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Impact of Surgical Margin Width and Postoperative Adjuvant Therapy on Long-Term Outcomes for Intrahepatic Cholangiocarcinoma: A Propensity Score Matching Analysis

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ABSTRACT

BACKGROUND

The objective of this study was to investigate the survival outcomes of surgical margin width in intrahepatic cholangiocarcinoma (ICC), and evaluate the efficacy of postoperative adjuvant therapy (p-AT) in ICC patients underwent narrow-margin hepatectomy (NMH).

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METHODS

Between November 2011 and August 2017, patients who underwent hepatectomy for ICC were collected from 13 major hepatopancreatobiliary centers in China. The survival outcomes for patients who underwent wide margin hepatectomy (WMH) were compared with those who underwent NMH using the 1:1 propensity score matching (PSM). For patients who underwent NMH, the relationship between p-AT and overall survival (OS) and disease-free survival (DFS) were analyzed.

RESULTS

Among 478 included patients, 195(40.8%) underwent WMH whereas 283(59.2%) underwent NMH. PSM yielded 79 matched patients with similar baseline characteristics. Patients underwent WMH had a significant better OS and DFS compared with those underwent NMH (before PSM: Median OS 27 *vs.* 17 months, P <0.05; Median DFS 15 *vs.* 8 months, P = 0.001), (after PSM: Median OS 41 *vs.* 22 months, p <0.05; Median DFS 16 *vs.* 10 months, p <0.05). However, based on the AJCC staging system, WMH could only improve the survival outcomes in early ICC patients (Stage I: OS, DFS, P <0.05; Stage II: OS, DFS, P >0.05; Stage III: OS, DFS, P >0.05). For patient underwent NMH, p-AT following NMH showed a better OS and RFS when compared to those who underwent NMH alone (OS, P = 0.05; DFS, p <0.05).

CONCLUSION

With the current data, we suggest surgeons should strive to achieve a wide surgical margin for patients with early ICC to optimize the long-term outcome. The effect of p-AT for the outcome of ICC patients underwent NMH need to be explored further.

KEYWORDS

Intrahepatic cholangiocarcinoma; Hepatectomy; Margin width; Postoperative adjuvant therapy; Overall survival; Disease-free survival

INTRODUCTION

Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies, which derived from any part of the biliary epithelium [1,2]. According to the location within the biliary system, CCA can be classified into intrahepatic, perihilar, and distal CCA [3]. Intrahepatic cholangiocarcinoma (ICC) is the second most common malignant tumor in liver, and its incidence has been increasing continuously in the past decades [4]. Surgical resection is the most effective treatment for patients with ICC. However, long-term outcome after radical resection is still unsatisfactory [5,6]. It has been reported that the current 5-years survival after resection of ICC is only 20%~35% [7-9]. Lots of factors, including tumor characteristics and resection factors, are associated with long-term survival after resection of ICC [10,11]. Among them, surgical margin status and width have attracted many attentions of surgeons and researchers.

Surgical margin status has been reported to be associated with overall survival (OS) and achieving R0 resection is the ultimate objective in resection of ICC [12,13]. However, the impact of surgical margin width on long-term survival remains controversial. Several studies reported that a gradual better long-term survival was observed as surgical margin width increased [14]. In contrast, some scholars concluded that not all patients with ICC could benefit from a wide margin hepatectomy (WMH) [15]. Assessing the prognostic value of surgical margin width is vital for clinical management of ICC. Besides, postoperative adjuvant therapy (p-AT) following hepatectomy has been used in the clinical management of ICC, although the effect of it is debatable [16,17]. There has been considerable interest in the effect of p-AT on outcomes in ICC patients underwent narrow-margin hepatectomy (NMH) [18]. Given this, we conducted this multicenter study to investigate the impact of surgical margin width and p-AT following NMH on long-term outcomes in ICC patients.

