%)	1.598 (0.829–3.082)	0.161		
Surgical approach, laparoscopic	15 (25.9%)	1.785 (0.861–3.701)	0.119		
Surgical procedure, anatomic	48 (82.8%)	1.143 (0.476–2.745)	0.765		
Lymphadenectomy, present	27 (46.6%)	0.843 (0.440–1.616)	0.607		
Operative time (min)		1.000 (0.998–1.002)	0.980		
Blood loss (mL)		1.000 (1.000–1.001)	0.377		
Adjuvant chemotherapy, present	34 (58.6%)	1.573 (0.796–3.106)	0.193		
SM, <1 mm	33 (56.9%)	2.769 (1.353–5.670)	0.005	2.087 (0.990–4.401)	0.053

CI, confidence interval.

Relationship of the clinicopathologic characteristics between the SM <1 mm and the SM ≥1 mm groups

We evaluated the relationship of the clinicopathologic characteristics between the SM <1 mm group and the SM ≥1 mm group in the full analysis set and the one-to-one propensity score–matched set (Table 3). In the full analysis set (n = 58), the patients in the SM <1 mm group were more likely to be female ($P = 0.024$) compared with the SM ≥1 mm group. In addition, tumor-related factors, including tumor size, tumor number, tumor location, lymph node metastasis, microvascular invasion, and morphologic type, tended to be different between the SM <1 mm group and the SM ≥1 mm group. Therefore, one-to-one propensity score matching was performed. The propensity scores were calculated based on these 6 tumor-related factors. After the matching procedure, the 6 above-mentioned factors exhibited comparable values in the SM <1 mm group (n = 24) and the SM ≥1 mm group (n = 24).

Prognoses of ICC patients with SM ≥1 mm or SM <1 mm according to the one-to-one propensity score–matching analysis

The OS and RFS rates of the SM <1 mm group were significantly lower than those of the SM ≥1 mm group ($P = 0.013$ and $P = 0.025$, respectively). The 1-, 3-, and 5-year OS rates of the SM ≥1 mm group were 95.2%, 83.5%, and 83.5%, respectively, whereas those of the SM <1 mm group were 82.6%, 40.7%, and 20.3%, respectively. The 1-, 3-, and 5-year RFS rates of the SM ≥1 mm group were 81.5%, 52.7%, and 46.8%, respectively, whereas those of the SM <1 mm group were 50.1%, 18.5%, and 18.5%, respectively (Fig. 2C and 2D).

Sites of recurrence

A total of 37 patients (63.8%) relapsed, including 26 patients (78.8%) in the SM <1 mm group ($P = 0.006$) and 11 patients (44.0%) in the SM ≥1 mm group. The initial sites of recurrence in the SM <1 mm and SM ≥1 mm groups were in the liver [n = 19 (57.6%) and n = 8 (32.0%), respectively; $P = 0.053$], lymph nodes [n = 13 (39.4%) and n = 5 (20.0%); $P = 0.097$], distant metastasis [n = 8 (24.2%) and 3 (12.0%); $P = 0.202$], and peritoneal dissemination [n = 8 (24.2%) and 0; $P = 0.007$]. Furthermore, multiorgan recurrence tended to be more frequent in the SM <1 mm group than in the SM ≥1 mm group [n = 16 (61.5%) and n = 4 (36.4%); $P = 0.149$; Table 4].

Postrecurrence survival

We evaluated the postrecurrence survival of the SM <1 mm and SM ≥1 mm groups. The postrecurrence survival rate of the SM <1 mm group was

Table 3 Clinicopathologic characteristics of the SM <1 mm and the SM ≥1 mm groups

