

# The Negative Effect of Preoperative Transcatheter Arterial Chemoembolization on Long-Term Outcomes for Resectable Hepatocellular Carcinoma: A Propensity Score Matching Analysis

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## ABSTRACT

**Background** Preoperative transcatheter arterial chemoembolization (TACE) is administered to improve long-term outcome after surgical resection of hepatocellular carcinoma (HCC). However, the survival benefit of preoperative TACE is controversial. We conducted a retrospective case-control study to evaluate the effect of preoperative TACE on prognosis.

**Methods** A total of 121 patients who underwent curative resection of HCC were divided into two groups according to whether they received preoperative TACE. We determined the control group ( $n = 34$ ) and TACE group ( $n = 34$ ) through propensity score matching. The primary endpoint of this study was overall survival, and the secondary endpoints were recurrence-free survival.

**Results** The overall survival rate and the recurrence free survival rate were significantly lower in the TACE group than in the control group ( $P = 0.014$  and  $P = 0.043$ , respectively). Furthermore, recurrence free survival within less than 2 years after resection was significantly worse in the TACE group than in the control group ( $P = 0.035$ ).

**Conclusion** Preoperative TACE seemed to worsen the long-term outcomes of the patients who underwent surgical resection for the treatment of resectable HCC. Therefore, preoperative TACE should not be considered as a standard therapy in patients with resectable HCC.

**Key words** surgical resection; survival; hepatectomy; neoadjuvant

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide.<sup>1</sup> Hepatic resection is considered a curative treatment for HCC, and the current the Japan Society of Hepatology, European Association for Study of the Liver and the American Association for the Study of Liver Diseases guidelines recommend resection as one of the first-line treatments for early stage HCC.<sup>2, 3</sup> However, survival of HCC patients after hepatic resection remains unsatisfactory. Tumor recurrence

in the liver remnant complicates 70% of cases at 5 years after resection, reflecting either intrahepatic metastasis from the primary tumor or the development of de novo tumors.<sup>3–8</sup> As a result, the 5-year overall survival rate after curative resection is reported to be 40%–50%.<sup>9</sup> To counter this, several therapies have been administered prior to surgical resection, in an attempt to improve overall survival.<sup>10–12</sup> Because the efficacy of preoperative therapy before curative resection remains unclear, there is no preoperative therapy that is currently recommended.

Transcatheter arterial chemoembolization (TACE) has been used since the beginning of the 1980s as a neoadjuvant therapy to improve long-term survival by preventing cancer cell dissemination and intrahepatic recurrence.<sup>13–15</sup> Several reports, including four randomized controlled trials, failed to demonstrate an improvement in survival rate with the administration of preoperative TACE.<sup>13, 16–18</sup> Other studies, however, presented conflicting results.<sup>19–21</sup> Key reasons for the continuing debate are the considerable variation in background factors and radiological techniques involving HCC in previous studies and the various improvements in the TACE technique over the period of study. Because TACE has been shown to offer a survival advantage for patients with unresectable HCC,<sup>22, 23</sup> in theory, preoperative TACE is considered to have positive effects on postoperative clinical course. Thus, the aim of the present study was to evaluate the survival benefit of preoperative TACE in patients who underwent resection of HCC.

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Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; HCC, hepatocellular carcinoma; ICG-R15, rate of indocyanine green disappearance 15 min after injection; IRB, institutional review board; MRI, magnetic resonance imaging; TACE, transcatheter arterial chemoembolization

## MATERIALS AND METHODS

### Patients

We used a propensity-based matching case-control design in this study. A series of 189 consecutive patients who underwent a curative hepatic resection of primary hepatic cancer at our hospital between January 2004 and December 2012 were included in the current study. All patients were diagnosed based on contrast-enhanced computed tomography (CT) or Gd ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (MRI). Intrahepatic cholangiocarcinoma and combined HCC-cholangiocarcinoma tumors were excluded based on histological findings in the resected specimens. Patients with extrahepatic lesions, preoperatively diagnosed as vascular invasion, positive surgical margins or macroscopic residuals were also excluded. Patients who had undergone liver transplantation or surgical resection combined with ablation therapy were also excluded. On the basis of this exclusion criteria, 121 patients were eligible in this study. Then, patients were divided into two groups according to whether they underwent preoperative TACE or not (the TACE group and control group). Thirty-four patients who had highly vascularized HCCs so that were considered to have sensitivity for preoperative TACE by hepatologists assigned to the TACE group were administered preoperative TACE for two reasons: to improve long-term outcome (29 cases), to be completely cured (5 cases).

Written informed consent was obtained from all patients prior to TACE and surgery. Medical records were reviewed retrospectively after approval by the Institutional Review Board (IRB) of our institution in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (IRB approval number: 1606A029).

### Variables

Data including patient characteristics [age, sex, body mass index (BMI), past medical history, presence or absence of prior local treatment for HCC, cause of hepatitis, Child–Pugh score, serum creatinine, albumin, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), cholinesterase, platelet count, prothrombin time, rate of indocyanine green disappearance 15 min after injection (ICG-R15)], tumor characteristics [number of tumors, maximum diameter of tumor, alpha-fetoprotein (AFP) level], intra-operative data (extent of resection, surgical procedure, duration of surgery, intraoperative hemorrhage volume, length of hospital stay after surgical resection, postoperative complications), tumor pathological findings (histotype and stage of fibrosis of nontumor-bearing liver according to the new Inuyama

classification of chronic hepatitis), tumor recurrence and patient survival were collected from our database. Tumor recurrence was diagnosed based on the findings of either CT or MRI.