PATIENTS AND METHODS

Study Cohort

Patients who underwent radical hepatic resection for ICC between November 2011 and August 2017 were identified from a multicenter database that included 13 major hepato-pancreato-biliary centers in China (Eastern Hepatobiliary Surgery Hospital of Navy Medical University, Second Hospital Affiliated to Zhejiang University School of Medicine, Mengchao Hepatobiliary Hospital of Fujian Medical University, First Hospital Affiliated to Army Medical University, Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Beijing Friendship Hospital Affiliated to Capital Medical University, West China Hospital of Sichuan University, Renji Hospital Affiliated to Shanghai Jiao Tong University School of medicine, Xuanwu Hospital Affiliated to Capital Medical University, Affiliated Hospital of North Sichuan Medical College, Beijing Tiantan Hospital Affiliated to Capital Medical University, Zhongda Hospital Southeast University). Diagnosis of all enrolled ICC patients were histopathologically confirmed. R0 Resection was defined as macroscopic and microscopic removal of all tumors [19]. Patients who underwent palliative resection and patients with positive surgical margin, mortality within 1 month of surgery, peritoneal seeding, distant metastasis and incomplete information were excluded. This study was approved by the institutional review board of each participating center.

Data Collection

Data, including patient demographics, perioperative variables, tumor-related clinicopathological characteristics, and follow-up data, were collected using a standardized data sheet. The resectability of the tumor was determined according to the performance status, liver function reserve and tumor imaging features of the patients before surgery. Operative information included the type of hepatectomy, receipt of lymph node dissection, margin status, intraoperative blood loss, transfusion. Postoperative pathological variables included tumor number, size, morphology, grade, vascular/perineural/biliary/adjacent organ invasion, lymph node metastasis, satellite nodules, and surgical margin width. Postoperative adjuvant therapy was performed after assessing by a multidisciplinary team. Tumor staging was evaluated according to the 8th edition of the AJCC staging system [20].

Patients were divided into two groups according to the surgical margin width: narrow (<10 mm) and wide (≥10 mm).

Follow Up

Patients were regularly followed up every 3 months - 6 months after surgery, during which serum carbohydrate antigen 19-9 (CA19-9) and imaging examinations were routinely performed. The endpoints of this study were OS and DFS. OS was defined as the interval between the date of surgery and the date of death from any cause or the date of the last follow-up. Disease-free survival (DFS) was defined as the interval between the date of surgery and the first recurrence or the last follow-up.

Statistical Analysis

Categorical variables were expressed as number and percentages, and differences were compared by Chisquare test or Fisher's exact test. OS and DFS were analyzed by the Kaplan-Meier method, and the log-rank test was used for between-group comparisons. The Cox proportional hazards model was used to identify risk factors of OS and DFS, and variables with statistically significant differences in the univariate analysis were included in the multivariate analysis.

Since patients who underwent WMH and NMH were not randomly distributed, propensity score matching (PSM) was used to minimize selection bias. The caliper was set at 0.01, and an optimal match ratio of 1:1 was used according to the nearest neighbor method. Statistical analyses were performed using R 3.6.1. A two-tailed P value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Figure 1 presented the flowchart of patients' enrollment. The median age of the enrolled 478 patients was 58 years (IQR, 49 years - 64 years) and 287 were male (60.0%). The median tumor size of patients was 6.7 cm, and the majority were single tumor (n = 344, 72.0%). In total, 283(59.2%) underwent NMH, whereas 195(40.8%) underwent WMH. Several factors, including gender, CA19-9, CEA, blood loss, transfusion, tumor diameter, tumor number, lymph node invasion, gross type, differentiation, satellite, perineural invasion and postoperative adjuvant therapy, were associated with margin width (Table 1). Wide margin resection was more frequently performed among patients had a small, single and CA19-9 level raised tumor. While age, HBsAg, MVI, and major hepatectomy have no difference between the two groups (P >0.05). After 1:1 PSM, there were 79 of the 195 WMH patients were matched with 79 of the 283 NMH patients, and all baseline characteristics were compared between the groups.

