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Surgical Resection versus Re-Ablation for Intrahepatic Recurrent Hepatocellular Carcinoma after Initial Ablation Therapy

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Keywords
Surgical resection · Ablation · Hepatocellular carcinoma · Outcomes

Abstract
Background and Aims: Whether surgical resection or repeated ablation should be recommended for intrahepatic recurrent hepatocellular carcinoma (HCC) conforming to the Milan criteria after initial ablation remains unclear. In this study, we compared the outcomes of patients who underwent surgical resection with those who underwent re-ablation for recurrent HCC after initial curative-intent ablation. ***Methods:*** The data of 28 and 98 patients who underwent surgical resection and re-ablation, respectively, for recurrent HCC after initial ablation between January 2003 and 2017 were analyzed using propensity score matching. ***Results:*** Before matching, the 1-, 3-, and 5-year overall survival (OS) rates were 95.7, 83.0, and 74.4% for the ablation group, compared to 92.9, 89.1, and 70.9% for the resection group (p = 0.490). The corresponding disease-free survival (DFS) rates were 67.5, 40.1, and 25.6% for the ablation group and were 85.4, 59.9, and 53.3% for the resection group (p = 0.018). After matching, the 1-, 3-, and 5-year OS rates for the ablation and resection group were 95.2, 85.5 and 81.8% versus 96.0, 96.0, and 76.4%, respectively (p = 0.550). The 1-, 3-, and 5-year DFS rates were 58.0, 39.5, and 29.9% for the ablation group and were 95.8, 67.2, and 59.8% for the resection group (p = 0.004). Cox proportional hazards model identified surgical resection as the only significant prognostic factor for DFS but not for OS. ***Conclusion:*** For intrahepatic recurrent HCC patients after initial ablation, surgical resection could provide better DFS than re-ablation, while no difference in OS was observed between the 2 treatment groups.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide, especially in eastern countries [1, 2]. Currently, surgical resection and local ablation are considered the main curative modalities

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for patients with early stage HCC, based on the Barcelona Clinic Liver Cancer (BCLC) system and the Milan criteria [1, 3, 4].

Local ablation, including radiofrequency ablation (RFA) and microwave ablation (MWA), was demonstrated as having similar efficacy compared to surgical resection in terms of survival outcomes for a single small HCC of ≤3 cm and may have several advantages over surgical resection, such as lower morbidity and mortality rates and better preservation of liver function [5–10]. However, local recurrence is more common in patients undergoing ablation compared with those undergoing surgical resection [10, 11]. Previous studies reported that local recurrence rates after ablation varied from 2.4 to 36% and had a cumulative 5-year intrahepatic recurrence rate ranging from 70 to 80% for patients within the Milan criteria and who received RFA as initial treatment in our previous study [8–10, 12]. So far, few reports have analyzed the short-term and long-term outcomes of surgical resection or repeated ablation after initial ablation therapy [10, 12, 13]. Therefore, the optimal treatment for local recurrent HCC is yet to be fully determined. In this study, we compared the outcomes of recurrent HCC patients who underwent surgical resection with those who underwent re-ablation after initial curative-intent ablation by using propensity score matching (PSM).

Materials and Methods

Patients

This was a retrospective analysis based on patients' data prospectively collected in the database of the Department of Liver Surgery, Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of SYSUCC. Written informed consent was obtained from each patient.

Between January 2003 and January 2017, 1,032 HCC patients underwent curative ablation (RFA and MWA) as initial treatment. We excluded patients who had initial recurrent HCC within 3 months or with recurrent HCC close to primary tumor (<0.5 cm) on radiological imaging to ensure the efficacy of initial ablation therapy, and the remaining 332 patients were identified by the inclusion and exclusion criteria below in our study. The inclusion criteria were as follows: (a) patients who underwent surgical resection or re-ablation (RFA and MWA) as salvage treatment, and the re-ablation should be the same as the initial treatment (MWA or RFA); (b) their largest recurrent tumor size was 5 cm in diameter for a single tumor or 3 cm in diameter for multiple tumors (1 < number of tumors ≤ 3), which conforms to the Milan criteria; (c) they had Child-Pugh A or B disease; (d) patients' Eastern Cooperative Oncology Group performance status was 0–1, and (e) their lesions were visible on ultrasound with an acceptable and safe path to perform interventions in the ablation group. The exclusion criteria for this study were as follows: (a) presence of severe preoperative physical condition (severe cardiovascular disease and renal insufficiency); (b) a history of second primary malignant tumors; (c) presented with radiological evidence of major portal/hepatic vein branch invasion; (d) extrahepatic metastasis; and/or (e) a history of hepatic encephalopathy, refractory ascites, and variceal bleeding. Finally, patients who underwent repeated ablation (n = 98) or surgical resection (n = 28) for intrahepatic recurrent HCC treatments were included.

Diagnosis and Treatment Selection

The diagnosis of recurrent HCC was pathologically confirmed for patients receiving resection. For patients in the ablation group, the diagnosis of HCC was confirmed by biopsy during the ablation procedure or based on the criteria from the European Association for the Study of Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) HCC management guidelines [4, 14]. A multidisciplinary treatment team, consisting of surgeons, medical oncologists, and interventional radiologists, evaluated the tumors' condition, that is, tumor size and location, to judge its resectability, complete ablation ability, or both treatments based on the patients' preferences.

Local Ablation Procedure

The interventional radiologists who performed RFA and MWA procedures had >6 years of experience in interventional treatment. The ablation procedure was performed as previously reported [11]. Briefly, 375-kHz computer-assisted RF generator (Elektrotom HiTT 106; Berchtold Medizinelektronik, Tuttlingen, Germany) and 2,450-MHz microwave generator (ECO-100C; ECO Microwave Electronic Institute, Nanjing, China) were used for RFA and MWA, respectively. A 15- or 20-cm 14-gauge electrode was placed into the center of the tumor, and the generator delivered an 8–10 min of 60 W of RFA or 70 W of MWA energy for each application. To achieve complete ablation, 1–2 cycles for a single applicator position were adopted. For tumors with diameters >3.0 cm, we used a multiple overlapping ablation technique to achieve adequate ablation volume. A successful ablation was defined as a hyperechoic area around the electrode tip which covered an area larger than 1 cm^2 around the lesions after ablation, which was assessed by real-time ultrasound monitoring.

