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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Impact of Anatomical Versus Non-anatomical Liver Resection on Short- and Long-Term Outcomes for Patients with Intrahepatic Cholangiocarcinoma

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ABSTRACT

Objective. The aim of this study was to examine the impact of anatomical resection (AR) versus non-anatomical resection (NAR) on the survival outcomes in patients with intrahepatic cholangiocarcinoma (ICC).

Patients and Methods. Data on 702 consecutive patients who underwent either AR (n = 319) or NAR (n = 383) for ICC were reviewed. Disease-free survival (DFS) and overall survival (OS) following AR versus NAR was compared using propensity score matching (PSM). Subgroups of patients who benefited from AR versus NAR were examined after being stratified by the 8th TNM staging of ICC.

Results. AR and NAR had similar complication rates (26.6% vs. 25.1%, p = 0.634). AR was associated with better 1-, 3-, and 5-year DFS and OS rates compared with NAR after PSM (58.1%, 35.7% and 28.1% vs. 44.1%, 23.9% and 18.0%; 72.9%, 45.7% and 36.0% vs. 62.0%, 30.8% and 25.3%; both p = 0.002). On multivariate analysis, NAR was associated with worse DFS and OS than AR [hazard ratio (HR) 1.461 and 1.488; 95% confidence interval (CI) 1.184–1.804 and 1.189–1.863, respectively]. Stratified analysis demonstrated similar outcomes following AR versus NAR for ICC at stages IA, II with vascular invasion, and III with visceral peritoneum perforation, local extrahepatic invasion and nodal metastasis, while NAR was associated with worse DFS and OS versus AR for stages IB (HR 1.897 and 2.321; 95% CI 1.179–3.052 and 1.376–3.914, respectively) or II ICC without vascular invasion (2.071 and 2.077; 95% CI 1.239–3.462 and 1.205–3.579, respectively).

Conclusions. AR was associated with better survival outcomes compared with NAR in ICC patients with stage IB or II tumors without vascular invasion.

Intrahepatic cholangiocarcinoma (ICC) is a primary hepatic malignancy with highly aggressive invasiveness.[1] The incidence and related mortality of ICC are dramatically increasing worldwide.[2] Currently, liver resection, with operation type of either anatomical resection (AR) or non-anatomical resection (NAR), is the only established treatment to achieve possible long-term survival for ICC patients.[2]

The differences in the long-term outcomes after AR versus NAR have frequently been reported in patients with hepatocellular carcinoma (HCC),[3,4] and AR has been

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suggested to be oncologically superior to liver resection with a narrow surgical margin.[5] While both ICC and HCC typically present as an intrahepatic mass, these cancers are distinct in their carcinogenesis, natural history, morphology, pathology and response to therapies.[6] In ICC, there has only been one study that included AR as a study variable and showed it was not independently associated with post-hepatectomy overall survival (OS).[7] In fact, evidence in terms of the effectiveness between AR versus NAR for ICC remains significantly insufficient.

The current study aimed to compare the differences in surgical morbidity and long-term outcomes following either AR or NAR among patients with ICC.

PATIENTS AND METHODS

Study Population

Overall, 915 consecutive patients underwent liver resection for histopathologically confirmed ICC between January 2006 and December 2010 at the Eastern Hepatobiliary Surgery Hospital (EHBH). Among these patients, 820 who received R0 resection were analyzed. An R0 resection was defined as complete removal of all macroscopic nodules with a microscopic tumor-free resection margin, without macroscopic tumor invasion into major portal/hepatic veins or extrahepatic distant metastasis.[8] Of these 820 patients, 118 were excluded due to Child–Pugh class B liver function or presence of portal hypertension (n = 38); tumors that were technically suitable for only one method of AR or NAR based on tumor size, intrahepatic location and distribution, and estimated volumes of future functional liver remnant (n = 46); a history of preoperative anticancer treatment (n = 13); a history of spontaneous tumor rupture prior to surgery (n = 4); a history of other malignancies (n = 5); and missing clinicopathological data (n = 12). Data of the remaining 702 patients were further analyzed. This study was approved by the Institutional Ethics Committee of the EHBH. Informed consent was obtained from all patients prior to surgery for their data to be used for research purposes.

Liver Resection and Definitions

All patients underwent routine preoperative laboratory and imaging examinations, as previously reported.[9] All liver resections were carried out with the intention of complete removal of macroscopic tumors with adequate resection margins. Liver resections based on systematic removal of Couinaud segment(s) containing the tumor together with the tumor-bearing portal vein and corresponding hepatic territory, were classified as AR, and all other resections that were not in accordance with the liver segment anatomy were classified as NAR.[3,4,10] Additional intrahepatic nodules and direct invasion of contiguous organs discovered intraoperatively were also resected if the surgeon considered the operation to be feasible. Regional lymph nodes were dissected if metastasis was suspected/diagnosed either preoperatively or intraoperatively, similar to previously reported data.[9]

The histopathological diagnosis of ICC was based on the WHO classifications.[11] The macroscopic type of ICC was classified using the criteria of the Liver Cancer Study Group of Japan.[12] Microvascular invasion (MVI) was defined as the presence of tumor in a portal vein, hepatic vein, or a large capsular vessel of the surrounding hepatic tissue lined by the endothelium that was only visible on microscopy.[13] Surgical complications were graded using the Clavien–Dindo classification, and perioperative mortality was defined as patient death within 90 days of surgery.[14]

Tumor Staging

Patients were stratified according to the category criteria of the 8th TNM staging system for ICC.[1] Patients who had stage I tumors (T1N0M0) were further classified as having stage IA tumor with a solitary tumor $\leq$ 5 cm without MVI (T1aN0M0), or stage IB tumor with a solitary tumor $>$ 5 cm without MVI (T1bN0M0). Stage II patients were further classified into two subgroups with multiple tumors without MVI, or with a solitary or multiple tumors with MVI. Patients with stage III tumors were stratified by tumor perforating the visceral peritoneum or local extrahepatic invasion without nodal metastasis (T3/4N0M0), or regional nodal metastasis (any T, N1M0).