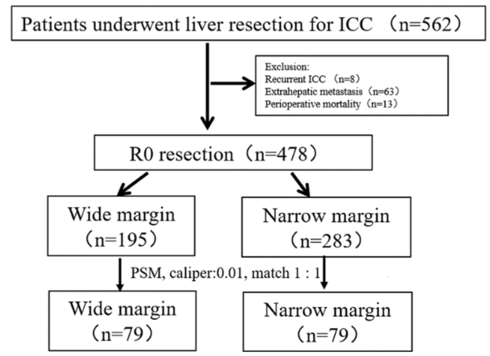

Figure 1: Flowchart of patients' enrollment.

Impact of Surgical Margin Width and Long-Term Outcomes

Among all patients, overall median, 1- year, 3- years, and 5- years OS was 21 months, 67.7%, 32.1%, and 18.7%, respectively. Overall median, 1- year, 3- years, and 5- years, DFS was 20 months, 57.7%, 36.9%, and 33.0%, respectively. Patients underwent WMH had a better OS and DFS compared with patients undergoing NMH (all P <0.05, Figure 2A and Figure 2B). Consistently, the median, 1- year, 3- years, and 5-years OS and DFS of patients in the WMH were still better than that in NMH (all p <0.05, Figure 2C and Figure 2D) after 1:1 PSM.

Univariate and Multivariate COX Analyses of OS and DFS in Patients with Intrahepatic Cholangiocarcinoma

Before PSM, univariate analysis identified surgical margin width was associated with OS and DFS (all P <0.05). Additionally, multivariable analysis showed that surgical margin width was an independent prognostic factor affecting OS and DFS (Table S1). After PSM, both univariate and multivariate COX regression analyses showed surgical margin width was significantly correlated with OS and DFS (Table 2).

		Before PSM			After PSM		
		Wide	Narrow	P-Value	Wide	Narrow	P-Value
		(n=195)	(n=283)		(n=79)	(n=79)	
Gender	Male	103 (52.8%)	184 (65.0%)	0.01	51 (64.6%)	47 (59.5%)	0.623
	Female	92 (47.2%)	99 (35.0%)		28 (35.4%)	32 (40.5%)	
Age	≤60 years	115 （590%）	177(62.5%)	0.489	42(53.2%)	50(63.3%)	0.259
	>60 years	80 （41.0%）	106(7.5%)		37(46.8%)	29(36.7%)	
HBsAg	Negative	144 (73.8%)	184 (65.0%)	0.052	55(69.6%)	59(74.7%)	0.594
	Positive	51 (26.2%)	99 (35.0%)		24(30.4%)	20(25.3%)	
CA19-9	≤200 U/mL	136 (69.7%)	253 (89.4%)	<0.001	63(79.7%)	65(82.3%)	0.839
	>200 U/mL	59 (30.3%)	30 (10.6%)		16(20.3%)	14(17.7%)	
CEA	≤5 μg/L	125 (64.1%)	234 (82.7%)	<0.001	56(70.9%)	56(70.9%)	1
	>5 μg/L	70 (35.9%)	49 (17.3%)		23(29.1%)	23(29.1%)	
Blood loss	≤400mL	141(72.3%)	229(80.9%)	0.036	61(77.2%)	57(72.2%)	0.583
	＞400mL	54(27.7%)	54(19.1%)		18(22.8%)	22(27.8%)	
Transfusion	No	148(75.9%)	246(86.9%)	0.003	60(75.9%)	61(77.2%)	1
	Yes	47(24.1%)	37(13.1%)		19(24.1%)	18(22.8%)	
Major hepatectomy	No	72 (36.9%)	80 (28.3%)	0.058	32(40.5%)	31(39.2%)	1
	Yes	123 (63.1%)	2083(71.7%)		47(59.5%)	48(60.8%)	
Tumor size	≤5 cm	86 (44.1%)	94 (33.2%)	0.02	37(46.8%)	34(43.0%)	0.749
	>5 cm	109 (55.9%)	189 (66.8%)		42(53.2%)	45(57.0%)	
Tumor number	Single	163 (83.6%)	181 (64.0%)	<0.001	61(77.2%)	60(75.9%)	1
	Multiple	32 (16.4%)	102 (36.0%)		18(22.8%)	19(24.1%)	
Lymph node invasion	No	140(71.8%)	250(88.3%)	<0.001	67(84.8%)	69(87.3%)	0.818
	Yes	55(28.2%)	33(11.7%)		12(15.2%)	10(12.7%)	
Mass-forming	No	38 (19.5%)	116 (41.0%)	<0.001	28(35.4%)	19(24.1%)	0.164
	Yes	157 (80.5%)	167 (59.0%)		51(64.6%)	60(75.9%)	
Tumor differentiation	Well &Moderate	139 (71.3%)	236 (83.4%)	0.002	64(81.0%)	60(75.9%)	0.561
	Poor	56 (28.7%)	47 (16.6%)		15(19.0%)	19(24.1%)	
Satellite	No	170 (87.2%)	181 (64.0%)	<0.001	65(82.3%)	62(78.5%)	0.689
	Yes	25 (12.8%)	102 (36.0%)		14(17.7%)	17(21.5%)	
MVI	No	165 (84.6%)	254 (89.8%)	0.124	72(91.1%)	68(86.1%)	0.453
	Yes	30 (15.4%)	29 (10.2%)		7(8.9%)	11(13.9%)	
Perineural invasion	No	164 (84.1%)	261 (92.2%)	0.008	66(83.5%)	69(87.3%)	0.652
	Yes	31 (15.9%)	22 (7.8%)		13(16.5%)	10(12.7%)	
p-AT	No	141(72.3%)	240(84.8%)	0.001	64(81.0%)	66(83.5%)	0.835
	Yes	54(27.7%)	43(15.2%)		15(19.0%)	13(16.5%)	