Surgical Resection

Surgery was performed by surgeons with 18–24 years of experience. The surgical plan was developed based on the tumor invasion extent and liver function, and the surgical resection was performed as previously detailed [11]. Briefly, the Pringle's maneuver was applied with 10 and 5 min cycles of clamping and unclamping and intraoperative ultrasound was routinely used to evaluate the tumor burden and resection margin status. The central venous pressure was lowered to 2–4 mm Hg during parenchyma dissection to control intraoperative bleeding.

Follow-Up

Posttreatment complications were graded according to the Clavien-Dindo classification. The results were independently reviewed by 2 authors, and any disagreement was settled by mutual discussion. The first follow-up visit was performed approximately 4 weeks after treatment to assess technique efficacy, and the pa-

Table 1. Demographic and clinical characteristics of the enrolled patients

Variable	Ablation (n = 98)	Resection (n = 28)	p value	Effect size
Age, years	54.00 (48.00, 64.00)	50.00 (36.50, 57.25)	0.025	0.539
Male, *n* (%)	86 (87.8)	26 (92.9)	0.677	0.173
Initial tumor number	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.131	0.273
Initial tumor size, cm	2.58 (1.80, 3.02)	2.54 (1.82, 2.87)	0.841	0.044
Tumor number	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	0.002	0.588
Tumor size, cm	1.80 (1.50, 2.48)	1.85 (1.50, 2.92)	0.486	0.277
Cirrhosis, *n* (%)	68 (69.40)	17 (60.7)	0.525	0.183
Portal hypertension, *n* (%)	32 (32.7)	4 (14.3)	0.062	0.444
AFP, ng/mL	18.82 (3.69, 108.38)	46.38 (5.76, 712.17)	0.201	0.241
Viral hepatitis, *n* (%)	91 (92.90)	27 (96.50)	0.897	0.192
HBV	87	26		
HCV	4	1		
PLT, $\times 10^9$	114.80 (76.75, 153.25)	156.00 (115.00, 187.22)	0.005	0.594
RBC, $\times 10^9$	4.50 (4.20, 4.94)	5.01 (4.78, 5.33)	<0.001	0.878
WBC, $\times 10^9$	4.83 (3.83, 5.70)	5.47 (4.47, 6.49)	0.036	0.384
ALB, g/L	41.85 (37.65, 44.58)	43.45 (41.58, 44.97)	0.029	0.604
ALT, U/L	31.30 (22.05, 49.10)	33.15 (23.48, 41.18)	0.937	0.019
AST, U/L	32.20 (25.33, 43.03)	25.45 (21.07, 33.97)	0.026	0.160
TBIL, μmol/L	15.55 (12.22, 20.48)	12.40 (9.35, 16.23)	0.020	0.555
PT, s	12.35 (11.50, 13.25)	11.50 (11.00, 12.25)	<0.001	0.838
Creatine, μmol/L	75.55 (66.88, 86.15)	76.45 (71.27, 82.58)	0.751	0.127

Continuous variables are reported as the median and interquartile range. Effect size was measured by calculating Cohen's *d* value. |value| < 0.2 indicated a negligible difference, |value| < 0.5 indicated a small difference, |value| < 0.8 indicated a moderate difference, and other values indicated a large difference. AFP, alpha fetoprotein; PLT, platelet; WBC, white blood cell; ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; TBIL, total bilirubin; HBV, hepatis B virus; HCV, hepatis C virus.

tients were followed up every 1–3 months in the first 2 years and every 3–6 months thereafter. Each follow-up consisted of a physical examination, liver function, and alpha fetoprotein (AFP) tests, and at least one imaging examination (CT/MRI). Local recurrence, which is defined as development of new tumor abutting in 1 cm of the previous ablation zone [15], was also evaluated according to radiological imaging. This study was censored on June 30, 2018.

PSM Analysis

To reduce the effect of selection bias and potential confounding, propensity scores for all patients were estimated [16]. Multivariable logistic regression models were applied to estimate the propensity scores, using the following baseline characteristics as covariates in the model: age, sex, tumor number, tumor size, cirrhosis, portal hypertension, AFP level, platelet (PLT) counts, RBC, white blood cell (WBC), serum albumin (ALB), creatine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), total bilirubin (TBIL) level, and hepatis B virus (HBV) or hepatis C virus (HCV) infection. A one-to-two nearest-neighbor matching algorithm with an optimal caliper of 0.2 without replacement was performed to generate 25 pairs of patients, and a one-to-one matching procedure was also performed to ensure the reliability of our results [17]. The PSM results were reported as effect size: |value| < 0.2 indicated a negligible difference, |value| < 0.5 indicated a small difference, |value| < 0.8 indicated a moderate difference, and any other value indicated a large difference [12, 18].

Statistical Analysis

The Mann-Whitney U test was employed to compare continuous variables in all cases. Binary variables were compared using the χ^2 test or two-tailed Fisher's exact test where appropriate, and ordinal categorical variables were compared using the Kruskal-Wallis test. Overall survival (OS) was defined as the time interval from liver resection to death from any cause or the last follow-up date. Disease-free survival (DFS) was defined as the time interval from liver resection to disease recurrence, death from disease, or the last follow-up date. OS and DFS were estimated from the date of treatment for recurrent HCC using the Kaplan-Meier method before and after matching; they were compared with the log-rank test before matching and the stratified log-rank test after matching. Factors with p values <0.1 in univariate analyses were introduced into the multivariate Cox proportional hazards model to determine the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were conducted with the R statistical package (R version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria) [19].

