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Prognostic significance of the number of hepatic lesions in multifocal intrahepatic cholangiocarcinoma after radical resection: an IPTW propensity-score analysis

Xin Zhang[1†], Xi-Tai Huang[1†], Jin-Zhao Xie[1], Ai-Qing Fu[1], Wei Chen[1], Jian-Peng Cai[1], Li-Jian Liang[1] and Xiao-Yu Yin[1*]

Abstract

Background Multifocal hepatic lesions represent a distinctive subgroup within intrahepatic cholangiocarcinoma(iCCA), the management of these patients remains controversial. This study aimed to compare the survival of intrahepatic cholangiocarcinoma (iCCA) with different numbers of hepatic lesions and select patients benefiting most from surgery in multifocal iCCA.

Methods A cohort of 354 consecutive iCCA patients were included. Based on the number of hepatic lesions, patients were classified as follows: solitary tumors (type I), 2 or 3 hepatic lesions in the same-sided hepatic lobe (type II), and more than three hepatic lesions in the same-sided hepatic lobe (type III). Stabilized inverse probability treatment weighting (IPTW) was conducted for accurate prognosis comparisons. Furthermore, the long-term prognosis was compared between different American Joint Committee on Cancer.

Results Among all patients, multifocal iCCA presented significantly worse overall survival (OS) and recurrence-free survival (RFS) than solitary tumor ($p<0.001$ and $p<0.001$), 11.9% ($n=42$), and 14.4% ($n=51$) patients were classified into type II, and type III, respectively. After IPTW, type II exhibited similar while type III exhibited worse RFS and OS to type I cohort (solitary tumors) ($p<0.001$and $p<0.001$). Multivariable Cox analysis also identified type III tumors as an independent risk factor for OS (HR 1.95, 95% CI:1.33–2.87, $p<0.001$). Among AJCC stage II (T2N0M0) patients, multifocal iCCA presented significantly worse OS than solitary tumors (vascular invasion) ($p=0.018$), and type II exhibited similar while type III exhibited worse OS than solitary tumors ($p=0.500$ and $p=0.040$). Compared with stage III patients, type II exhibited better while type III exhibited similar OS ($p<0.001$ and $p=0.300$).

Conclusions Multifocal iCCA presented a significantly worse prognosis, the number of hepatic lesions significantly influenced the prognosis of multifocal iCCA. Patients with type II tumors may derive comparable oncological benefits from surgery compared with solitary tumors, radical surgery still be strongly recommended as the preferred treatment.

Keywords Multifocal intrahepatic cholangiocarcinoma, IPTW analysis, Radical surgery, Prognosis

†Xin Zhang and Xi-Tai Huang contributed equally to this work.

*Correspondence:
Xiao-Yu Yin
yinxy@mail.sysu.edu.cn

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer following hepatocellular carcinoma, which presents a worse prognosis [1, 2]. Curative resection is considered the preferred treatment option for patients with resectable iCCA. However, even among patients who underwent surgical resection, the prognosis of iCCA remains poor, with early recurrence and metastasis [3]. Therefore, radical surgery should be performed after balancing the oncological benefits and surgical risks. It is significantly important to identify patients who could acquire the most survival benefits from surgical intervention.

Multifocal hepatic lesions represent a distinctive subgroup within iCCA, and the management of these patients remains conflicting. Despite being categorized as T2 stage according to the American Joint Committee on Cancer (AJCC) staging system [4], previous literature elucidated that patients harboring multifocal iCCA exhibit an inferior prognosis compared with solitary tumors with vascular invasion [5, 6]. According to the latest guidelines published by the European Association for the Study of the Liver and the Liver Cancer Study Group of Japan, the oncological benefits of surgery for these patients remain debated [7, 8]. Previous research showed that the distribution and number of tumor nodules both significantly influence the prognosis of multifocal iCCA [9]. Accordingly, it remains unclear whether specific patients with multifocal iCCA could benefit from radical surgery according to different numbers of multifocal lesions.

Hence, this study aimed to compare the long-term outcomes of patients who underwent radical resection for iCCA based on the number of hepatic nodules and select patients who might derive oncological prognostic benefits from surgery in multifocal iCCA.

Materials and methods

Patient selection

A retrospective cohort study was conducted in the First Affiliated Hospital of Sun Yat-sen University. All consecutive patients who underwent curative-intent surgery for iCCA between January 2007 and August 2022 at the First Affiliated Hospital of Sun Yat-sen University were included. The entry criteria were as follows: (i) patients underwent curative-intent surgery; (ii) pathologically proved as iCCA; (iii) absence of distant metastasis. The exclusion criteria were as follows: (i) accompanied by other concurrent malignancies; (ii) preoperative neoadjuvant chemotherapy; (iii) incomplete clinicopathological data and follow-up data; (iv) occurrence of death during hospitalization. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for descriptive cohort studies [10]. The flow chart is shown in Fig. 1. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University.