Follow-Up and Endpoints

Patients were followed-up once every 2 months within the first 2 years after surgery and once every 3–6 months thereafter. At each visit, the tests for liver and renal functions, α-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), and an abdominal ultrasound were performed. Contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) was performed once every 4–6 months, or earlier if clinically indicated.[9] The endpoints were OS, which was calculated from the date of surgery to the date of patient death or last follow-up; and disease-free survival (DFS) which was defined as the interval between the date of surgery and the date of diagnosis of the first recurrence, death, or last follow-up visit; and surgical safety.

Statistical Analysis

Categorical variables were compared using the Chi square test, Yates' correction test, or Fisher's exact test. Continuous variables were expressed as median and interquartile range (IQR), and compared using the *t* test or Mann–Whitney *U* test. Survival curves were analyzed using the Kaplan–Meier method and log-rank test. Multivariate Cox regression analysis was used to assess the impact of AR or NAR on prognosis among subgroups of patients stratified by the 8th TNM system after adjustment for age, sex, schistosomiasis, hepatolithiasis, hepatitis B surface antigen (HBsAg), CEA, CA19-9, total bilirubin (TBIL), albumin (ALB), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), Child–Pugh grade, cirrhosis, blood transfusion, tumor diameter, differentiation, perineural invasion, and macroscopic type.

A one-to-one propensity score matching (PSM) analysis was used to adjust for the baseline features between AR and NAR patients.[15] The variables used in PSM analysis were based on the preoperative imaging data on tumor size, number, distribution, and cirrhosis, which would be evaluated by the surgeon in choosing a resection type,[16] and further identified by logistic regression analysis. The nearest-neighbor matching method was used and the pairs on the propensity-score logit were then matched to within a range of 0.02 of standard deviation.[17]

Data analysis was performed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA) and R software 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). All reported p values were two-sided, and a p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Among all 915 patients with ICC who underwent liver resection, 95 received non-R0 resection. Of these patients, 46 (48.4%) and 49 (51.6%) underwent AR and NAR, respectively. In the 702 patients who underwent R0 resection and met all the eligibility criteria of this study, 319 (45.4%) and 383 (54.6%) underwent AR and NAR, respectively. In the AR group, segmentectomy was performed in 73 (22.9%) patients, bi-segmentectomy was performed in 132 (41.4%) patients, and tri-segmentectomy or hemihepatectomy was performed in 114 (35.7%) patients.

Surgical Morbidity and Mortality

Among these 702 patients, surgical morbidity after AR and NAR occurred in 85 (26.6%) and 96 (25.1%) patients, respectively ($p = 0.634$), with grade I/II complications in 56 (65.9%) and 68 (70.8%) patients, and grade III/IV in 29 (34.1%) and 28 (29.2%) patients, respectively ($p = 0.474$). Of the 31 mortality patients, 14 (4.4%) and 17 (4.4%) underwent AR and NAR, respectively ($p = 0.974$).

Surgical morbidity and mortality rates after AR ($n = 258$) versus NAR ($n = 267$) among non-cirrhotic patients were 25.2% versus 24.3% and 3.9% versus 3.7%, respectively ($p = 0.822$ and 0.938, respectively). The above rates between AR ($n = 61$) and NAR ($n = 116$) among cirrhotic patients were 32.8% versus 26.7% and 6.6% versus 6.0%, respectively ($p = 0.397$ and 1.000, respectively).

The median postoperative hospital stays after AR and NAR were both 10.0 days (IQR 9.0–12.0 and 8.0–12.0 days, respectively; $p = 0.876$).

Long-Term Prognoses in the Entire Cohort

Among the 702 patients, 671 were further analyzed for the long-term outcomes after excluding the 31 mortality patients.

Of these 671 patients, 338, 156 and 177 had stage I, II, and III ICC, respectively (electronic supplementary Table S1), and 305 (45.5%) and 366 (54.5%) received AR and NAR, respectively. AR was associated with better 1-, 3-, and 5-year DFS and OS rates than NAR, i.e. 57.7%, 35.7% and 29.1% versus 42.1%, 23.4% and 17.2%; and 74.4%, 45.8% and 36.3% versus 61.2%, 30.5% and 24.2% (both $p < 0.001$) (Fig. 1a, b).

Multivariate analysis identified NAR to be associated with worse DFS and OS compared with AR [hazard ratio (HR) 1.429 and 1.410, respectively; 95% confidence interval (CI) 1.199–1.704 and 1.171–1.698, respectively] (electronic supplementary Tables S2 and S3).