Abbreviations: PSM: Propensity Score Matching; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; HBsAg: Hepatitis B Surface Antigen; MVI: Microvascular Invasion; p-AT: Postoperative Adjuvant Therapy.

Table 1: Clinicopathological characteristics before and after PSM.

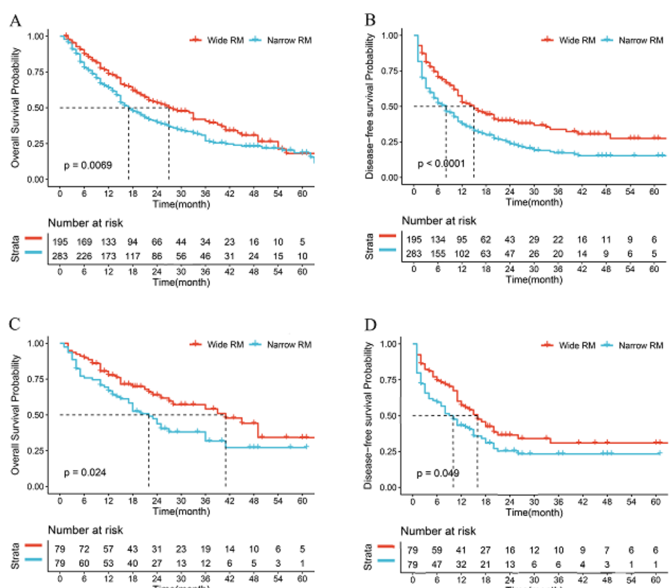

Figure 2: (A,C) Overall survival and (B,D) disease-free survival before and after propensity score matching of patients underwent wide margin hepatectomy and narrow margin hepatectomy for intrahepatic cholangiocarcinoma.