Definitions and outcomes

Clinical data were retrieved from the retrospective database at our center. The distribution of tumor nodules for the analysis was defined according to the postoperative pathological evaluation. Patients were further classified as follows: single tumor (type I), 2 or 3 hepatic lesions in the same-sided hepatic lobe (type II), and hepatic lesions more than three in the same-sided hepatic lobe (type III). To minimize the impact of the resection margin on prognosis, we included patients who underwent radical surgery, specifically those who achieved an R0 resection. Furthermore, the major hepatectomy was defined as the resection of ≥ 3 Couinaud segments, and the minor hepatectomy was defined as the resection of fewer than three Couinaud segments, including wedge excisions and single-segment resections [11, 12]. The histopathologic criteria of this study were according to the WHO Classification [13]. All patients after radical surgery were routinely followed up. Recurrence was defined as the radiological finding of the recurrent lesions including contrast-enhanced ultrasound, computer tomography (CT) / magnetic resonance imaging (MRI), or pathological result (percutaneous fine-needle biopsy). Overall survival (OS) was calculated from the date of surgery to the date of the last follow-up or death. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence.

Statistical analysis

Statistical analyses were conducted with R 4.0.0 (http://www.Rproject.org). Continuous data were reported as medians with interquartile range (IQR), and were compared using Mann–Whitney U tests. Categorical parameters were presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test. Kaplan–Meier curve and log-rank test were performed to compare the long-term survival. The Cox proportional hazard model was used to determine the independent predictive factors based on the statistically significant factors selected by univariate analyses ($p < 0.05$), and the results were shown as the hazard ratio with 95% confidence intervals. Two-tailed P value less than 0.05 was considered significantly different. The R packages "survival" and "survminer" were applied to determine the optimal cut-off values of continuous variables for OS (Supplementary Figures).

Stabilized inverse probability treatment weighting (IPTW) was conducted to balance patient characteristics between the treatment cohorts [14]. Propensity scores

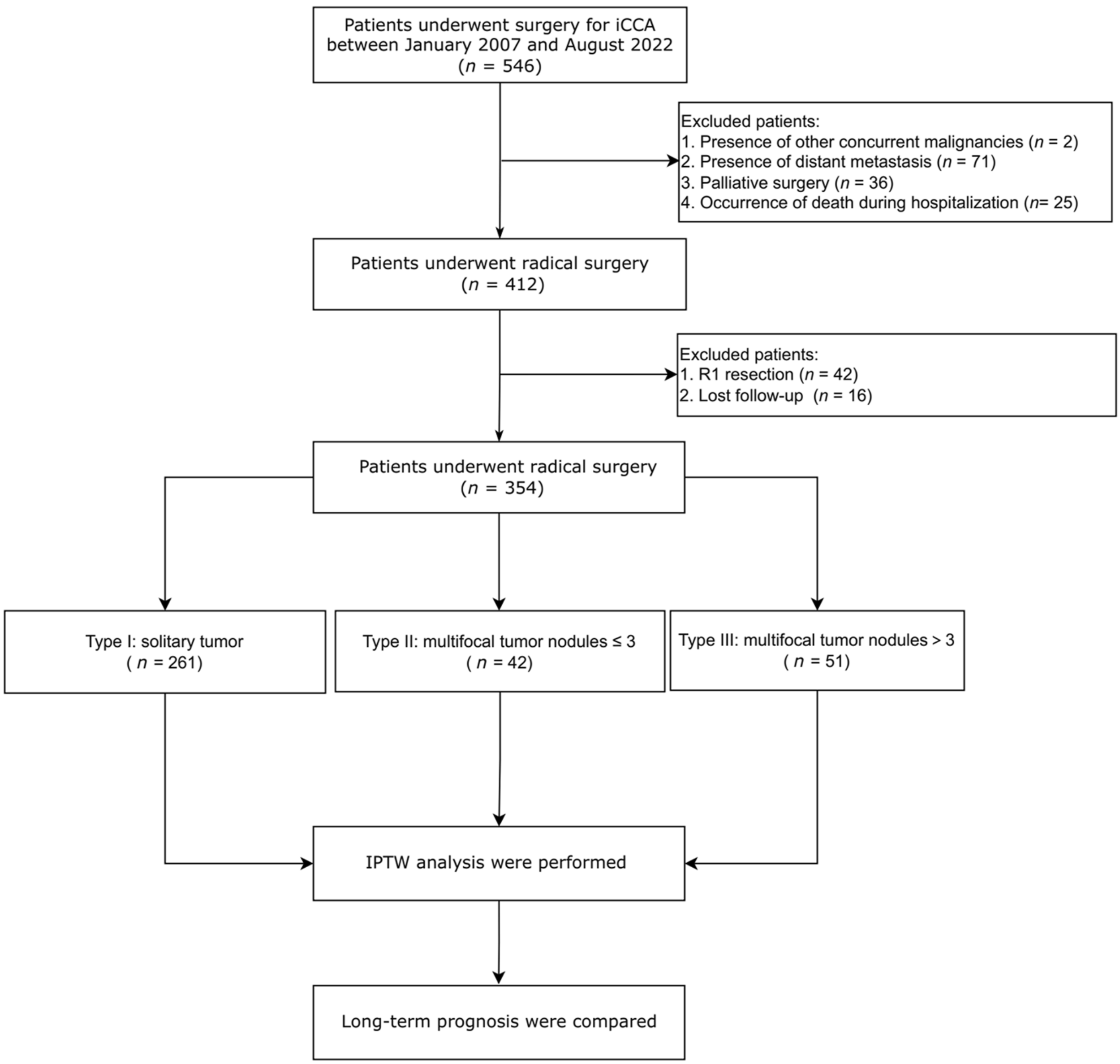

Fig. 1 Flow chart of patient selection. Abbreviations: iCCA, intrahepatic cholangiocarcinoma; IPTW, inverse probability treatment weighting