Long-Term Prognoses in the PSM Cohort

As shown in Table 1, when compared with patients who underwent AR, NAR patients were more likely to be older (median 55 vs. 54 years), had higher levels of TBIL (13.2 vs. 12.7 μmol/L) and AST (28.7 vs. 26.4 U/L), lower level of ALB (41.9 vs. 42.6 g/L), and larger tumor size (5.8 vs. 5.1 cm); a larger proportion of NAR patients had multiple nodules (31.9% vs. 23.5%) and cirrhosis (30.3% vs. 19.1%) (all $p \leq 0.036$). PSM was used, and selection of the variables was based on univariate and multivariate logistic regression analysis (electronic supplementary Table S4). After PSM, 229 patients were allocated to each of the AR

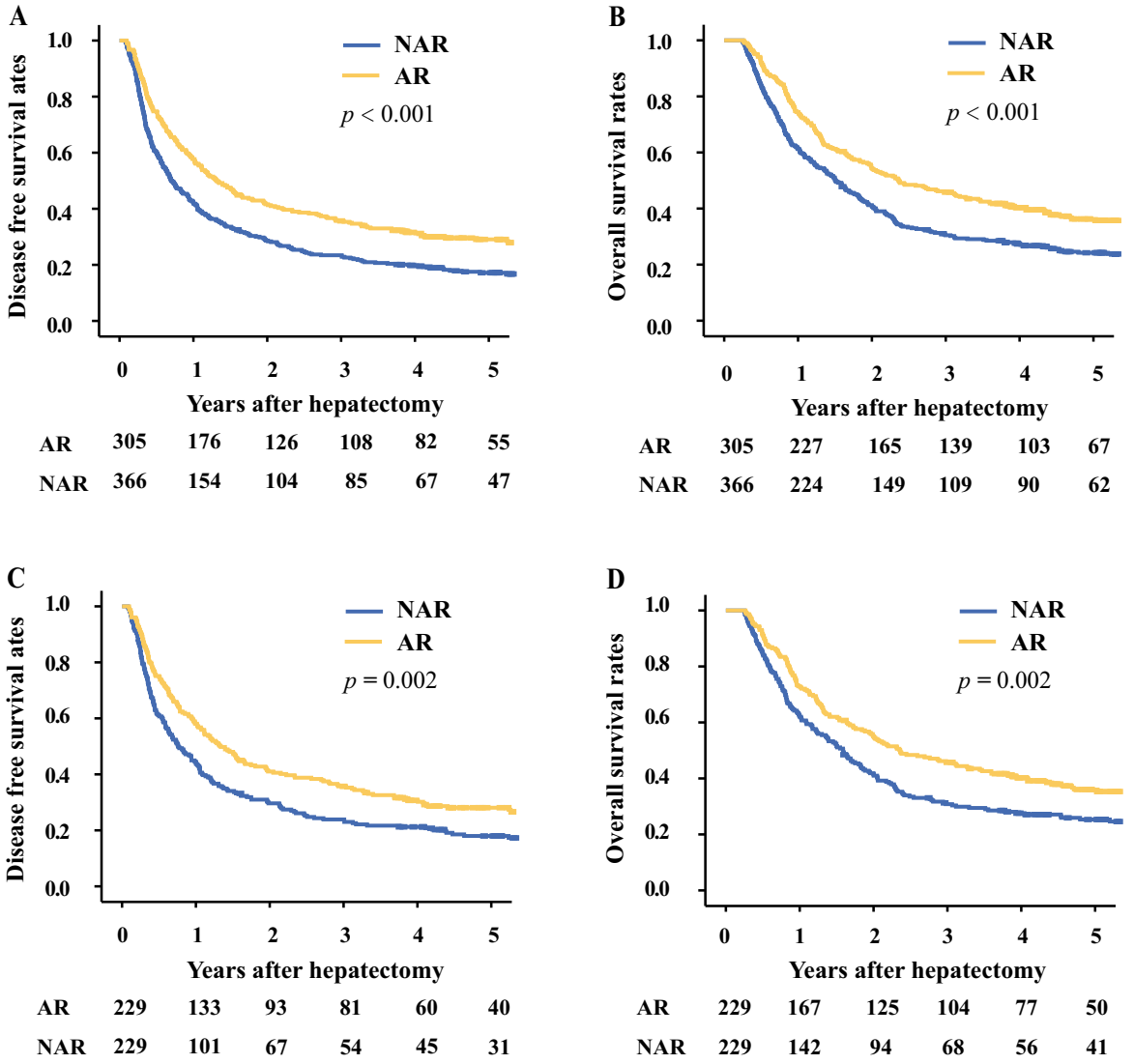

FIG. 1 DFS and OS rates after AR versus NAR for ICC patients. **a** DFS rates in the entire cohort; **b** OS rates in the entire cohort; **c** DFS rates in the PSM cohort; **d** OS rates in the PSM cohort. *DFS* disease-free survival, *OS* overall survival, *AR* anatomical resection, *NAR* non-anatomical resection, *ICC* intrahepatic cholangiocarcinoma, *PSM* propensity score matching

and NAR groups. The baseline characteristics between the two groups were well-balanced (Table 1).

AR was associated with better 1-, 3-, and 5-year DFS and OS rates compared with NAR, i.e. 58.1%, 35.7% and 28.1% versus 44.1%, 23.9% and 18.0% ($p = 0.002$); and 72.9%, 45.7% and 36.0% versus 62.0%, 30.8% and 25.3% ($p = 0.002$) (Fig. 1c, d).