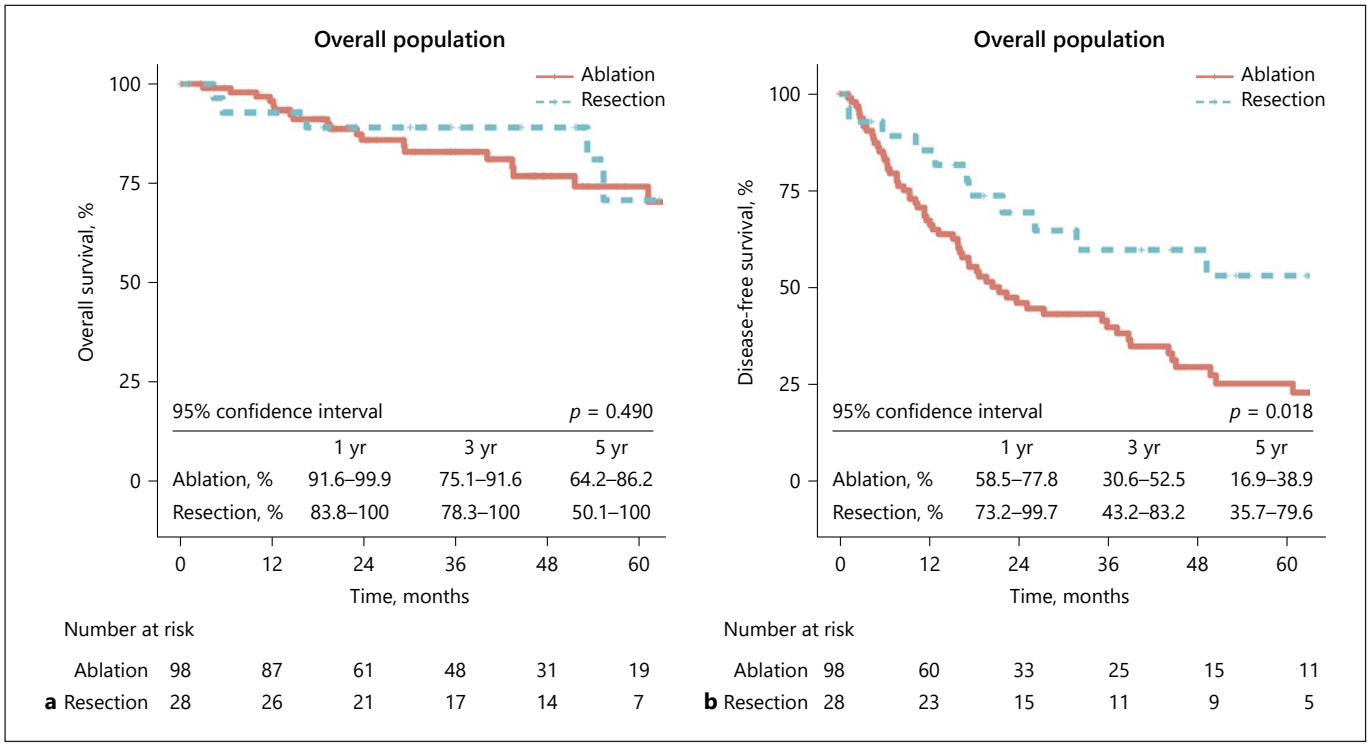

Fig. 1. OS and DFS curves (Kaplan-Meier method) with risk tables for patients with recurrent HCC conforming to the Milan criteria treated with ablation or resection. OS between the ablation and resection groups was not significantly different (**a**); however, DFS in the resection group was better than that in the ablation group (**b**). HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; CI, confidence interval.

Results

Patient Characteristics

A total of 126 patients with 158 tumors underwent curative-intent treatments, either ablation or resection, were included in the present study. During the follow-up period, 21 of 98 (21.4%) patients in the ablation group and 5 of 28 (17.9%) patients in the resection group had died ($p = 0.680$). Before PSM, the median follow-up duration was 35.7 months in the ablation group (range: 1–158 months) and 48.1 months in the resection group (range: 1–103 months), respectively.

The baseline characteristics of the entire investigated cohort are summarized in Table 1. Before PSM, the ablation group was associated with older age ($p = 0.025$), lower PLT level ($p = 0.005$), lower RBC level ($p < 0.001$), lower WBC level ($p = 0.036$), lower ALB level ($p = 0.029$), higher AST level ($p = 0.026$), higher TBIL level ($p = 0.020$), and longer PT ($p < 0.001$). We observed that there were more patients with multiple tumors in the resection group than those in the ablation group ($p = 0.002$).

Comparisons of Survival Result between the Two Groups before PSM

The 1-, 3-, and 5-year OS rates were 95.7, 83.0, and 74.4% in the ablation group and were 92.9, 89.1, and 70.9% in the resection groups, respectively; there was no significant difference between the 2 treatment groups ($p = 0.490$) (Fig. 1a). In regard to DFS, we observed that patients who underwent re-ablation had significantly greater chance of recurrence compared with those who underwent resection since the 1-, 3-, and 5-year DFS rates were 67.5, 40.1, and 25.6% in the ablation group and 85.4, 59.9, and 53.3% in the resection group, respectively ($p = 0.018$) (Fig. 1b).

Cox regression analysis showed that re-ablation was not associated with decreased OS (resection vs. ablation, hazard ratio [HR] = 0.84; 95% CI, 0.31–2.29, $p = 0.737$) in the entire study cohort before matching. In terms of OS, ALB <35 g/L was the only independent prognosis factor for OS (HR = 2.61; 95% CI, 1.01–6.81, $p = 0.048$). Regarding DFS, resection (resection vs. ablation, HR = 0.47; 95% CI, 0.24–0.91, $p = 0.025$) was identified as the only independent prognosis factor for DFS (Table 2).