	All patients			Propensity-matched patients		
Variables	SM <1 mm (n = 33; 56.9%)	SM ≥1 mm (n = 25; 43.1%)	*P* value	SM <1 mm (n = 24; 50%)	SM ≥1 mm (n = 24; 50%)	*P* value
Age (y)	69.0 ± 9.4	70.6 ± 7.1	0.227	71.1 ± 7.4	69.7 ± 9.0	0.450
Sex			0.024			0.106
Male	17 (51.5)	20 (80.0)		14 (58.3)	19 (79.2)	
Female	16 (48.5)	5 (20.0)		10 (41.7)	5 (20.8)	
Cardiovascular disease			0.912			0.558
Absent	15 (45.5)	11 (44.0)		9 (37.5)	11 (45.8)	
Present	18 (54.5)	14 (56.0)		15 (62.5)	13 (54.2)	
Diabetes mellitus			0.213			0.174
Absent	31 (93.9)	21 (84.0)		23 (95.8)	20 (83.3)	
Present	2 (6.1)	4 (16.0)		1 (4.2)	4 (16.7)	
Liver function			0.777			0.768
Normal	21 (63.6)	15 (60.0)		15 (62.5)	14 (58.3)	
Chronic hepatitis	12 (36.4)	10 (40.0)		9 (37.5)	10 (41.7)	
Tumor number			0.443			0.500
Single	28 (84.8)	20 (80.0)		20 (83.3)	19 (79.2)	
Multiple	5 (15.2)	5 (20.0)		4 (16.7)	5 (20.8)	
Tumor size			0.306			0.365
<3 cm	9 (27.3)	10 (40.0)		7 (29.2)	10 (41.7)	
≥3 cm	24 (72.7)	15 (60.0)		17 (70.8)	14 (58.3)	
Tumor location			0.620			0.558
Superficial	19 (57.6)	16 (64.0)		13 (54.2)	15 (62.5)	
Nonsuperficial	14 (42.4)	9 (36.0)		11 (45.8)	8 (37.5)	
Lymph node metastasis			0.217			0.333
Negative	26 (78.8)	23 (92.0)		20 (83.3)	22 (91.7)	
Positive	7 (21.2)	2 (8.0)		4 (16.7)	2 (8.3)	
Microvascular invasion			0.059			0.233
Negative	8 (24.2)	12 (48.0)		7 (29.2)	11 (45.8)	
Positive	25 (75.8)	13 (52.0)		17 (70.8)	13 (54.2)	
Morphologic type			0.174			0.304
Mass forming	26 (78.8)	22 (88.0)		23 (95.8)	21 (87.5)	
Periductal infiltrating	1 (3.0)	3 (12.0)		1 (4.2)	3 (12.5)	
Mass forming + periductal infiltrating	2(6.1)	0		0	0	
Papillary	2(6.1)	0		0	0	
Mass forming + papillary	2(6.1)	0		0	0	
CEA[a]			0.218			0.203
<5 ng/mL	23 (69.7)	19 (82.6)		16 (66.7)	18 (81.8)	
≥5 ng/mL	10 (30.3)	4 (17.4)		8 (33.3)	4 (18.2)	
CA 19-9[a]			0.789			0.758
<37 ng/mL	17 (51.5)	13 (56.5)		12 (50.0)	12 (54.5)	
≥37 ng/mL	16 (48.5)	10 (43.5)		12 (50.0)	10 (45.5)	
Surgical approach			0.778			1.000
Open	24 (72.7)	19 (76.0)		18 (75.0)	18 (75.0)	
Laparoscopic	9 (27.3)	6 (24.0)		6 (25.0)	6 (25.0)	
Surgical procedure			0.443			0.500
Partial	5 (15.2)	5 (20.0)		4 (16.7)	5 (20.8)	
Anatomic	28 (84.8)	20 (80.0)		20 (83.3)	19 (79.2)	
Lymphadenectomy			0.847			0.558
Absent	18 (54.5)	13 (52.0)		15 (62.5)	13 (54.2)	
Present	15 (45.5)	12 (48.0)		9 (37.5)	11 (45.8)	
Operative time (min)	371.9 ± 171.3	307.8 ± 125.5	0.415	364.3 ± 193.9	302.6 ± 125.7	0.151
Blood loss (mL)	796.1 ± 1207.4	461.4 ± 417.1	0.131	869.1 ± 1380.4	449.0 ± 421.3	0.072
Adjuvant chemotherapy			0.724			0.771
Absent	13 (39.4)	11 (44.0)		10 (41.7)	11 (45.8)	
Present	20 (60.6)	14 (56.0)		14 (58.3)	13 (54.2)	

[a]Data not available for 2 patients.