Characteristic	Variables	OS				DFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Gender	Female vs Male	0.72(0.45-1.14)	0.158			0.77(0.51-1.16)	0.217		
Age (y)	≤60 vs >60	0.92(0.59-1.43)	0.706			0.71(0.48-1.06)	0.098		
HBsAg	Negative vs Positive	1.08(0.67-1.75)	0.75			1.08(0.70-1.66)	0.738		
ECOG score	≤2 vs >2	1.00(0.64-1.55)	0.986			0.80(0.54-1.18)	0.255		
CA19-9 (U/ml)	≤200 vs >200	1.23(0.71-2.14)	0.458			0.88(0.53-1.47)	0.625		
CEA (ng/ml)	≤5 vs >5	1.03(0.63-1.67)	0.912			0.91(0.59-1.39)	0.653		
Blood loss (ml)	≤400 vs >400	1.02(0.61-1.71)	0.947			0.74(0.46-1.19)	0.216		
Transfusion	No vs Yes	1.15(0.69-1.90)	0.6			0.61(0.37-1.02)	0.058		
Major hepatectomy	No vs Yes	1.34(0.84-2.15)	0.215			1.02(0.69-1.52)	0.92		
Resectionmargin (cm)	≤1 vs >1	1.65(1.06-2.58)	0.026	1.61(1.03-2.52)	0.037	1.49(1.01-2.20)	0.046	1.64(1.17-2.30)	0.004
Tumor size (cm)	≤5 vs >5	1.33(0.85-2.08)	0.214			1.15(0.77-1.70)	0.497		
Tumor number	Solitary vs Multiple	1.31(0.81-2.12)	0.267			1.14(0.73-1.80)	0.558		
Lymphnode invasion	No vs Yes	2.03(1.15-3.57)	0.014	2.09(1.17-3.72)	0.012	1.15(0.65-2.02)	0.638		
Mass-forming	No vs Yes	1.17(0.73-1.87)	0.524			1.33(0.87-2.05)	0.187		
Tumor differentiation	Well &Moderate vs Poor	1.33(0.85-2.08)	0.214			0.80(0.48-1.34)	0.399		
Satellite	No vs Yes	1.27(0.77-2.11)	0.352			1.32(0.84-2.09)	0.231		
MVI	No vs Yes	2.03(1.12-3.69)	0.02			2.42(1.39-4.22)	0.002	2.65(1.147-4.76)	0.001
Perineural invasion	No vs Yes	0.94(0.50-1.79)	0.86			0.69(0.38-1.26)	0.232		
p-AT	No vs Yes	0.38(0.18-0.83)	0.016	0.40(0.18-0.88)	0.022	0.73(0.43-1.24)	0.244		

Abbreviations: PSM: Propensity Score Matching; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; HBsAg: Hepatitis B Surface Antigen; MVI: Microvascular Invasion; p-AT: Postoperative Adjuvant Therapy; OS: Overall Survival; DFS: Disease-Free Survival; HR: Hazard Ratio.

Table S1: Univariate and multivariate analysis of overall survival and disease-free survival for patients with intrahepatic cholangiocarcinoma before PSM.

Characteristic	Variables	OS				DFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Gender	Female vs Male	0.79 (0.62-1.00)	0.055	0.65(0.51-0.84)	0.001	0.77(0.61-0.97)	0.023	0.77(0.61-0.98)	0.035
Age (y)	≤60 vs >60	0.99 (0.78-1.25)	0.941			0.85(0.68-1.06)	0.145		
HBsAg	Negative vs Positive	1.02(0.79-1.30)	0.9			1.16(0.92-1.46)	0.222		
ECOG score	< 2 vs ≥2	0.99 (0.78-1.25)	0.942			0.86(0.69-1.07)	0.183		
CA19-9 (U/mL)	≤200 vs >200	1.17(0.87-1.57)	0.303			0.81(0.60-1.09)	0.156		
CEA (μg/L)	≤5 vs >5	1.14 (0.88-1.49)	0.325			0.84(0.65-1.09)	0.186		
Blood loss (ml)	≤400 vs >400	0.97 (0.73-1.29)	0.834			0.80(0.61-1.05)	0.109		
Transfusion	No vs Yes	0.89(0.65-1.22)	0.48			0.66(0.48-0.90)	0.009		
Major hepatectomy	No vs Yes	1.47 (1.13-1.91)	0.004			1.43(1.13-1.83)	0.003		
Resection margin (cm)	≤1 vs >1	1.39 (1.09-1.77)	0.007	1.33(1.04-1.72)	0.03	1.66(1.32-2.08)	<0.001	1.30(1.02-1.67)	0.037
Tumor size (cm)	≤5 vs >5	1.53 (1.19-1.96)	0.001			1.46(1.16-1.83)	0.001		
Tumor number	Solitary vs Multiple	1.54 (1.20-1.97)	0.001			1.54(1.22-1.96)	0.001		
Lymph node invasion	No vs Yes	1.53(1.15-2.02)	0.003	1.81(1.32-2.47)	<0.001	1.14(0.86-1.50)	0.369		
Mass-forming	No vs Yes	0.91(0.72-1.16)	0.443			0.83(0.66-1.04)	0.102		
Tumor differentiation	Well &Moderate vs Poor	1.00(0.75-1.33)	0.976			0.75(0.57-1.00)	0.049		
Satellite	No vs Yes	1.68(1.31-2.15)	<0.001			1.87(1.48-2.36)	<0.001	1.78(1.22-2.59)	0.003
MVI	No vs Yes	2.10(1.53-2.88)	<0.001	1.77(1.27-2.46)	0.005	2.23(1.66-2.99)	<0.001	2.45(1.80-3.33)	<0.001
Perineural invasion	No vs Yes	0.91 (0.63-1.33)	0.641			0.75(0.52-1.09)	0.132		
p-AT	No vs Yes	0.60 (0.43-0.83)	0.002	0.61(0.44-0.86)	0.005	0.75(0.56-0.99)	0.043		