Table 2. Prognostic factors for overall survival and DFS before PSM

Variable	Overall survival				DFS			
	univariate		multivariate		univariate		multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Procedure (resection/ablation)	0.71 (0.27, 1.89)	0.493	0.84 (0.31, 2.29)	0.737	0.47 (0.25, 0.89)	0.020	0.47 (0.24, 0.91)	0.025
Age >60 years	1.64 (0.74, 3.62)	0.220			1.31 (0.80, 2.13)	0.287		
Male	0.56 (0.19, 1.64)	0.291			0.91 (0.43, 1.90)	0.799		
Initial multiple tumors	0.47 (0.06, 3.44)	0.454			0.37 (0.12, 1.18)	0.093		
Initial tumor >3 cm	1.14 (0.50, 2.63)	0.755			1.41 (0.86, 2.31)	0.174		
Multiple tumors	0.824 (0.25, 2.75)	0.752	0.95 (0.27, 3.29)	0.930	1.14 (0.60, 2.19)	0.685	1.35 (0.68, 2.67)	0.388
Tumor >3 cm	1.47 (0.79, 2.70)	0.223	1.841 (0.70, 4.80)	0.212	1.31 (0.73, 2.35)	0.367	1.21 (0.67, 2.20)	0.523
Cirrhosis	1.48 (0.62, 3.52)	0.377			1.57 (0.93, 2.70)	0.092		
Portal hypertension	1.32 (0.61, 2.85)	0.481			1.12 (0.77, 1.94)	0.402		
AFP >200 ng/mL	1.25 (0.52, 2.98)	0.615			1.02 (0.59, 1.76)	0.957		
Viral hepatitis	1.04 (0.14, 7.73)	0.972			0.53 (0.21, 1.32)	0.173		
PLT $<100 \times 10^9$/L	1.36 (0.62, 3.02)	0.441			0.97 (0.58, 1.61)	0.918		
RBC $<4.3 \times 10^9$/L	1.36 (0.61, 3.06)	0.456			1.19 (0.72, 1.97)	0.496		
WBC $<4.0 \times 10^9$/L	1.41 (0.61, 3.24)	0.419			1.04 (0.60, 1.79)	0.893		
ALB <35 g/L	3.07 (1.29, 7.34)	0.012	2.62 (1.01, 6.81)	0.048	0.88 (0.40, 1.92)	0.742		
ALT <50 U/L	0.60 (0.26, 1.38)	0.228			0.58 (0.35, 0.96)	0.035	0.80 (0.42, 1.51)	0.484
AST <40 U/L	0.39 (0.18, 0.85)	0.018	0.49 (0.22, 1.01)	0.082	0.56 (0.35, 0.91)	0.019	0.68 (0.38, 1.24)	0.208
TBIL >17.1 μmol/L	1.93 (0.89, 4.20)	0.095			1.02 (0.63, 1.65)	0.926		
PT prolongation >3 s	0.48 (0.07, 3.57)	0.475			0.97 (0.39, 2.42)	0.948		
Creatine >97 μmol/L	1.19 (0.41, 3.47)	0.745			1.41 (0.74, 2.70)	0.291		

Treatment option, tumor number, tumor size, and variables with *p* value <0.05 in univariate analysis were retained for multivariate analysis. AFP, alpha fetoprotein; PLT, platelet; WBC, white blood cell; ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; TBIL, total bilirubin; HR, hazard ratio; CI, confidence interval; PSM, propensity score matching; DFS, disease-free survival.

Comparisons of Survival Result between the Two Groups after PSM

After PSM, no significant different covariates were found between ablation and resection groups (Table 3). We first performed PSM using a 1:2 ratio. After the matching, the estimated 1-, 3-, and 5-year OS rates were 95.2, 85.5, and 81.8% in the ablation group and 96.0, 96.0, and 76.4% in the resection group, respectively ($p = 0.550$) (Fig. 2a), while the 1-, 3-, and 5-year DFS rates were 58.0, 39.5, and 29.9% in the ablation group and 95.8, 67.2, and 59.8% in the resection group ($p = 0.004$) (Fig. 2b), respectively. However, no significant difference in overall survival was observed between the 2 treatment groups. Then, we performed a 1:1 matching analysis and found similar results. After PSM, the 1-, 3-, and 5-year OS rates in the ablation and resection group were 95.0, 71.1 and 71.1% versus 90.9, 90.9, and 66.3%, respectively ($p = 0.490$) (Fig. 3a). The 1-, 3-, and 5-year DFS rates were 43.3, 21.7, and 14.4% for the ablation group and 86.1, 58.0, and 48.3% for the resection group ($p = 0.003$) (Fig. 3b). These results were all similar to those before PSM.

For patients after the 1:2 matching, Cox regression analysis showed that resection or re-ablation treatment was not associated with OS (resection vs. ablation, HR = 0.40; 95% CI, 0.11–1.51, $p = 0.178$) in the entire study cohort after matching. In terms of DFS, resection (resection vs. ablation, HR = 0.39; 95% CI, 0.18–0.83, $p = 0.014$) was identified as the only independent factor, similar to before PSM (Table 4).

Complications between the Two Groups

In both treatment groups, 6 patients developed grade II complication which required blood transfusion (4/28, [14.3%] in the resection group and 2/98 [2.04%] in the ablation group [$p = 0.022$]). Besides, patients in the resection group exhibited higher rate of diarrhea than those in the ablation group (1/98 patients vs. 4/28 patients, respectively; $p = 0.009$). No significant difference was observed for other complications, such as pain, fever, ascites, vomiting, and hyperbilirubinemia between the 2 groups (Table 5). Also, no procedure-related mortality was observed between them.

Table 3. Comparison of demographic and clinical characteristics of patients after PSM

Variable	Ablation (n = 46)	Resection (n = 25)	p value	Effect size
Age ≥60 years (%)	17 (37.00)	4 (16.00)	0.115	0.489
Male, n (%)	40 (87.00)	23 (92.00)	0.803	0.165
Initial multiple, n (%)	4 (8.70)	1 (4.00)	0.463	0.191
Initial tumor >3 cm	13 (28.26)	5 (20.00)	0.448	0.191
Multiple number, n (%)	8 (17.40)	6 (24.00)	0.722	0.164
Tumor >3 cm	7 (15.20)	5 (20.00)	0.856	0.126
Cirrhosis	27 (58.70)	16 (64.00)	0.855	0.109
Portal hypertension	13 (28.30)	4 (16.00)	0.387	0.299
AFP ≥200 ng/mL	16 (34.80)	9 (36.00)	1.000	0.025
PLT ≥100 × 10^9/L	32 (69.60)	18 (72.00)	1.000	0.054
RBC ≥4.3 × 10^9/L	35 (76.10)	24 (96.00)	0.071	0.600
WBC ≥4.0 × 10^9/L	34 (73.90)	22 (88.00)	0.278	0.365
ALB ≥35 g/L	43 (93.50)	24 (96.00)	1.000	0.113
ALT ≥50 U/L	7 (15.20)	4 (16.00)	1.000	0.022
AST ≥40 U/L	5 (10.90)	4 (16.00)	0.805	0.151
TBIL ≥17.1 μmol/L	13 (28.30)	5 (20.00)	0.632	0.194
HBV	44 (95.70)	24 (96.00)	1.000	0.017
Creatine ≥97 μmol/L	5 (10.90)	2 (8.00)	1.000	0.098

Values in parentheses are percentages. Effect size was measured by calculating Cohen's d value. Threshold definition of the effect size: |value| < 0.2, "negligible"; |value| < 0.5, "small"; |value| < 0.8, "medium"; and other values "large." HR of treatment covariate (resection vs. ablation) adjusted for propensity score for overall survival was 0.51 (95% confidence interval, 0.11–2.29, p = 0.377) and for DFS was 0.26 (95% confidence interval, 0.11–0.61, p = 0.002). AFP, alpha fetoprotein; PLT, platelet; WBC, white blood cell; ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; HBV, hepatis B virus; DFS, disease-free survival; HR, hazard ratio; PSM, propensity score matching.