were used to obtain estimates of the average treatment effect using a logistic model with the cohorts [15]. After the propensity score calculation was made, the patient was weighted by the inverse of the probability of their treatment option (treatment groups: weight = 1/propensity score, compared group: weight = 1/ (1-propensity score)) [16]. The weights were stabilized by multiplying the original weights with a constant, which was equal to the expected value of being in the treatment or comparison cohorts, respectively. Potential high-risk factors for long-term prognosis were matched, including age, sex, CA199 level, hepatectomy, tumor size, vascular invasion, local extrahepatic invasion, lymph metastasis, differentiation, and chemotherapy. Furthermore, the long-term prognosis was compared between different AJCC stages to explore the prognosis values of the number of hepatic lesions.

Results

Clinicopathological features

The clinicopathological features of patients were shown in Table 1. A total of 354 patients who underwent curative-intent surgery for iCCA were included, 192 patients (54.2%) were males and 162 patients (45.8%) were

Table 1 Clinicopathological features of patients undergoing radical resection for iCCA

Features	Total (*n* = 354)	Type I (*n* = 261)	Type II (*n* = 42)	Type III (*n* = 51)	*P* values[a]	*P* values[b]	*P* values[c]
Age, years, median (IQR)	59 (52-66)	59 (52-66)	58 (51-68)	57 (51-62)	0.256	0.084	0.026
Sex, n (%)					0.879	0.497	0.533
Female	162 (45.76)	121 (46.36)	20 (47.62)	21 (41.18)			
Male	192 (54.24)	140 (53.64)	22 (52.38)	30 (58.82)			
CA199, U/ml, median (IQR)	110.5 (10.9-1200)	8.8 (63.6-804.0)	222.0 (16.0-1489.9)	177.7 (12.9-2226.3)	0.138	0.115	0.978
MELD, Mean ± SD	9.41 ± 10.72	9.60 ± 11.19	7.52 ± 6.17	10.02 ± 11.29	0.240	0.810	
MELD-Na, Mean ± SD	10.73 ± 10.28	10.86 ± 10.71	8.80 ± 6.06	11.71 ± 10.78	0.226	0.620	
Type of surgery, n (%)					0.711	0.004	0.041
Minor hepatectomy	100 (28.25)	82 (31.42)	12 (28.57)	6 (11.76)			
Major hepatectomy	254 (71.75)	179 (68.58)	30 (71.43)	45 (88.24)			
Tumor size, cm, median (IQR)	5.5 (3.8-7.0)	5.0 (3.5-7.0)	5.2 (3.5-7.0)	6.5 (5.0-8.0)	0.609	0.001	0.054
Tumor size, n (%)					0.771	<.001	0.024
≤ 5cm	180 (50.85)	143 (54.79)	22 (52.38)	15 (29.41)			
>5cm	174 (49.15)	118 (45.21)	20 (47.62)	36 (70.59)			
Vascular invasion, n (%)					0.264	0.242	0.082
Negative	257 (72.60)	190 (72.80)	34 (80.95)	33 (64.71)			
Positive	97 (27.40)	71 (27.20)	8 (19.05)	18 (35.29)			
Local extrahepatic invasion, n (%)					0.154	0.844	0.305
Negative	320 (90.40)	233 (89.27)	41 (97.62)	46 (90.20)			
Positive	34 (9.60)	28 (10.73)	1 (2.38)	5 (9.80)			
Tumor distribution on preoperative images, n (%)	-	285 (109.20)	43 (102.38)	36 (70.59)	-	-	-
Histological grade, n (%)					0.512	0.919	0.806
Well + moderated	243 (68.64)	181 (69.35)	27 (64.29)	35 (68.63)			
Poor	111 (31.36)	80 (30.65)	15 (35.71)	16 (31.37)			
AJCC pT stage, n (%)					0.154	0.844	0.305
I+II	320 (90.40)	233 (89.27)	41 (97.62)	46 (90.20)			
III+IV	34 (9.60)	28 (10.73)	1 (2.38)	5 (9.80)			
AJCC pN stage n (%)					0.525	0.060	0.557
N0	151 (42.66)	102 (39.08)	20 (47.62)	29 (56.86)			
N1	82 (23.16)	64 (24.52)	10 (23.81)	8 (15.69)			
Nx	121 (34.18)	95 (36.40)	12 (28.57)	14 (27.45)			
Postoperative chemotherapy, n (%)					0.970	0.864	0.924
Negative	240 (68.38)	179 (68.58)	28 (68.29)	33 (67.35)			
Positive	111 (31.62)	82 (31.42)	13 (31.71)	16 (32.65)			

Abbreviations: IQR Interquartile range, *MELD* Model for End-stage Liver Disease, *Type I* single tumors, *Type II* 2 or 3 hepatic lesions in the same side hepatic lobes, *Type III* more than three hepatic lesions in the same side hepatic lobes, *AJCC* American Joint Committee on Cancer