Table 4 Initial recurrence sites of the SM <1 mm and the SM ≥1 mm groups

Sites of recurrence	SM <1 mm (n = 33; 56.9%)	SM ≥1 mm (n = 25; 43.1%)	*P* value
Whole	26 (78.8)	11 (44.0)	0.006
Liver	19 (57.6)	8 (32.0)	0.053
Lymph nodes	13 (39.4)	5 (20.0)	0.097
Distant metastasis	8 (24.2)	3 (12.0)	0.202
Peritoneal dissemination	8 (24.2)	0	0.007
Single-organ recurrence	10 (38.5)	7 (63.6)	0.149
Liver	5 (19.2)	5 (45.5)	
Lymph nodes	1 (3.8)	2 (18.2)	
Lung	1 (3.8)	0	
Peritoneal dissemination	3 (11.5)	0	
Multiorgan recurrence	16 (61.5)	4 (36.4)	

significantly lower than that of the SM ≥1 mm group ($P = 0.012$; Fig. 3A). Furthermore, we compared the postrecurrence survival of the patients with single-organ recurrence and those with multiorgan recurrence. The postrecurrence survival rate of the patients with multiorgan recurrence was significantly lower than that for those with single-organ recurrence ($P = 0.029$; Fig. 3B).

Discussion

The present study investigated the prognostic impact of SM in ICC patients who underwent macroscopically curative resection. Previous studies have reported that SM was significantly associated with the survival of ICC patients; however, the optimal margin width remains controversial. A margin width of 1.0 cm was associated with significantly improved survival in ICC.[9–11] Furthermore, other studies concluded that a margin of at least 5 mm should be created.[8,14] On the contrary, several studies reported that SM was not significantly associated with the prognosis of ICC.[15–18] In the present study, there were no significant differences in the OS rates among the SM 1 to <5 mm, SM 5 to <10 mm, and SM ≥10 mm groups. Importantly, the multivariate analysis identified SM <1 mm as an independent poor prognostic factor of OS. The baseline characteristics of the SM ≥1 mm and SM <1 mm groups were not significantly different. However, the SM <1 mm group tended to have more advanced tumor status than the SM ≥1 mm group. Thus, we performed propensity score matching based on tumor-related factors. It clearly showed that SM ≥1 mm has a positive influence on OS regardless of tumor status in ICC patients. These results suggest that an SM of at least 1 mm should be achieved regardless of tumor status during ICC resection.

We also investigated the association between SM and the sites of recurrence. Spolverato *et al*[12] reported that most recurrences following resection were intrahepatic, and the margin width was not associated