Subsequent Recurrence Treatment and Survival Results between the Two Groups

At the time of censoring, 59 patients in the ablation group and 11 patients in the resection group developed second HCC recurrence within 5 years after initial recurrence. The baseline characteristics of patients who developed second HCC recurrence are summarized in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000511157). No significantly different covariates were found between the ablation and resection groups. The treatments for second HCC recurrence in the ablation group included local ablation (26 patients), surgical resection (4 patients), TACE (24 patients), and other types of treatments (5 patients), while those in the resection group included local ablation (5 patients), surgical resection (1 patient), TACE (4 patients), and other types of treatments (1 patient) (online suppl. Table 2). The differences of DFS between the 2 groups could not be compared directly because almost half of the patients who developed second HCC recurrence received TACE as palliative treatment. Instead, their progression-free survival rates were evaluated. The 1-, 3-, and 5-year OS rates were 91.5, 81.4, and 79.7% for patients from the ablation group and were 81.8, 72.7, and 72.7% for those from the resection groups, but no significant difference was found between them (p = 0.990) (Fig. 4a). As for the PFS, we observed that patients from the ablation group had greater risk of third recurrence or progression compared with those from the resection group since the 1-, 3-, and 5-year PFS rates were 44.1, 23.7, and 20.3% in the ablation group and 81.8, 45.5, and 45.5% in the resection group, respectively (p = 0.044) (Fig. 4b).

Comparison of Local Recurrence Rates between the Two Groups

Compared to the patients in the re-ablation group, patients in the resection group had less chance of second recurrence in the same segment (p = 0.014) (online suppl. Table 3). Furthermore, local recurrence between the 2 cohorts was also compared. As shown in online suppl. Table 4, the local recurrence rates of initial recurrence were similar between the 2 treatment groups. For patients who had second recurrence, compared to re-ablation, resection could significantly reduce both the local recurrence rate per patient (p = 0.048) and the local recurrence rate per tumor (p = 0.018).

Further, for patients who received resection as salvage treatment, since the types of resection and resection margin may determine the survival, we also compared the types of resection and surgical margin among these patients. Overall, there were 9 patients who received anatomical hepatectomy and 19 patients who received non-anatomical hepatectomy; 16 patients had surgical margin ≥1 cm and 12 patients had surgical margin <1 cm. Further survival analysis showed that neither the types of resection nor surgical margin significantly affects the OS and DFS of those patients (online suppl. Fig. 1, 2).

Discussion

Due to the high cumulative 5-year recurrence rate of intrahepatic recurrent HCC after initial ablation, optimal treatment strategy for those patients is urgently warranted. However, because of limited data available regarding

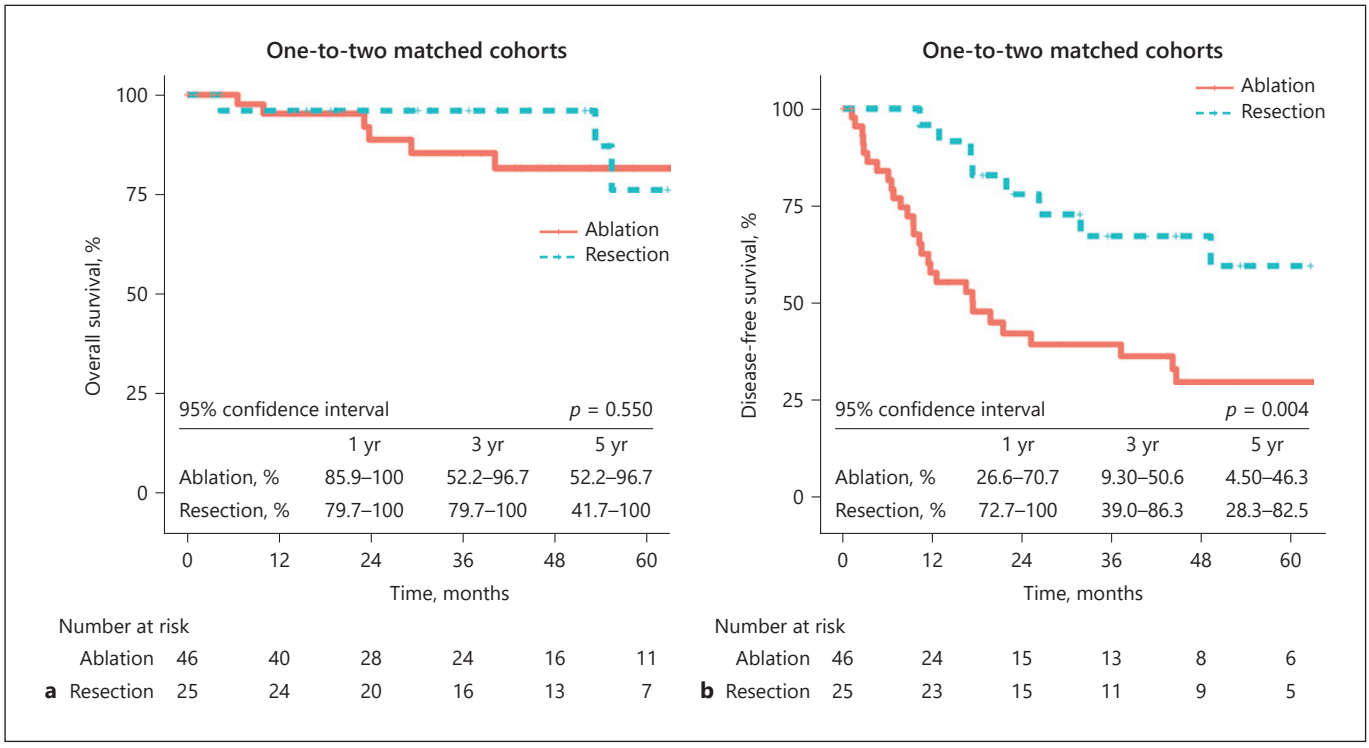

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Fig. 2. OS and DFS curves (Kaplan-Meier method) with risk tables for patients with recurrent HCC conforming to the Milan criteria treated with ablation or resection after 1:2 PSM. **a** OS between the ablation and resection groups was not significantly different after 1:2 PSM. However, DFS in the resection group was better than that in the ablation group after 1:2 PSM (**b**). HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; PSM, propensity score matching; CI, confidence interval.