On multivariate analysis, NAR was associated with worse DFS and OS compared with AR (HR 1.461 and 1.488; 95% CI 1.184–1.804 and 1.189–1.863, respectively). Other risk factors were hepatolithiasis, CEA > 10 μg/L, CA19-9 > 39 U/L, tumor > 5 cm, multiple tumors, nodal metastasis, and local extrahepatic invasion (electronic supplementary Table S5 and Table 2).

Long-Term Prognoses among Stage I Patients

Among 338 patients with stage I disease, AR ($n = 159$) was associated with better prognoses than NAR ($n = 179$). The 1-, 3-, and 5-year DFS and OS rates were 70.4%, 49.6% and 42.9% versus 53.6%, 33.9% and 24.8% ($p < 0.001$); and 84.9%, 60.3% and 50.9% versus 69.8%, 44.0% and 33.8% ($p = 0.001$) (Fig. 2a, b).

Stage I patients were further classified into stage IA (≤ 5 cm, $n = 189$) and IB (> 5 cm, $n = 149$) subgroups. Among stage IA patients, the 1-, 3-, and 5-year DFS and OS rates after AR ($n = 95$) versus NAR ($n = 94$) were comparable (73.7%, 53.6% and 47.4% vs. 62.8%, 41.3% and 34.1%; and 86.3%, 60.8% and 52.5% vs. 76.6%, 51.8% and 44.4%; $p = 0.058$ and 0.151, respectively)

TABLE 1 Baseline characteristics between NAR and AR patients (n = 671)

Variable	Before PSM (n [%]/median [IQR])			After PSM (n [%]/median [IQR])		
	NAR (n = 366)	AR (n = 305)	p value	NAR (n = 229)	AR (n = 229)	p value
Age, years	55.4 (47.0–65.0)	52.9 (46.0–60.0)	0.002	54.0 (46.0–61.5)	54.0 (48.0–60.0)	0.996
Sex, male	236 (64.5)	192 (63.0)	0.681	133 (58.1)	149 (65.1)	0.124
Schistosomiasis, yes	14 (3.8)	20 (6.6)	0.108	11 (4.8)	14 (6.1)	0.537
Hepatolithiasis, yes	56 (15.3)	44 (14.4)	0.751	36 (15.7)	30 (13.1)	0.425
HBsAg, positive	171 (46.7)	143 (46.9)	0.966	104 (45.4)	108 (47.2)	0.708
HBeAg, positive	36 (9.8)	28 (9.2)	0.773	21 (9.2)	16 (7.0)	0.391
Anti-HCV, positive	7 (1.9)	7 (2.3)	0.730	2 (0.9)	5 (2.2)	0.446
AFP, μg/L	3.7 (2.3–10.7)	3.7 (2.2–8.0)	0.653	3.5 (2.2–11.6)	3.8 (2.3–8.0)	0.872
CEA, μg/L	2.5 (1.6–4.2)	2.4 (1.6–4.2)	0.340	2.5 (1.5–5.0)	2.5 (1.7–4.3)	0.557
CA19-9, U/L	37.9 (14.1–242.3)	36.2 (14.7–141.8)	0.610	38.1 (13.6–218.5)	40.1 (16.8–166.0)	0.730
TBIL, μmol/L	13.2 (10.1–18.5)	12.7 (9.6–16.8)	0.030	13.2 (10.2–18.9)	12.7 (10.0–17.0)	0.074
ALB, g/L	42.0 (39.2–44.3)	42.7 (40.2–45.4)	0.006	42.6 (39.9–44.6)	42.7 (40.4–45.8)	0.158
ALT, U/L	28.2 (17.7–45.1)	26.1 (18.5–38.8)	0.155	27.6 (17.1–44.6)	26.2 (18.9–41.7)	0.585
AST, U/L	28.7 (20.9–39.9)	26.0 (19.3–34.4)	0.004	28.6 (20.6–39.1)	26.8 (20.0–35.0)	0.151
ALP, U/L	103.0 (76.0–139.0)	100.0 (75.5–137.0)	0.952	102.0 (73.5–132.0)	101.0 (79.0–136.0)	0.320
Tumor distribution (I)[a]						
Left hemiliver	136 (37.2)	115 (37.7)	0.532	86 (37.6)	81 (35.4)	0.562
Right hemiliver	188 (51.4)	163 (53.4		128 (55.9)	127 (55.5)	
Both hemilivers	42 (11.5)	27 (8.9)		15 (6.6)	21 (9.2)	
Cirrhosis (I)[a], yes	102 (27.9)	55 (18.0)	0.003	43 (18.8)	46 (20.1)	0.723
Tumor diameter, cm (I)[a]	5.8 (3.8–8.0)	5.0 (3.4–7.0)	0.001	5.0 (3.6–7.6)	5.1 (3.5–7.2)	0.607
Tumor number (I)[a], multiple	108 (29.5)	61 (20.0)	0.005	56 (24.5)	55 (24.0)	0.913
Operative blood loss, mL	250.0 (200.0–400.0)	300.0 (150.0–500.0)	0.619	300.0 (200.0–400.0)	300.0 (150.0–475.0)	0.830
Blood transfusion, yes	64 (16.7)	60 (18.8)	0.468	31 (13.5)	40 (17.5)	0.245
Tumor distribution						
Left hemiliver	135 (36.9)	112 (36.7)	0.886	86 (37.6)	78 (34.1)	0.262
Right hemiliver	186 (50.8)	159 (52.1)		126 (55.0)	124 (54.1)	
Both hemilivers	45 (12.3)	34 (11.1)		17 (7.4)	27 (11.8)	
Cirrhosis, yes	109 (29.8)	57 (18.7)	0.001	49 (21.4)	48 (21.0)	0.909
Tumor diameter, cm	5.7 (4.0–8.0)	5.0 (3.4–7.0)	0.001	5.2 (3.8–7.9)	5.1 (3.6–7.3)	0.483
Tumor number, multiple	113 (30.9)	71 (23.3)	0.028	59 (25.8)	61 (26.6)	0.832
Surgical margin $\geq$ 0.5, cm	160 (43.7)	144 (47.2)	0.365	100 (43.7)	110 (48.0)	0.348
MVI, presence	34 (9.3)	32 (10.5)	0.603	18 (7.9)	25 (10.9)	0.262
Nodal metastasis, yes	64 (17.5)	55 (18.0)	0.854	40 (17.5)	40 (17.5)	1.000
Local extrahepatic invasion, yes	27 (7.4)	19 (6.2)	0.558	14 (6.1)	14 (6.1)	1.000
Tumor differentiation						
Well	5 (1.4)	9 (3.0)	0.105	2 (0.9)	7 (3.1)	0.144
Moderate	314 (85.8)	269 (88.2)		197 (86.0)	199 (86.9)	
Poor	47 (12.8)	27 (8.9)		30 (13.1)	23 (10.0)	
Perineural invasion, yes	11 (3.0)	11 (3.6)	0.663	7 (3.1)	9 (3.9)	0.611
Macroscopic type						
MF	351 (95.9)	289 (94.8)	0.507	219 (95.6)	216 (94.3)	0.572
PI	10 (2.7)	13 (4.3)		7 (3.1)	11 (4.8)	
IG	5 (1.4)	3 (1.0)		3 (1.3)	2 (0.9)	