[a] *P* value: Type I vs. type II

[b] *P* value: Type I vs. type III

[c] *P* value: Type II vs. type III

females, with a median age of 59 (IQR: 52–66) years. The median size of the tumor was 5.5 cm (IQR: 3.8–7.0) in the biggest diameter. Of 354 patients, 97 patients (27.4%) had vascular invasion, and 111 patients (31.4%) had poorly differentiated tumors. A total of 82 patients had lymph node metastasis. Postoperative chemotherapy was administered for 111(31.4%) patients, and the mean follow-up time of the cohort was 51 months. Based on the postoperative pathological evaluation, 73.7% ($n = 261$), 11.9% ($n = 42$), and 14.4% ($n = 51$) of patients were classified as type I, type II, and type III, respectively.

Impacts of the number of hepatic lesions on the long-term survival in multifocal iCCA

The median survival time of the entire cohort was 29.0 months. Compared with the solitary tumor,

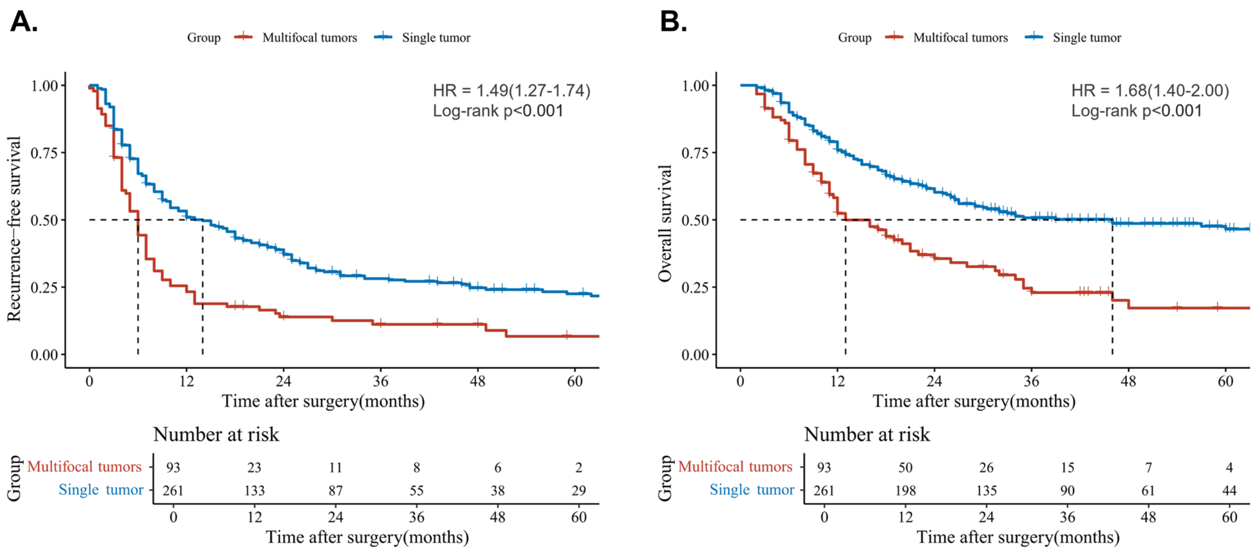

Fig. 2 Kaplan–Meier curve shows the prognostic difference between the multifocal and solitary tumors. **A** Kaplan–Meier curve for RFS in iCCA patients; **B** Kaplan–Meier curve for OS in iCCA patients

multifocal iCCA presented significantly worse OS and DFS (HR $p<0.001$ and $p<0.001$) (Fig. 2). Then, we divided the multifocal iCCA cohorts into different cohorts (type II and type III). Furthermore, the median survival time of the type I, type II, and type III cohorts were 46.0, 24.0, and 12.0 months, respectively. IPTW adjustment resulted in an excellent balance of baseline characteristics between groups (Table 2). After baseline characteristic adjustments, the OS was compared between the three groups (Fig. 3B). Compared with solitary tumors (type I), type II cohorts showed a similar prognosis (type I vs. type II, $p=0.700$). Type III cohort exhibited a worse OS compared with solitary tumors (type I vs. type III, $p<0.001$).