the optimal therapeutic strategy for recurrent HCC receiving local ablation as initial treatment, the selection between providing re-ablation or resection as salvage therapy for recurrent HCC still remains highly debatable [13, 20–25]. Prospective randomized trials could provide reliable evidence; however, these are difficult to perform because treatment courses are determined considering various clinical factors, such as tumor size and location. Therefore, the results of our study, which were obtained after balancing patient demographics, liver function reserves, and tumor characteristics between the repeated ablation and resection groups, could provide supporting data to establish guidelines for the management of intrahepatic recurrent HCC after local ablation.

In this study, we retrospectively investigated a cohort of patients with recurrent HCC to classify the impact of treatment selection on clinical outcomes. Our results demonstrated that re-ablation had similar OS rates compared with resection. However, re-ablation was observed to have a higher risk of recurrence rate than resection using the Kaplan-Meier method. Further, we explored the prognosis factors for recurrent HCC after initial ablation and found that re-ablation was independently associated with the increased tumor recurrence rate. These results remained unchanged when they were compared after PSM. Moreover, we explored the OS and PFS of subsequent recurrent HCC, and the results we observed were similar to the initial recurrence.

In the present study, although no significant difference in long term survival outcome between the 2 treatment groups was observed, a tendency toward a longer OS in the resection group was observed. Considering potential selection bias due to the differences in each group's baseline characteristics, paired matching according to propensity score analysis was performed. Although significantly better recurrence-free survival was observed in the resection group, neither PSM using a 1:2 ratio nor 1:1 ratio showed significant difference in OS. This may be explained by the following reasons. First, the favorable 5-year OS rate in the ablation group could be attributed

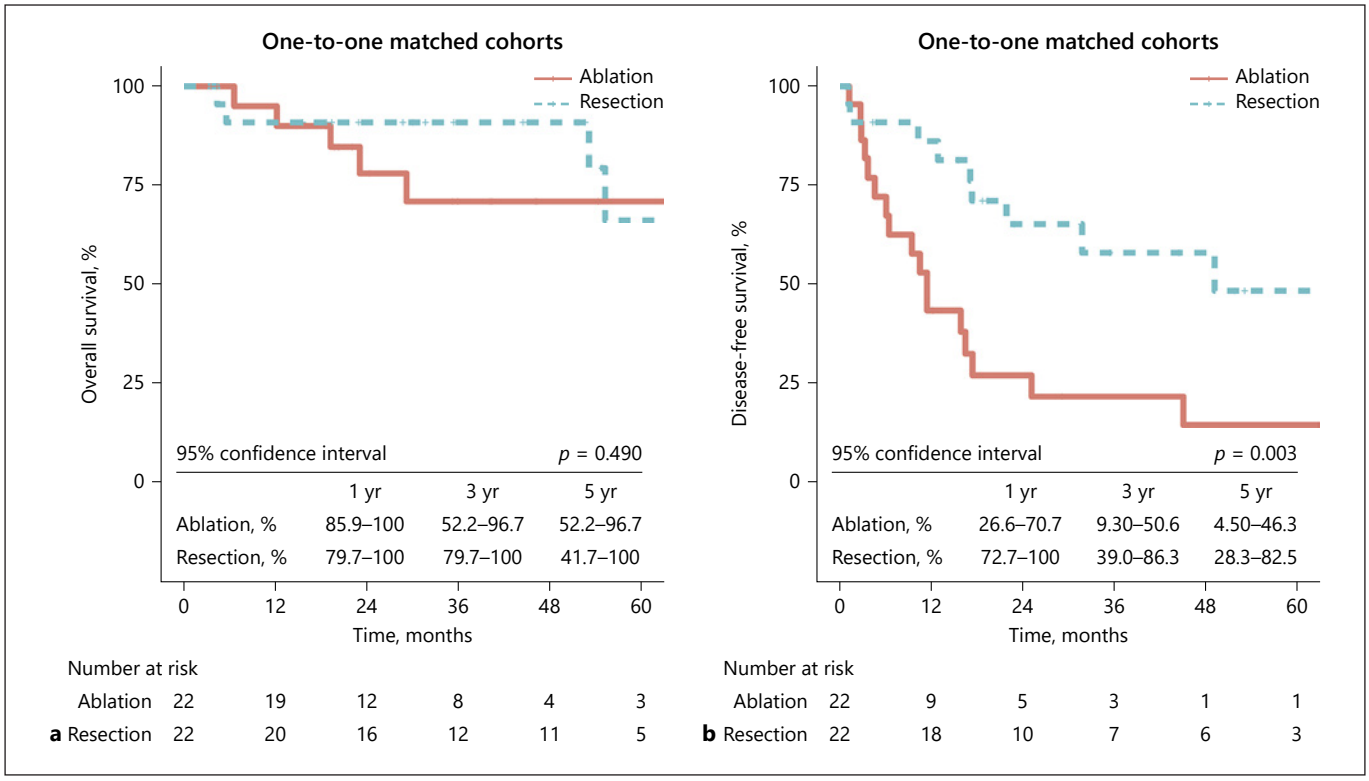

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Fig. 3. OS and DFS curves (Kaplan-Meier method) with risk tables for patients with recurrent HCC conforming to the Milan criteria treated with ablation or resection after 1:1 PSM. **a** OS between the ablation and resection groups was not significantly different after 1:1 PSM. However, DFS in the resection group was still better than that in the ablation group after 1:1 PSM (**b**). HCC, hepatocellular; OS, overall survival; DFS, disease-free survival; PSM propensity score matching; CI, confidence interval.

to the intensive surveillant approach to detect recurrent lesions, which could detect recurrent HCC in its early stage. Second, the effective salvage treatments provided for recurrent HCC in its early stage after local ablation could have significantly contributed in prolonging the patients' survival. For instance, a patient in the ablation group, who developed recurrence just 3 months after ablation for initial recurrence, received different treatments (TACE, ablation, etc.) for 9 times, which could have prolonged his life for 7 years after initial recurrence. Third, the tumor size in our study was relatively small. In general, as the tumor size decreases, the rate of complete tumor ablation increases and the possibility of the presence of satellite nodules decreases [26]. Fourth, sample size in the present study was relatively small.