TABLE 1 continued

Variable	Before PSM (*n* [%]/median [IQR])			After PSM (*n* [%]/median [IQR])		
	NAR (*n* = 366)	AR (*n* = 305)	*p* value	NAR (*n* = 229)	AR (*n* = 229)	*p* value
8th TNM staging						
I	179 (48.9)	159 (52.1)	0.675	118 (51.5)	116 (50.7)	0.783
II	89 (24.3)	67 (22.0)		51 (22.3)	57 (24.9)	
III	98 (26.8)	79 (25.9)		60 (26.2)	56 (24.4)	
Operation time, min	120.0 (90.0–150.0)	120.0 (90.0–150.0)	0.852	120.0 (90.0–150.0)	120.0 (90.0–150.0)	0.534
Surgical morbidity, yes	94 (25.7)	83 (27.2)	0.654	50 (21.8)	65 (28.4)	0.106
Grade of complications						
I/II	67 (71.3)	55 (66.3)	0.472	35 (70.0)	44 (67.7)	0.791
III/IV	27 (28.7)	28 (33.7)		15 (30.0)	21 (32.3)	
Postoperative hospital stay, days	10.0 (8.0–12.0)	10.0 (9.0–12.0)	0.964	10.0 (8.0–12.0)	10.0 (9.0–12.0)	0.253
Adjuvant treatment[b], yes	81 (22.1)	74 (24.3)	0.514	51 (22.3)	55 (24.0)	0.658

AR anatomical resection, *NAR* non-anatomical resection, *IQR* interquartile range, *PSM* propensity score matching, *HBsAg* hepatitis B surface antigen, *HBeAg* hepatitis B e antigen, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *TBIL* total bilirubin, *ALB* albumin, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *MVI* microvascular invasion, *MF* mass-forming, *PI* periductal infiltrating, *IG* intraductal growth, *TNM* tumor-node-metastasis, *TACE* transarterial chemoembolization, *SC* systemic chemotherapy, *RT* radiotherapy, *PRFA* percutaneous radiofrequency ablation

[a]Variables marked with (I) were based on preoperative imaging studies and were only used in logistic analysis for selecting variables into PSM analysis; all other tumor-related variables and cirrhosis not marked with (I) were based on histopathological examination

[b]Included TACE (*n* = 108), SC (*n* = 19), RT (*n* = 15), PRFA (*n* = 1), TACE/RT (*n* = 6), RT/PRFA (*n* = 3), TACE/SC (*n* = 2) and TACE/PRFA/RT (*n* = 1) in the entire cohort; and TACE (*n* = 86), SC (*n* = 14), RT (*n* = 11), TACE/RT (*n* = 3), RT/PRFA (*n* = 1) and TACE/SC (*n* = 1) in the PSM cohort

(Fig. 2c, d). However, among stage IB patients, AR (*n* = 64) was associated with better 1-, 3-, and 5-year DFS and OS rates versus NAR (*n* = 85; 65.6%, 43.8% and 36.3% vs. 43.5%, 25.9% and 14.8%, *p* = 0.002; and 82.8%, 59.4% and 48.5% vs. 62.4%, 35.3% and 22.2%, *p* = 0.001) (Fig. 2e, f). After adjustment for other potential prognostic variables, NAR was associated with an increased risk of DFS and OS versus AR among stage IB patients (HR 1.897, 95% CI 1.179–3.052; and HR 2.321, 95% CI 1.376–3.914, respectively) (electronic supplementary Table S6).