Table 2 IPTW of characteristics of patients undergoing radical surgery for iCCA

Variables	Unmatched			*P* values	After IPTW			*P* values
	Type I (*n* = 261)	Type II (*n* = 42)	Type III (*n* = 51)		Type I (*n* = 261.2)	Type II (*n* = 40.4)	Type III (*n* = 53.4)	
Age > 65 years (%)	71 (27.2)	15 (35.7)	8 (15.7)	0.084	69.2 (26.5)	12.0 (29.7)	17.5 (32.8)	0.744
Male sex (%)	140 (53.6)	22 (52.4)	30 (58.8)	0.768	138.9 (53.2)	22.3 (55.1)	33.6 (63.0)	0.539
CA199 > 32(%)	151 (57.9)	29 (69.0)	34 (66.7)	0.239	151.1 (57.9)	29.1 (71.9)	30.3 (56.8)	0.385
Major hepatectomy (%)	179 (68.6)	30 (71.4)	45 (88.2)	0.017	187.7 (71.8)	29.2 (72.1)	37.1 (69.5)	0.943
Tumor size > 50 mm (%)	118 (45.2)	20 (47.6)	36 (70.6)	0.004	128.8 (49.3)	21.4 (52.9)	23.9 (44.8)	0.793
Vascular invasion (%)	71 (27.2)	8 (19.0)	18 (35.3)	0.215	71.6 (27.4)	10.9 (26.9)	13.4 (25.1)	0.956
Local extrahepatic invasion (%)	28 (10.7)	1 (2.4)	5 (9.8)	0.234	25.0 (9.6)	2.5 (6.1)	4.7 (8.8)	0.85
Lymph node metastases (%)	64 (24.5)	10 (23.8)	8 (15.7)	0.586	60.4 (23.1)	9.7 (24.0)	10.8 (20.2)	0.991
Low-grade differentiation (%)	80 (30.7)	15 (35.7)	16 (31.4)	0.806	81.0 (31.0)	12.9 (31.8)	13.6 (25.4)	0.745
Postoperative chemotherapy (%)	82 (31.4)	13 (31.0)	16 (31.4)	0.998	81.6 (31.3)	11.9 (29.4)	20.6 (38.6)	0.669

Abbreviations: *IPTW* Inverse probability treatment weighting, *iCCA* intrahepatic cholangiocarcinoma, *CA19-9* Carbohydrate antigen 19–9

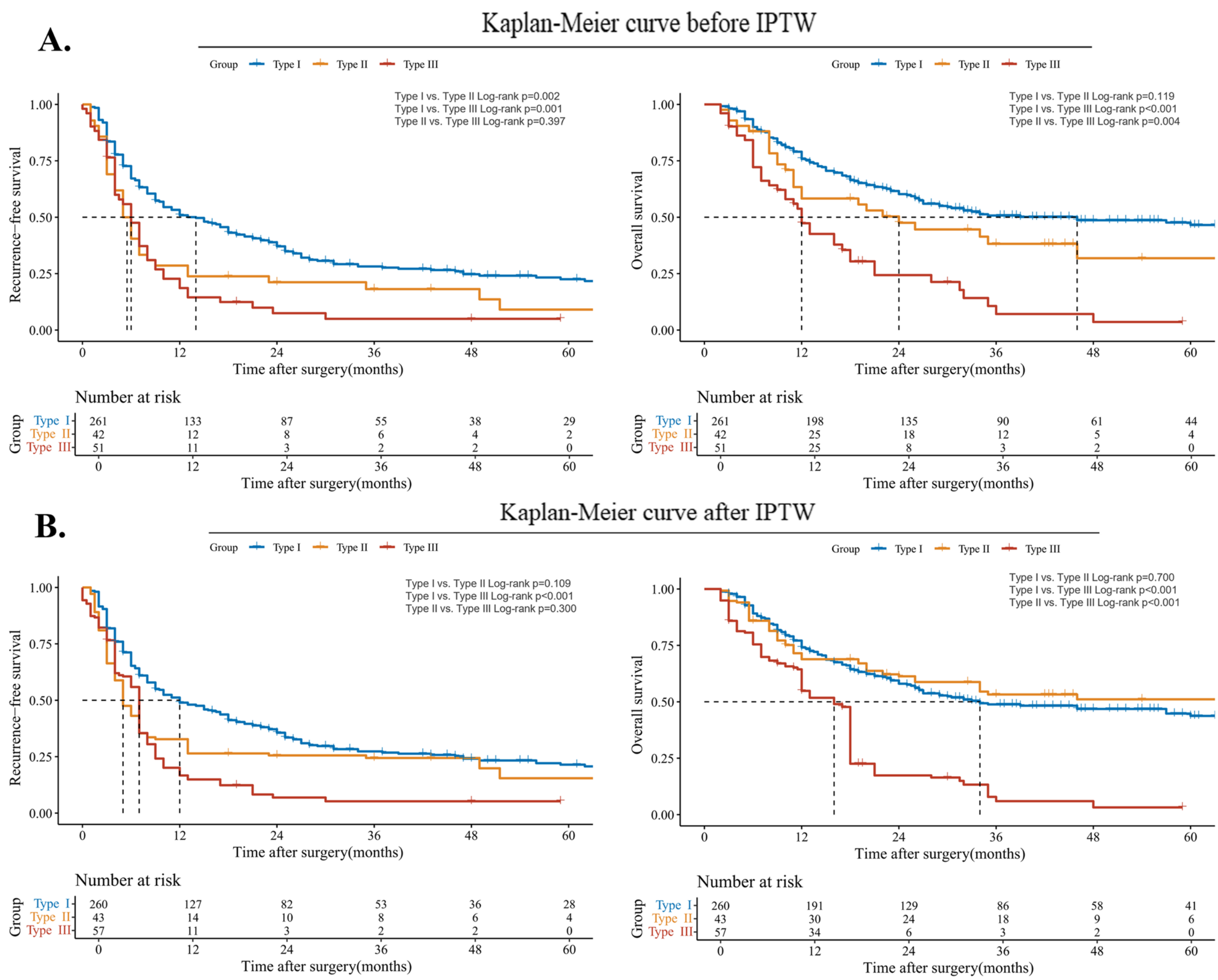

Fig. 3 Kaplan–Meier curve shows the prognostic value of the number of hepatic lesions. **A** Kaplan–Meier curve shows the prognostic value of the number of hepatic lesions for RFS (left) and OS (right) in iCCA patients before IPTW; **B** Kaplan–Meier curve shows the prognostic value of the number of hepatic lesions for RFS (left) and OS (right) in iCCA patients after IPTW. Abbreviations: iCCA, intrahepatic cholangiocarcinoma; Type I, patients with single tumor; Type II, patients with 2 or 3 hepatic lesions; Type III, patients with more than three hepatic lesions