Recently, the survival rates of patients receiving salvage hepatic resection or non-surgical second treatment for recurrent HCC after initial local ablation have been reported [20–24]. Sugo et al. [21] reported that the 1-, 3-, and 5-year OS and DFS rates of patients receiving salvage resection were 91.0, 91.0, and 67.0% and 65.0, 41.0, and 33.0%, respectively, which were comparable with our results. Morimoto et al. [20] documented that the 1-, 3-, and 5-year OS rates of patients receiving non-surgical second treatment were 93.0, 73.0, and 44.0%. When compared with OS rates of patients from the ablation group in our study, it seems that patients who received PEI or TACE as salvage treatments may have poorer prognosis.

Meanwhile, other researchers reported unsatisfactory outcomes after salvage resection when compared with patients from the resection group in our study, with a median 5-year overall survival ranging from 34.8 to 52% [22–24]. We speculated that these differences could be attributed to the unbalanced baseline characteristics between previous studies and our present study. Hu et al. [23] enrolled patients with multiple intrahepatic recurrences and extrahepatic metastases. Moreover, patients with primary tumor size >3 cm and tumor number >1

Table 4. Prognostic factors for overall survival and DFS after PSM

Variable	Overall survival				DFS			
	univariate		multivariate		univariate		multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Procedure (resection/ablation)	0.40 (0.11, 1.51)	0.178	0.42 (0.11, 1.57)	0.195	0.39 (0.18, 0.83)	0.014	0.39 (0.18, 0.83)	0.014
Age >60 years	1.50 (0.45, 5.01)	0.506			1.73 (0.87, 3.44)	0.116		
Male	1.25 (0.16, 9.68)	0.833			0.95 (0.33, 2.68)	0.918		
Initial multiple tumors	0.04 (0, 754)	0.531			1.13 (0.35, 3.70)	0.838		
Initial tumor >3 cm	1.68 (0.50, 5.58)	0.400			1.28 (0.61, 2.67)	0.515		
Multiple tumors	0.70 (0.15, 3.24)	0.652	0.76 (0.17, 3.53)	0.730	1.11 (0.52, 2.39)	0.788	1.26 (0.58, 2.74)	0.553
Tumor >3 cm	1.36 (0.37, 5.04)	0.645	1.22 (0.33, 4.55)	0.766	1.55 (0.72, 3.30)	0.261	1.40 (0.66, 2.99)	0.385
Cirrhosis	0.63 (0.20, 1.95)	0.419			1.48 (0.73, 3.00)	0.278		
Portal hypertension	0.49 (0.13, 1.81)	0.289			1.15 (0.60, 2.20)	0.679		
AFP >200 ng/mL	0.76 (0.20, 2.80)	0.674			0.70 (0.34, 1.46)	0.342		
Viral hepatitis	0.51 (0.07, 3.96)	0.517			0.47 (0.14, 1.54)	0.213		
PLT $<100 \times 10^9$/L	1.03 (0.28, 3.80)	0.969			0.80 (0.36, 1.75)	0.570		
RBC $<4.3 \times 10^9$/L	1.63 (0.44, 6.03)	0.464			0.78 (0.32, 1.91)	0.589		
WBC $<4.0 \times 10^9$/L	1.60 (0.43, 5.92)	0.483			0.79 (0.33, 1.91)	0.601		
ALB <35 g/L	2.63 (0.70, 9.83)	0.150			2.43 (1.17, 5.07)	0.017	1.34 (0.33, 5.41)	0.681
ALT <50 U/L	0.52 (0.07, 4.05)	0.534			1.07 (0.45, 2.58)	0.874		
AST <40 U/L	1.91 (0.57, 6.35)	0.294			1.10 (0.50, 2.41)	0.819		
TBIL >17.1 μmol/L	2.85 (0.92, 8.86)	0.070			0.75 (0.35, 1.59)	0.451		
PT prolongation >3 s	1.06 (0.13, 8.35)	0.959			0.27 (0.04, 1.98)	0.196		
Creatine >97 μmol/L	1.98 (0.43, 9.10)	0.378			1.73 (0.67, 4.46)	0.260		

Treatment option, tumor number, tumor size, and variables with *p* value <0.05 in univariate analysis were retained for multivariate analysis. AFP, alpha fetoprotein; PLT, platelet; WBC, white blood cell; ALB, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; TBIL, total bilirubin; CI, confidence interval; PSM, propensity score matching; DFS, disease-free survival.

Table 5. Complications after treatment

Variable	Before PSM			After PSM		
	ablation (*n* = 98)	resection (*n* = 28)	*p* value	ablation (*n* = 46)	resection (*n* = 25)	*p* value
Diarrhea	1	4	0.009	0	4	0.013
Blood transfusion	2	4	0.022	0	4	0.013
Pain	26	12	0.154	11	12	0.071
Fever	17	5	1.000	6	3	1.000
Ascites	0	1	0.222	0	1	0.352
Vomiting	9	2	1.000	6	1	0.409
Hyperbilirubinemia	11	3	1.000	5	3	1.000

Data represent the number of patients. PSM, propensity score matching.

were 28% (14/50) and 12% (6/50), respectively. Ueno et al. [24] enrolled patients with macroscopic vascular invasion, direct invasion to adjacent organs, and extrahepatic lesion. Furthermore, the tumor size and tumor number were larger than our study. In a study by Yamashita et al. [22], patients with portal invasion, venous invasion, bile duct invasion, and intrahepatic metastasis rates were 50, 15, 4, and 7%, respectively.