Long-Term Prognoses among Stage II Patients

Among 156 patients with stage II diseases, AR (*n* = 67) and NAR (*n* = 89) patients had similar 1-, 3-, and 5-year DFS rates (52.2%, 29.9% and 20.5% vs. 34.8%, 16.9% and 12.0%, *p* = 0.072). However, AR patients had higher OS rates than NAR patients (64.2%, 40.3% and 29.0% vs. 60.7%, 20.2% and 17.6%, *p* = 0.065) (Fig. 3a, b).

Stage II patients were further classified into two subgroups. For patients with multiple tumors without MVI, AR (*n* = 38) was associated with better 1-, 3-, and 5-year DFS and OS than NAR (*n* = 65; 55.3%, 34.2% and 21.1% vs. 32.3%, 13.8% and 7.4%, *p* = 0.020; and 63.2%, 39.5% and 29.6% vs. 56.9%, 16.9% and 15.0%, *p* = 0.043) (Fig. 3c, d). After adjustment for other variables, NAR was associated with worse DFS and OS compared with AR (HR 2.071, 95% CI 1.239–3.462; and HR 2.077, 95% CI 1.205–3.579, respectively) (electronic supplementary Table S6).

However, for patients with a solitary or multiple tumors with MVI (*n* = 53), the 1-, 3-, and 5-year DFS and OS rates between AR (*n* = 29) and NAR (*n* = 24) were comparable (*p* = 0.790 and 0.904, respectively) (Fig. 3e, f).

Long-Term Prognoses among Stage III Patients

Among 177 patients with stage III diseases, no significant differences in 1-, 3-, and 5-year DFS and OS after AR (*n* = 79) versus NAR (*n* = 98) were identified (34.1%, 11.8% and 8.1% vs. 25.2%, 9.3% and 7.4%, *p* = 0.142; 62.0%, 21.5% and 13.0% vs. 45.9%, 15.3% and 13.1%, *p* = 0.193) (electronic supplementary Figs. S1a, b). In subgroup analyses, the corresponding DFS and OS rates between AR and NAR were also similar among patients with stage IIIA ICC without nodal metastasis (*n* = 24 and 34; *p* = 0.334 and 0.576, respectively), and IIIB ICC with nodal metastasis (*n* = 55 and 64; *p* = 0.269 and 0.188, respectively) (electronic supplementary Figs. S1c–f).

TABLE 2 Multivariate Cox regression analysis of DFS and OS in the PSM matched cohort

Variable[a]	DFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Hepatolithiasis, yes versus no	–	–	1.390 (1.028–1.880)	0.032
CEA, μg/L (> vs. ≤ 10)	1.980 (1.482–2.646)	< 0.001	2.381 (1.758–3.224)	< 0.001
CA19-9, U/L (> vs. ≤ 39)	1.719 (1.379–2.141)	< 0.001	1.731 (1.372–2.184)	< 0.001
Tumor diameter, cm (> vs. ≤ 5)	1.288 (1.034–1.605)	0.024	1.269 (1.004–1.602)	0.046
Tumor number, multiple versus solitary	1.439 (1.140–1.816)	0.002	1.426 (1.113–1.828)	0.005
Nodal metastasis, yes versus no	1.665 (1.272–2.180)	< 0.001	1.761 (1.326–2.340)	< 0.001
Local extrahepatic invasion, yes versus no	1.782 (1.181–2.689)	0.006	1.572 (1.026–2.408)	0.038
Type of liver resection, NAR versus AR	1.461 (1.184–1.804)	< 0.001	1.488 (1.189–1.863)	0.001

PSM propensity score matching, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *AR* anatomical resection, *NAR* non-anatomical resection, *DFS* disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

[a]All tumor-related variables were based on histopathological examination

DISCUSSION

The current study showed that AR conferred advantages over NAR in OS outcomes in patients with ICC. Subgroup analyses further identified the patients who would benefit the most from AR based on the 8th TNM staging system of ICC.[1]

In this study, AR was associated with better long-term survival than NAR in stage I and II ICC patients, but not in stage III patients. Further stratified analysis demonstrated that AR was better than NAR in survival outcomes in patients with stage IB tumors, or stage II tumors without MVI. Those individuals who had resectable ICC with less aggressively invasive features, accounting for 37.6% (264/702) of all patients in this study, could benefit from AR.

In contrast, two extreme subgroups of patients failed to benefit from AR. Among stage IA patients with ICC ≤ 5 cm, who accounted for 27.2% (191/702) of all patients, there was no significant difference in the 1-, 3-, and 5-year DFS and OS after AR or NAR. In addition, both types of resection had similar outcomes among patients with relatively advanced ICC, classified as stage II with MVI, stage III with or without nodal metastasis. These patients accounted for 35.2% (247/702) of all patients. It is possible that an R0 resection using NAR is adequate for stage IA ICC without any invasive feature. This is important, especially for patients with compromised liver function. On the other hand, among patients with more advanced tumors, the invasiveness of ICC, rather than the resection type, influenced long-term outcomes. Previous studies have demonstrated that nodal metastasis markedly influenced the prognostic impact of other risk factors in ICC.[18]

For pre-hepatectomy evaluation of patients who are suitable or unsuitable for AR, the conventional tumor classification factors, tumor morphology, liver remnant volume and cirrhosis can be evaluated preoperatively. For assessment of tumor invasiveness features, nodal abnormality and local extrahepatic invasion can be examined on medical imaging and surgical exploration. However, as the presence of MVI can only be diagnosed histopathologically after surgery, its impact on decision making in selection of the type of hepatectomy is limited. The preoperative prediction of MVI has been developed in HCC and identification of high-risk patients with MVI is becoming increasingly possible.[19] However, such a study on ICC is still lacking and needs further pioneering work.