Abbreviations: PSM: Propensity Score Matching; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; HBsAg: Hepatitis B Surface Antigen; MVI: Microvascular Invasion; p-AT: Postoperative Adjuvant Therapy; OS: Overall Survival; DFS: Disease-Free Survival; HR: Hazard Ratio.

Table 2: Univariate and multivariate analysis of overall survival and disease-free survival for patients with intrahepatic cholangiocarcinoma after PSM.

Subgroup Analysis Based on AJCC Staging System

To identify the optimal ICC patients for WMH, subgroup analysis was conducted based on the 8th AJCC staging system. In total, there were 258(54.0%), 132(27.6%), and 88(18.4%) patients were assigned to stage I/II/III groups. The impact of the surgical margin width depended on the context. As for stage I, patients underwent NMH had an inferior OS and DFS than patients underwent WMH (median OS was 37 *vs.* 22 months, P <0.05, Figure 3A; median DFS was 20 *vs.* 11 months, P <0.05, Figure 3D). However, we did not observe a significant difference between the WMH and NMH in terms of OS and DFS for ICC patients with stage II or III (Stage II: median OS was 15 *vs.* 14 months, P = 0.63, Figure 3B; median DFS was 6 *vs.* 4 months, P = 0.45, Figure 3E; Stage III: median OS was 16 *vs.* 12 months, P = 0.20, Figure 3C; median DFS was 10 *vs.* 5 months, P = 0.16, Figure 3F).