Although many previous studies reported that local ablation had comparable long-term outcomes compared with hepatectomy in early-stage HCC, the treatment strategies should not be the same due to the different fea-

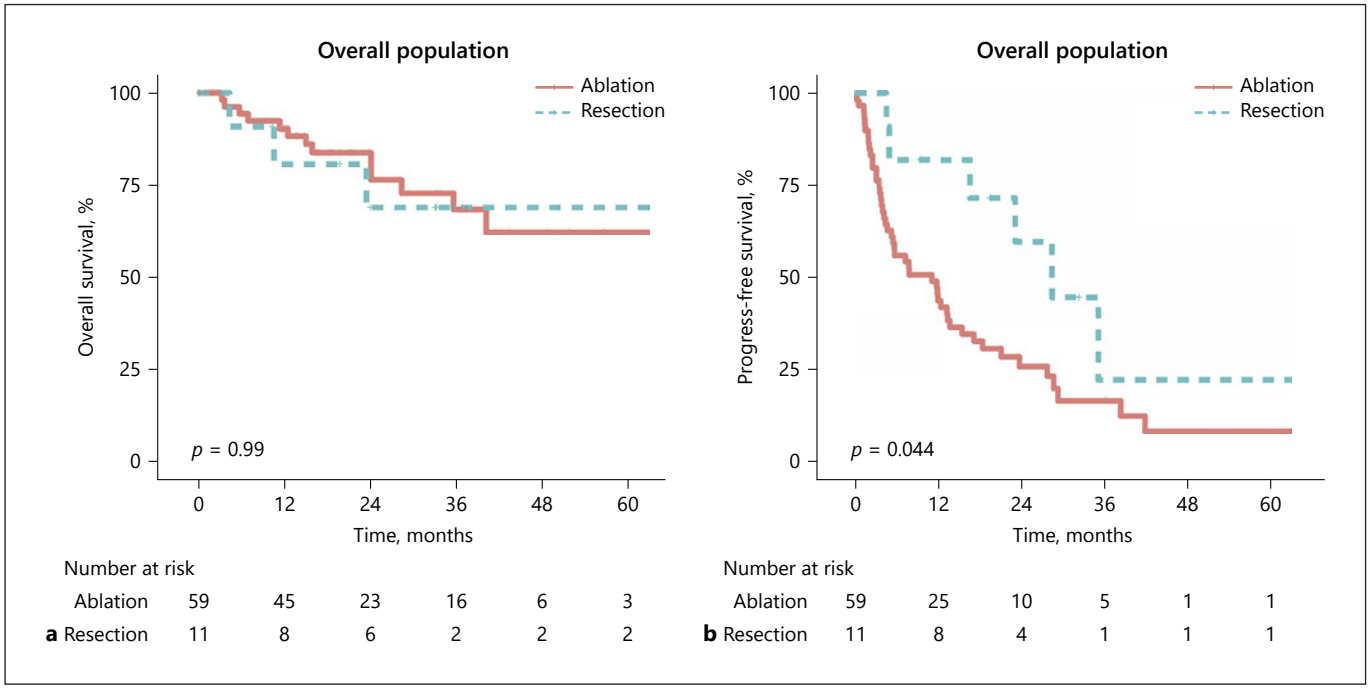

Fig. 4. OS and PFS curves (Kaplan-Meier method) with risk tables for patients with second HCC recurrence after initial recurrence treatments. **a** OS between the ablation and resection groups was not significantly different. However, PFS in the resection group was still better than that in the ablation group (**b**). HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival.

tures of primary and recurrent HCC [5, 8, 27–29]. Recurrent HCC is more aggressive than the primary HCC [30]. Undetectable satellite lesions and neoplastic emboli may be more frequent in recurrent HCC than in primary HCC. In contrast, surgical resection could remove not only the recurrent tumor, but also the potential satellite nodule and microvascular invasion [31, 32]. Our results demonstrated that patients after re-ablation had significantly greater chance to have local recurrence, while resection could reduce the risk of local recurrence. However, we also observed that the types of resection and surgical margin status seemed to have little influence on OS and DFS, which could have been because of the limited sample size.

No treatment-related death was observed during the study period. This may be partly explained by the long experience of the surgeons and the recent advances in both surgical and ablative techniques, which may have contributed in making both modalities less invasive, safer, and more effective. Our results indicated that both ablation and resection were safe for patients with recurrent HCC.

This study had several limitations. First, although we performed PSM analysis, selection bias might have not been completely avoided due to the retrospective nature of the present study. Second, this was a single-center study, and the decision in choosing ablation or resection as the salvage treatment was largely dependent on the expertise and experience of the treating oncologists. Third, the data were from Chinese patients in mainland China and the HCC were largely HBV related, so it may be difficult to generalize our results to those of other institutions where the main cause of HCC might not be hepatitis B viral infection; thus external validation from different areas is still warranted. Fourth, the sample size of the present study was relatively small. Hence, a prospective multi-center study with larger sample size could provide confirmatory evidence of the present study findings.

In conclusion, compared with surgical resection, local ablation therapy demonstrated similar long-term outcomes for recurrent HCC receiving local ablation as the primary treatment. However, local efficacy of surgical resection could be better than the local ablation. Thus, surgical resection may be recommended as first-line treatment to selected patients with well-preserved liver function.

Statement of Ethics

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Ethics Committee of Sun Yat-sen University Cancer Center approved this study. Written informed consent was also obtained from each patient.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Binkui Li and Yunfei Yuan designed the study; Yongjin Wang Yadi Liao and Wenwu Liu, Yuanping Zhang, Yichuan Yuan, Yuxiong Qiu, Jiliang Qiu, Zhiwen Yang, Wei He, Chenwei Wang, Kai Li, Yunxing Shi, and Dinglan Zuo collected the data; Yongjin Wang Yadi Liao and Wenwu Liu analyzed the data; all the authors interpreted the results; Yongjin Wang and Yadi Liao wrote the paper; Binkui Li and Yunfei Yuan gave critical comments and revised the manuscript; all the authors discussed the results and revised the manuscript. All the authors approved the final version of the manuscript.

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