Our study had several limitations, including (1) being a single-institutional study; (2) having the potential to introduce surgical and selection biases due to its retrospective nature (we did use PSM with grouping and subgrouping of our patients into various tumor stages in an attempt to decrease these biases); and (3) some patients who had normal lymph nodes as identified by preoperative imaging studies and surgical exploration did not undergo lymphadenectomy, which might affect the results to a certain extent.

CONCLUSION

Our study demonstrated that AR was associated with better survival outcomes compared with NAR in ICC patients, with the exception of two subgroups based on the 8th TNM system, i.e. the less invasive subgroup with stage IA tumors, or the more invasive subgroup with tumors at stage II with vascular invasion, and at stage III.

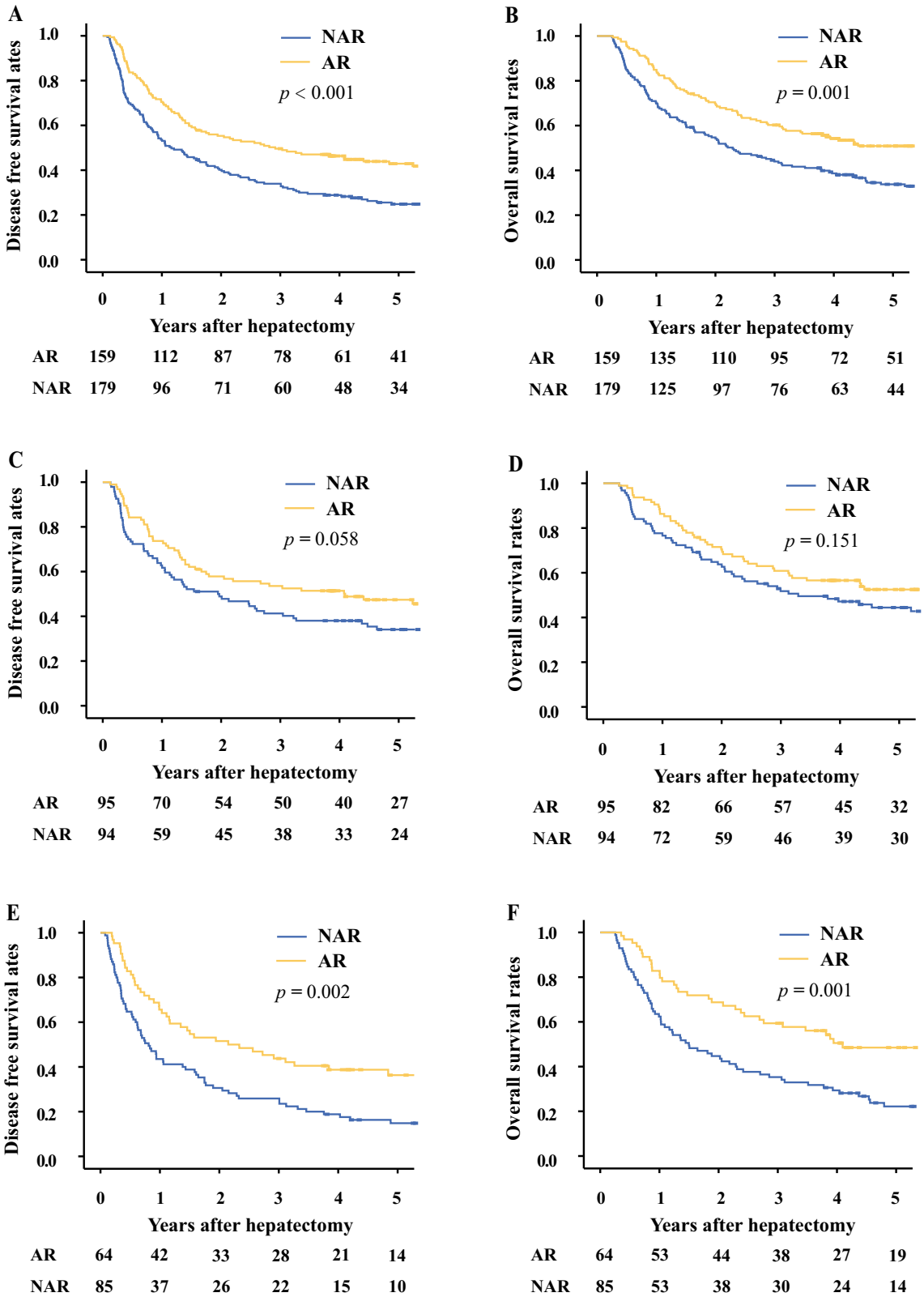

FIG. 2 DFS and OS rates after AR versus NAR for stage I ICC patients. **a** DFS rates in all stage I patients; **b** OS rates in all stage I patients; **c** DFS rates in stage IA patients with a solitary tumor $\leq$ 5 cm; **d** OS rates in stage IA patients with a solitary tumor $\leq$ 5 cm; **e** DFS rates in stage IB patients with a solitary tumor $>$ 5 cm; **f** OS rates in stage IB patients with a solitary tumor $>$ 5 cm. *DFS* disease-free survival, *OS* overall survival, *AR* anatomical resection, *NAR* non-anatomical resection, *ICC* intrahepatic cholangiocarcinoma