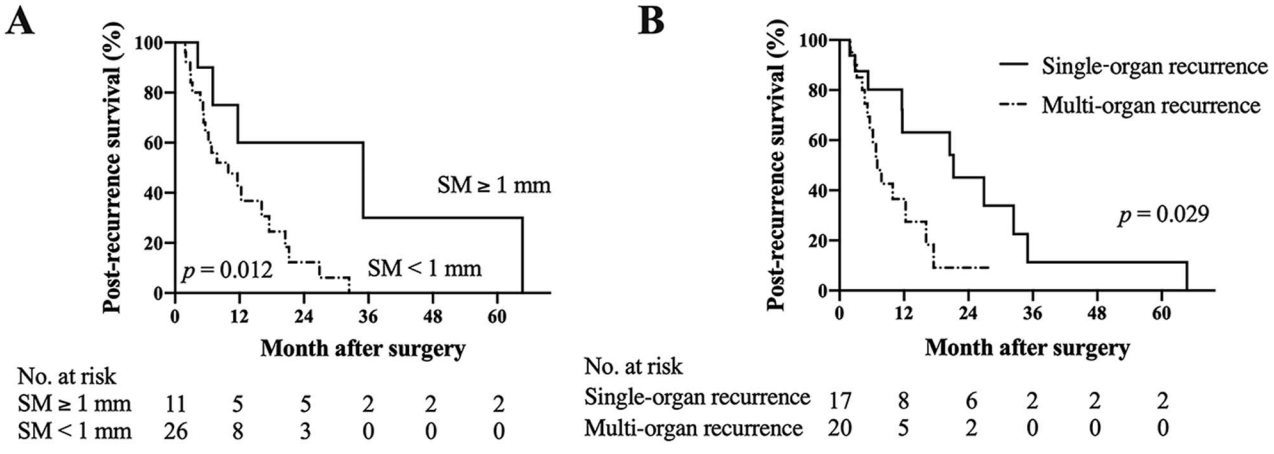


Fig. 3 (A) Postrecurrence survival according to SM <1 mm or SM ≥1 mm ($P = 0.012$). (B) Postrecurrence survival according to single-organ recurrence or multiorgan recurrence ($P = 0.029$).

with a pattern of recurrence. Similarly, Bartsch *et al*[15] showed that SM was not significantly associated with the sites of recurrence. Our result showed that microvascular invasion and multiple tumors were as independent predictors of RFS. Furthermore, SM <1 mm was not an independent prognostic factor of RFS; however, it was close to significance (hazard ratio, 2.087; $P = 0.053$). We also investigated the detailed sites of initial recurrence and found several important results. Recurrence in the liver, lymph node, and distant metastasis tended to be higher in the SM <1 mm group than in the SM ≥1 mm group. In particular, the rate of recurrence in peritoneal dissemination was significantly higher in the SM <1 mm group than in the SM ≥1 mm group. These results indicate that a <1 mm resection may cause peritoneal dissemination in ICC patients, although SM <1 mm failed to appear as an independent prognostic factor of RFS on multivariate analysis. In cases in which the margin width is unequivocal, neoadjuvant chemotherapy and intensive adjuvant chemotherapy may be required to improve the long-term outcome.

In addition, we evaluated the postrecurrence survival of ICC patients. The patients with SM <1 mm had a significantly lower postrecurrence survival rate compared with those with SM ≥1 mm. Furthermore, multiorgan recurrence tended to be more frequent in the SM <1 mm group than in the SM ≥1 mm group, although SM <1 mm was not an independent prognostic factor of RFS. The postrecurrence survival rate of patients with multiorgan recurrence was significantly lower than it was in those with single-organ recurrence. Moreover, the SM ≥1 mm group had only residual liver recurrence. Some of these patients underwent hepatic arterial infusion chemotherapy and had a relatively good prognosis after recurrence (data not shown). These results suggest that SM <1 mm might be associated with multiorgan recurrence, resulting in poor survival after recurrence.

In our data, ICC patients with R1 resection were included. Several studies evaluated the relationship between R1 margin and prognosis; however, the results are still unclear. Spolverato *et al*[12] reported that an R1 margin was associated with an inferior long-term outcome. Bartch *et al*[15] reported that the resection margin, including R1, showed no significant differences for OS and RFS. In the present study, the OS rate of the R1 group tended to be lower than that of the SM <1 mm group. However, there were no significant differences in the OS rate between the 2 groups. Thus, close resection with SM <1 mm might cause a poor prognosis, regardless of whether the margin status was R1 or not. Because whether R1 or not is determined by postoperative pathologic examination, these results might be useful in determining the surgical procedure for ICC and in making intraoperative decisions. Further studies are required to verify the present study's results.

This study has several limitations. First, it was a retrospective study from a single center with a relatively small population. In addition, the number of patients in each SM group was small. Second, chemotherapies were newly introduced during the follow-up, such as gemcitabine/cisplatin, gemcitabine/S-1, and gemcitabine/cisplatin/S-1. These agents may have affected the prognosis of patients receiving adjuvant or postrelapse chemotherapy. These limitations make it difficult to draw any definite conclusions. Despite these limitations, this study provides useful information about the associations of SM with prognosis and recurrence pattern.

In conclusion, the present study suggests that an SM of at least 1 mm should be achieved regardless of tumor status during ICC resection. An SM < 1 mm may suggest a higher risk of peritoneal dissemination.

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