The 3-year RFS rate of the entire cohort was 26.1%. Furthermore, 30.8%, 18.6%, and 8.5% were the 3-year RFS rates for type I, type II, and type III cohorts, respectively. After baseline characteristic adjustments, the RFS between different groups also exhibited significant differences (Fig. 3A). Compared with solitary tumors (type I), type II exhibited similar while type III exhibited worse RFS compared with solitary tumors (type I vs. type II, $p = 0.109$; type I vs. type III, $p < 0.001$, respectively).

Prognostic factors in patients with multifocal iCCA

Multivariable Cox analysis was conducted to show the independent risk factors for OS. Based on univariate and multivariate Cox analysis, CA199 > 32U/ml, lymph node metastasis, low-grade differentiation, local extrahepatic invasion, and multifocal hepatic lesions were identified as independent risk factors for OS (Table 3). From the multivariable Cox analysis for OS, 2 or 3 hepatic lesions didn't significantly influence the OS of patients, while hepatic lesions of more than three emerged as an independent risk factor (HR 1.95, 95% CI:1.33–2.87, $p < 0.001$).

Prognostic impacts of the number of hepatic lesions in different AJCC stages

According to the 8th AJCC stage system, 175, 114, and 65 patients were classified as AJCC stage I, II, and III (T3-4N0M0 and TxN1M0), respectively. In the T2N0M0 cohorts, multifocal iCCA (without vascular invasion) presented worse OS compared with solitary iCCA with

Table 3 Univariable and multivariable Cox analyses of OS in iCCA

Variables	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age				
≤ 65 years old	1.00			
> 65 years old	1.28 (0.94 ~ 1.74)	0.122	-	
Sex				
Female	1.00			
Male	0.89 (0.67 ~ 1.18)	0.417	-	
CA199				
≤ 32 U/ml	1.00			
> 32 U/ml	2.31 (1.69 ~ 3.15)	< .001	1.87 (1.35 ~ 2.58)	< .001
Tumor size				
≤ 5 cm	1.00			
> 5 cm	1.38 (1.04 ~ 1.83)	0.026	1.31 (0.97 ~ 1.77)	0.074
Multifocal lesions				
Type I	1.00			
Type II	1.40 (0.91 ~ 2.16)	0.121	-	
Type III	2.92 (2.04 ~ 4.18)	< .001	1.95 (1.33 ~ 2.87)	< .001
Vascular invasion				
No	1.00			
Yes	1.72 (1.27 ~ 2.33)	< .001	1.36 (0.99 ~ 1.88)	0.060
Local extrahepatic invasion				
No	1.00			
Yes	4.19 (2.80 ~ 6.29)	< .001	4.06 (2.65 ~ 6.24)	< .001
Histological grade				
Well + moderately	1.00			
Poorly differentiated	1.59 (1.18 ~ 2.13)	0.002	1.58 (1.17 ~ 2.14)	0.003
Lymph metastasis				
Negative				
Positive	2.99 (2.20 ~ 4.05)	< .001	2.02 (1.45 ~ 2.84)	< .001
Postoperative chemotherapy				
No	1.00			
Yes	0.78 (0.57 ~ 1.07)	0.126	-	
MELD	1.01 (0.99 ~ 1.02)	0.357	-	
MELD-Na	1.01 (0.99 ~ 1.03)	0.180	-	

Values in parentheses are 95% confidence intervals

Abbreviations: *OS* Overall survival, *iCCA* intrahepatic cholangiocarcinoma, *CA19-9* Carbohydrate antigen 19–9, *MELD* Model for End-stage Liver Disease

vascular invasion ((HR 1.98, 95% CI:1.11–3.55, Cox-$p = 0.019$) (Fig. 4A). Furthermore, the multifocal iCCA (T2N0M0) still presents better OS compared with AJCC stage III cohorts (HR 0.51, 95% CI: 0.32–0.80, Cox-$p = 0.003$) (Fig. 4B).

Of 53 patients with multifocal iCCA, 24 and 29 patients were classified into type I and type II, respectively. Compared with patients with solitary iCCA (vascular invasion), type III cohorts exhibited a worse OS and type II cohorts exhibited a similar OS ($p = 0.037$ and $p = 0.490$, respectively) (Fig. 4C). Furthermore, 65 patients with solitary tumors were classified as AJCC stage III, including 44 patients with lymph metastasis and 21 patients who had local extrahepatic invasion. From Fig. 4D, compared with this cohort of patients, patients of type III cohorts exhibited a similar OS ($p = 0.511$). Furthermore, the patients of type II cohorts presented a significantly better OS compared with AJCC stage III cohorts (HR 0.29, 95% CI:0.15–0.59, Cox-$p = 0.001$).