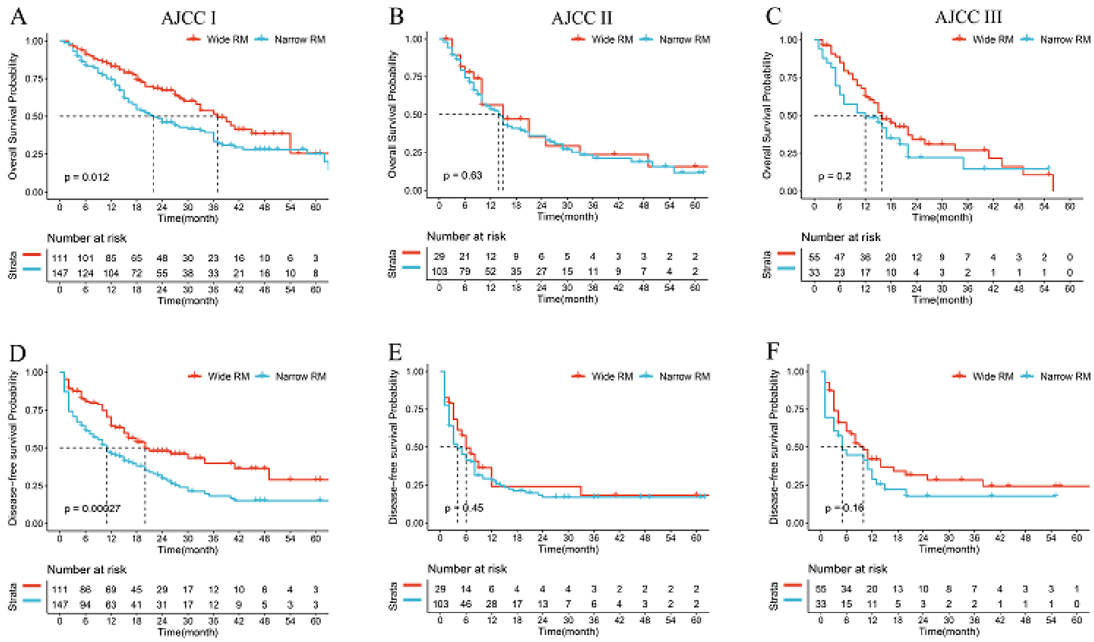

Figure 3: Subgroup analyses of overall survival and disease-free survival in ICC patients with stage I (A,D), stage II (B,E), and stage III (C,F) according to the 8th AJCC staging system who underwent wide margin hepatectomy and narrow margin hepatectomy.

Impact of p-AT on Patient Underwent Narrow Margin Hepatectomy

The long-term outcomes of patient underwent NMH were compared according to whether or not receiving p-AT.

The result showed that patients underwent p-AT following NMH had a better OS and RFS when compared to those who did not receive p-AT (median OS was 16 *vs.* 36 months, P = 0.05, Figure 4A; median DFS was 7 *vs.* 14 months, P = 0.029, Figure 4B).

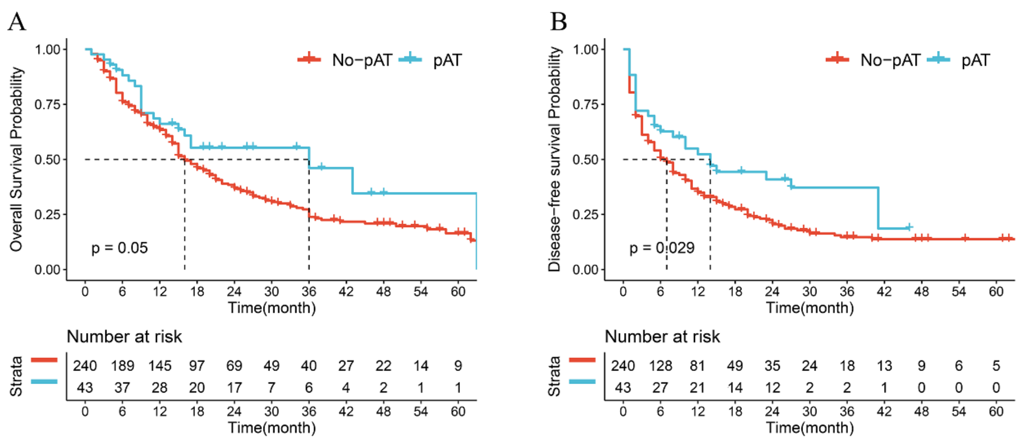

Figure 4: Overall survival (A) and disease-free survival (B) of patients underwent narrow margin hepatectomy according to receiving p-AT or not.

DISCUSSION

For ICC, liver resection remains the most effective treatment strategy at present. While surgical margin status was identified as a prognostic factor, the impact of surgical margin width on long-term outcome following R0 resection of ICC has been less well studied and remains controversial. Among single-center studies focused on the effect of resection margins on survival, a small amount demonstrated a significant survival benefit for patients underwent WMH [21-27]. While all three multi-institutional studies and a meta-analysis show a consistent result that WMH could benefit long-term survival in patients with ICC [12,14,15]. In this study, we conducted a PSM analysis using multicenter ICC data, and discovered that patients underwent WMH had better outcomes compared with patients undergoing NMH. To our knowledge, this is the first study to evaluate the impact of surgical margin width on the outcome of ICC using PSM.