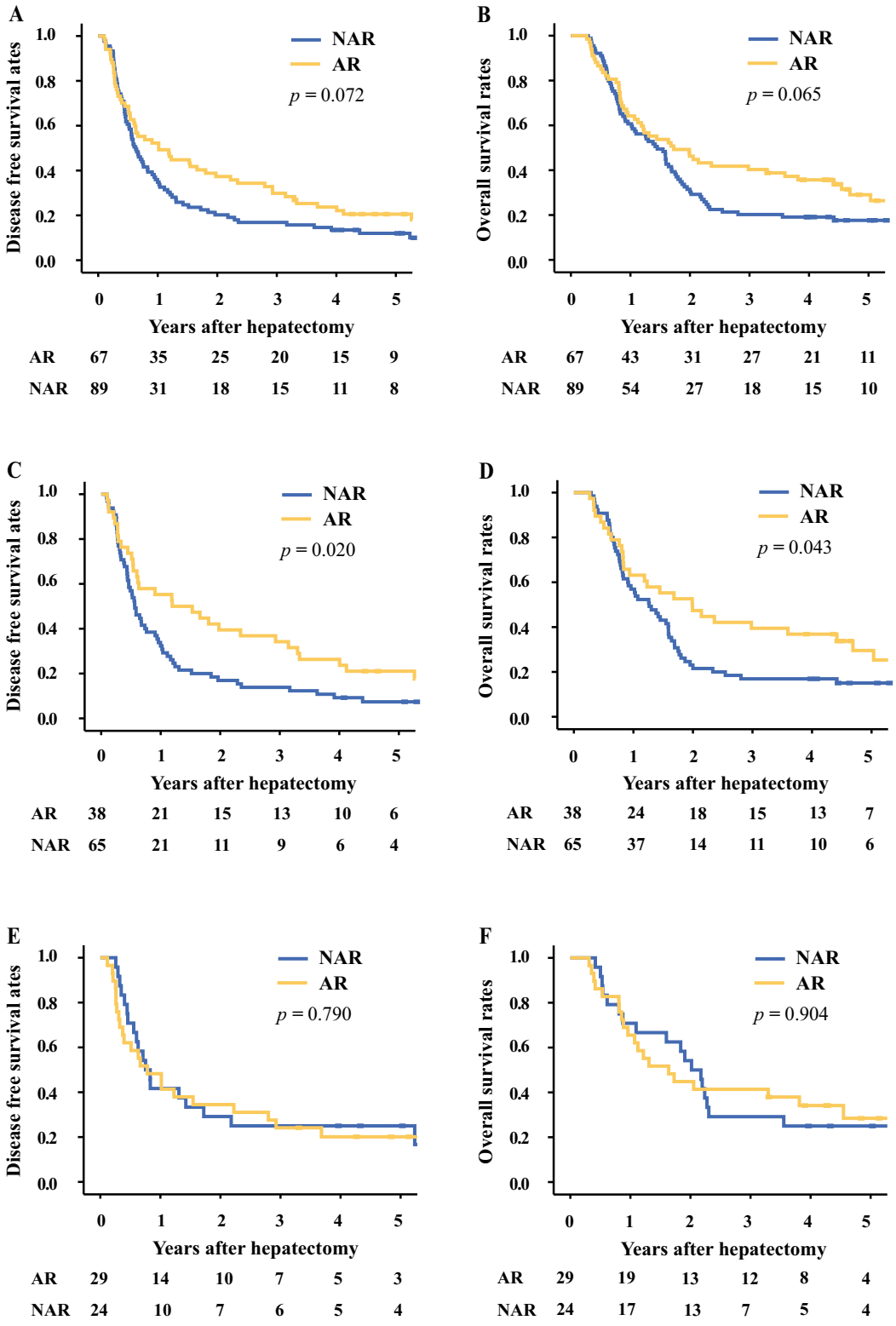

FIG. 3 DFS and OS rates after AR versus NAR for stage II ICC patients. **a** DFS rates in all stage II patients; **b** OS rates in all stage II patients; **c** DFS rates in stage II patients with multiple tumors without MVI; **d** OS rates in stage II patients with multiple tumors without MVI; **e** DFS rates in stage II patients with a solitary tumor or multiple tumors with MVI; **f** OS rates in stage II patients with a solitary tumor or multiple tumors with MVI. *DFS* disease-free survival, *OS* overall survival, *AR* anatomical resection, *NAR* non-anatomical resection, *ICC* intrahepatic cholangiocarcinoma, *MVI* microvascular invasion

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AUTHOR'S CONTRIBUTIONS FS had full access to all the data in the study and is responsible for the integrity of the data and accuracy of the data analyses. FS, AS, JL, ZY: study concept and design, and drafting of the manuscript. AS, JL, ZY, YX, TY, ZL: Collection and assembly of the data. FS, AS, JL, TY, ZC: data collection, analysis and interpretation. FS, TMP, WYL: critical revision of the manuscript for important intellectual content and administrative support. All authors read and approved the final version of the manuscript.

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