Discussion

This study aims to identify the specific subgroup of patients with multifocal iCCA who could benefit from radical surgery. Based on the number of tumor nodules, the current study classified patients into three types and then compared the prognosis after radical surgery. An IPTW analysis was performed to clarify the prognosis impact of multifocal nodules. Following baseline characteristic adjustments, the type III cohort exhibited a significantly worse OS and RFS compared with solitary tumors. Notably, the type II cohort presented OS and RFS similar to those of the cohort with solitary tumors. In the multivariable analysis, multifocal nodules of 2 or 3 hepatic lesions didn't emerge as the independent risk factors of OS. These results suggest that patients with only 2 or 3 hepatic lesions in the same side may derive comparable survival benefits from surgery compared with solitary tumors.

Actually, previous research has emphasized the significance of the numbers and distribution of hepatic lesions for long-term prognosis in multifocal iCCA. Several studies reported the number of hepatic lesions was associated with the prognosis of the multifocal iCCA, but the optimal number of hepatic lesions remains controversial [17, 18]. In addition, the prognosis difference caused by the distribution of hepatic lesions also remains unclear. Addeo reported that patients having tumors with satellites in the same Couinaud liver segment had inferior OS compared with patients with contralateral tumors [19]. On the contrary, Simone prompted that the single tumor with satellite nodules in the same Couinaud liver segment presented a better prognosis in multifocal iCCA [6]. Nevertheless, the survival difference might partly be attributed to the more frequent R1 resection of multifocal iCCA. Therefore, to better assess the prognosis difference, we selected patients who underwent R0 resection and then conducted an IPTW analysis to balance the baseline difference. From our study, the type II cohorts presented a similar long-term prognosis with solitary tumors when R0 resection was achieved. A similar trend