However, every treatment option has its limitations and it is particularly important to identify appropriate tumor characteristics that match the treatment strategy. Several previous studies conducted subgroup analysis to evaluate the impact of WMH on the outcome of patients with lymph node metastasis (LNM). Papers of Farges et al. and Watanabe et al. documented that WMH could not provide benefit for patients with LNM [14,15]. Similarly, we found patients with LNM (stage III) had no benefit from WMH. This reflects that LNM was a factor that played a fatal role for the outcome of patients with ICC and WMH is not enough to improve the prognosis of these patients.

Furthermore, whether WMH provides enough benefit for all N0 patients is of concern for the management of ICC patient. Shimada documented that a narrow surgical margin width did not adversely affect survival for patients without LNM [22]. While two multicenter studies demonstrated a gradual better long-term survival was observed as surgical margin width increased for patients without LNM [14,15]. In this study, we found WMH had a longer OS and RFS than NMH in patients without LNM. However, when stratified these patients according to the stage I and stage II, differential results were observed that only patients with stage I benefit from WMH.

In clinical practice, the operation of WMH in ICC patients would be affected by many factors, including inadequate residual liver volume, tumors adherent to major vessels. Some researchers suggested preoperative portal vein embolization could improve the resectability and increase the percent of WMH in these patients, although the following surgical delay may cause tumor progression [14]. Besides, approaches such as extend resection and vascular reconstruction were considered to improve outcome further [28,29]. In this study, 40.9% patients had a wide surgical margin (≥1 cm) among patients underwent R0 resection. Of note, aggressive approaches used to achieve a WMH may lead to an increase in adverse events, such as liver failure and massive bleeding [15]. In this study, a higher rate of intraoperative blood loss and transfusion were observed in WMH group. Given that, we suggested that surgeons should make every effort to achieve a wide surgical margin for early ICC patients with stage I to get a better long-term outcome. As for patients with stage II or III, WMH alone could not improve the survival, and more effective treatments are still needed.

Postoperative adjuvant therapy has been used in the clinical management of ICC although the effect of it is debatable [16,17]. Recently, a meta-analysis reported that ICC patients with positive resection margin or LNM could benefit from p-AT [30]. And our previous study demonstrated that p-AT could improve the outcome of "middle-risk" ICC patients based on an established nomogram [17]. However, whether patients underwent NMH could benefit from p-AT is less discussed. Zheng et al. concluded that postoperative radiotherapy following NMH was effective and well-tolerated for ICC patients with tumor adjacent to major vessels [18]. In this study, p-AT following NMH showed a better OS and RFS when compared to those who did not receive p-AT.

There are several limitations that should be acknowledged when interpreting this study. First, this was a retrospective study and selection bias may have been present. To mitigate this bias, we conducted PSM to match the prognostic factors between the two groups. Second, detailed surgical margin width was lacked in this database, and further subgroup analyses focused on the influence of different width groups were affected. Third, due to the low proportion of patients underwent p-AT following resection, its effect on the prognosis of patients underwent NMH need to be explored further.

CONCLUSION

In conclusion, we suggest surgeons should strive to achieve a wide surgical margin for patients with early ICC to optimize the long-term outcome. As for ICC patients with AJCC stage II or III, WMH alone could not improve the survival and more effective treatments are still needed. In addition, the effect of p-AT for the outcome of ICC patients underwent NMH need to be explored further.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Yongyi Zeng, Hongzhi Liu, Lianku Lin and Ziguo Lin contributed to the study conception and design. Hongzhi Liu, Lianku Lin, Ziguo Lin, Yifan Chen, Qizhen Huang and Lei Ding contributed to analysis and interpretation of data. Yongyi Zeng, Jianying Lou, Shuguo Zheng, Xinyu Bi, Jianming Wang, Wei Guo, Fuyu Li, Jian Wang, Yamin Zheng, Jingdong Li, Shi Cheng and Zhangjun Cheng and Weiping Zhou contributed to offering the data. Hongzhi Liu, Lianku Lin and Ziguo Lin drafting the manuscript. Yongyi Zeng contributed to revising the article, critical revision, and final approval.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

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