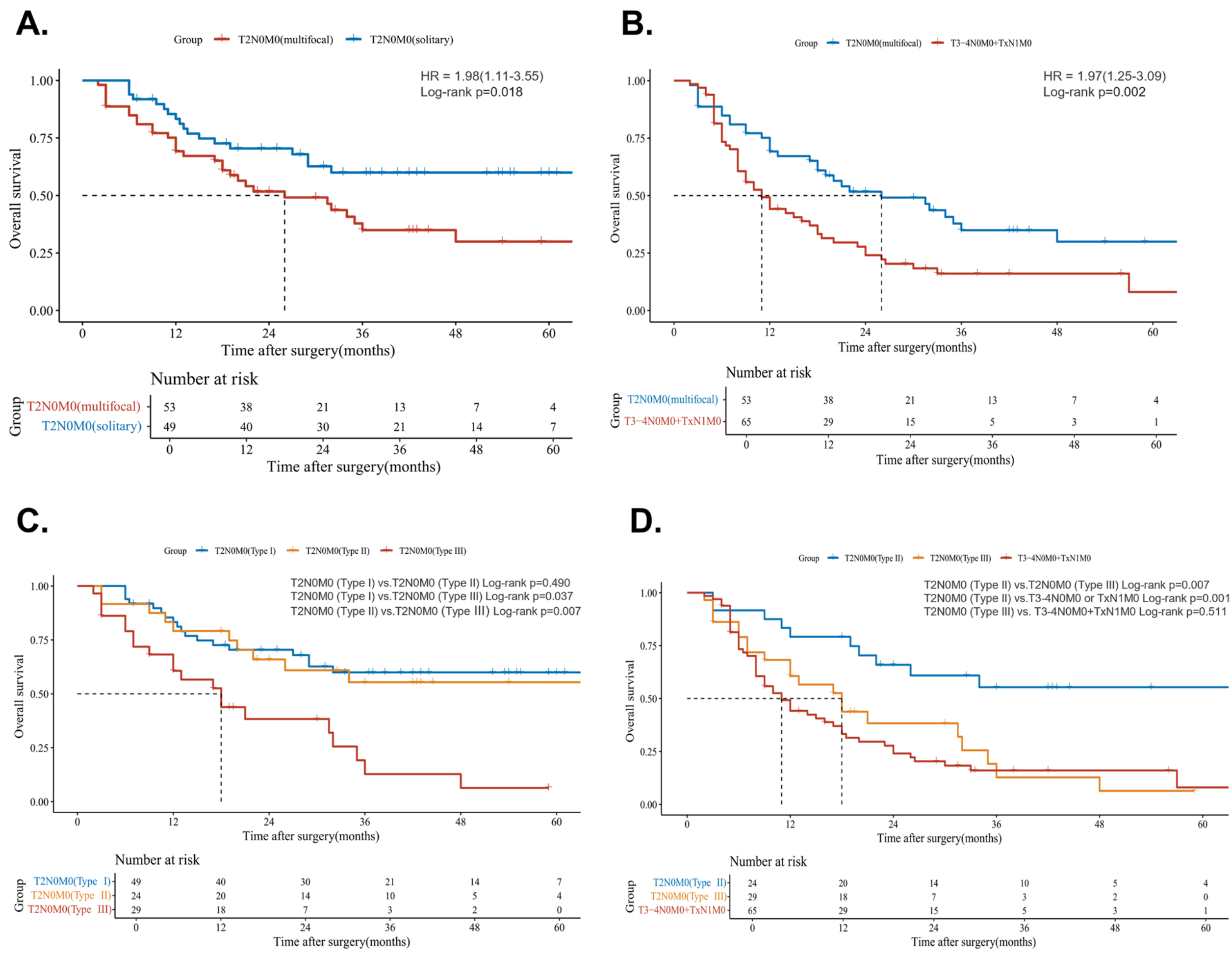

Fig. 4 Kaplan–Meier curve shows the comparison of different AJCC stages of OS in iCCA patients after radical surgery. **A** Kaplan–Meier curve for OS in the T2N0M0 cohorts iCCA; **B** Kaplan–Meier curve for OS between the AJCC stage III (T3-4N0M0 and TxN1M0) and multifocal iCCA (T2N0M0); **C** Kaplan–Meier curve for OS of different cohorts in T2N0M0 cohorts iCCA; **D** Kaplan–Meier curve for OS between different cohorts and AJCC stage III T3-4N0M0 and TxN1M0) cohorts iCCA. Abbreviations: AJCC, the American Joint Committee of Cancer the 8th edition staging system for iCCA; Type II, patients with 2 or 3 hepatic lesions; Type III, patients with more than three hepatic lesions

was observed in previous research, a large-scale and multicenter comparative research compared the prognosis effect of hepatic arterial infusion pump (HAIP) with surgical resection in multifocal iCCA [20]. Consistent with our result, they found that radical surgery could yield a better OS for multifocal iCCA with only 2 or 3 hepatic lesions. For the specific patients of multifocal iCCA, radical resection still provides the most oncologic benefits instead of non-surgery locoregional therapy.

Notably, the stage of multifocal iCCA has been complicated by conflicting results in previous research [21]. Although multifocal hepatic lesions still fall into the T2 category, significant prognosis differences were observed. In a large-scale study based on the Surveillance, Epidemiology, and End Results database, the M1a stage was proposed to represent multifocal iCCA, which presented a worse prognosis than AJCC stage III [22]. Similarly, Kevin M recommended that solitary T2N0 disease and multifocal T2N0 should be classified as stage IIA and IIB, respectively [23]. However, it's noteworthy that these staging recommendations did not fully consider the influence of the distribution and number of multifocal iCCA lesions, which might significantly affect the prognosis of patients. In our study, we observed that patients with more than three hepatic lesions consistently showed a worse long-term prognosis compared to patients with solitary tumor and vascular invasion and similar prognosis with patients classified to AJCC stage III. In contrast, patients with only 2 or 3 hepatic lesions exhibit a significantly better OS than patients classified to AJCC stage III. Our findings suggest the importance of hepatic lesions in the staging system for iCCA to better stratify patient prognosis. The distribution and quantity of multifocal nodules must be noted to better assess the tumor stage and guide more tailored treatment decisions.

The operation of multifocal iCCA means an enlarged extent of hepatectomy, which requires a rigorous operative assessment to acquire the best oncological benefits. This study demonstrated that the distribution of hepatic lesions significantly influences the prognosis of multifocal iCCA, and even determines the clinical decision-making. Notably, we proposed the classification based on postoperative histopathology, which minimized the influence of preoperative imaging misjudgments. The accuracy of tumor distribution assessment significantly improved with the combination of CT, MRI, and even PET/CT, which enhanced the clinical application of our classification. Therefore, under the conditions where R0 resection is possible, for patients with only 2 or 3 lesions in the same side, radical surgery should still be strongly considered as the preferred treatment. For patients with more than 3 hepatic lesions, surgery-alone therapy might not be recommended to improve the long-term prognosis.

This study also has several limitations. Firstly, our study is a retrospective analysis spanning 15 years. During this period, significant changes occurred in the practice of postoperative adjuvant chemotherapy, which were not detailed in this study. Liver transplantation offers a potentially curative treatment option for iCCA; however, it was not addressed in this study due to its low incidence in our center. Furthermore, it might be subject to certain selection biases due to its retrospective nature. Finally, due to the low incidence of multifocal iCCA, external validation and large-scale prospective multicenter studies are required to verify the conclusion further.

Conclusion

The number of hepatic lesions significantly influenced the prognosis of multifocal iCCA. Patients with only 2 or 3 hepatic lesions in the same side hepatic lobes may derive comparable oncological benefits from surgery compared with solitary tumors, radical surgery is strongly recommended as the preferred treatment. Patients with more than three hepatic lesions had a significantly worse prognosis, and the benefits of surgery should be carefully evaluated.

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Supplementary Information

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Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

Protocol/project development: Yin; Data collection or management: Zhang, Huang, Xie, Fu; Data analysis: Zhang, Chen, Cai; Manuscript writing/editing: Zhang, Yin, Huang; Manuscript review: Yin, Huang, Liang; All authors read and approved the submitted version.

Data availability

The datasets generated in this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

The research protocol was approved by the Institutional Ethical Review Boards of the First Affiliated Hospital of Sun Yat-sen University in accordance with the declaration of Helsinki. The need for written informed consent was waived by the Ethical Committee of the First Affiliated Hospital of Sun Yat-sen University due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pancreato-Biliary Surgery, The First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan 2nd Rd, Guangzhou, Guangdong 510080, People's Republic of China.

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