Propensity score matching was performed using R version 3.1.3 software; the grouping variable was preoperative TACE and the matching variables were age, presence or absence of prior treatment, cause of hepatitis, Child–Pugh score, comorbidity (cardio-vascular disease and diabetes mellitus), serum albumin, bilirubin, AFP level, platelet count, prothrombin time, ICG-R15, number of tumors, tumor size, and stage of fibrosis of nontumor-bearing liver. The stage of fibrosis was the only histological finding included in this list of variables because this stage was rarely affected by preoperative TACE,<sup>24</sup> and played an important role in the development of de novo tumors in the remnant liver.<sup>25</sup> Because histological findings concerning the primary tumor in the TACE group were believed to be affected by preoperative TACE, histological findings were not included in the list of variables to be matched.

### Statistical analysis

We used R version 3.1.3 software for comparative statistical analysis. All continuous values are presented as the mean  $\pm$  standard deviation and the median with inter quartile range. Statistical analysis was conducted using the chi-square test for categorical variables and Welch's two-sample *t* test for continuous variables, with the exception of categorical variables containing factors less than 5, which were analyzed using Fisher's exact test. Overall survival and recurrence free survival rates were calculated according to the Kaplan–Meier method and compared using the Gehan-Breslow-Wilcoxon test. All *P* values  $< 0.05$  were considered significant. The primary endpoint of this study was overall survival, and the secondary endpoints were recurrence-free survival and postoperative complications.

## RESULTS

### Patient characteristics

Table 1 shows the characteristics of the 121 eligible patients before matching. Propensity score matching was carried out using 16 selected patient characteristics, tumor-related factors and surgical factors. Thirty-four patients were selected as the control group and included for further analysis. Tables 2 and 3 detail the clinicopathological characteristics and perioperative clinical outcomes, respectively, of the patients included in the current study. There were no significant differences in patient characteristics and perioperative outcomes between the control and TACE groups. To determine

**Table 1. Patient background before propensity score matching**

	Control group (87)		TACE (34)		<i>P</i>
	Mean, SD	Median [IQR]	Mean, SD	Median [IQR]	
Age (y)	67, <i>s</i> = 10.8	69 [62–74]	71.0, <i>s</i> = 8.5	72.5 [66.8–77.0]	0.036
Prior treatment (%)	17 (20)		8 (24)		0.812
Gender (male; %)	73 (84)		30 (88)		0.777
BMI (kg/m <sup>2</sup> )	22.9, <i>s</i> = 3.0	22.8 [21.1–24.5]	23.1, <i>s</i> = 2.8	24.2 [20.6–25.4]	0.737
Cause of hepatitis (%)	NBNC	15 (17)	4 (11)		0.098
	HBV	39 (45)	10 (29)		
	HCV	24 (28)	14 (41)		
	Alcohol	9 (10)	5 (15)		
	Other	1 (1)	3 (9)		
Child-Pugh score (%)	5	70 (80)	26 (76)		0.538
	6	13 (15)	8 (24)		
	7	2 (2)	0		
	8	2 (2)	0		
Comorbidity (%)	Cardio-vascular disease	9 (10)	5 (15)		0.534
	Diabetes	27 (31)	11 (32)		1.000
Creatinine (mg/dL)	17.6, <i>s</i> = 9.1	0.75 [0.66–0.88]	0.78, <i>s</i> = 0.13	0.8 [0.70–0.87]	0.321
Albumin (g/dL)	3.9, <i>s</i> = 0.5	4 [3.6–4.3]	3.9, <i>s</i> = 0.42	3.9 [3.7–4.2]	0.504
Bilirubin (mg/dL)	0.73, <i>s</i> = 0.27	0.7 [0.5–0.9]	0.68, <i>s</i> = 0.22	0.7 [0.5–0.8]	0.292
AST (IU/L)	38.5, <i>s</i> = 21.9	31 [23.5–48]	37.8, <i>s</i> = 21.9	33 [26.8–39.0]	0.881
ALT (IU/L)	41.2, <i>s</i> = 46.2	26 [19–46]	36.3, <i>s</i> = 24.7	30 [23.3–39.8]	0.451
Cholinesterase (IU/L)	195.1, <i>s</i> = 74.3	196.5 [135.2–241.5]	205.6, <i>s</i> = 80.0	191.5 [152.8–249.5]	0.510
AFP (ng/mL)	7645.4, <i>s</i> = 39707	9.8 [3.7–80.5]	1251.4, <i>s</i> = 4445.4	10.1 [4.3–110]	0.144
Platelet (/10 <sup>3</sup> μL)	167, <i>s</i> = 63.2	161 [119.5–200.5]	179.5, <i>s</i> = 80.7	172.5 [120.5–213]	0.420
Prothrombin time (%)	86.3, <i>s</i> = 18.0	87.7 [78.1–96.6]	88.8, <i>s</i> = 9.8	90 [81–97.6]	0.340
ICG-R15 (%)	13.5, <i>s</i> = 6.9	13 [9–16]	17.8, <i>s</i> = 13.9	15 [13–20]	0.101
Extent of hepatic resection (%)	Non-anatomic	38 (44)	17 (50)		0.851
	Segmentectomy	14 (16)	4 (12)		
	Sectorectomy	20 (23)	7 (21)		
	Lobe hepat-ectomy	14 (16)	8 (24)		
	Hemi-hepat-ectomy	11 (13)	3 (9)		
Number of tumor (%)	1	69 (79)	25 (74)		0.758
	2	14 (16)	8 (24)		
	3	2 (2)	1 (3)		
	≥ 4	2 (2)	0		
Maximum diameter (mm)	48.7, <i>s</i> = 41.5	30.5 [22–57.3]	40.8, <i>s</i> = 30.0	30 [21.3–48.8]	0.333
Histotype (%)	Well	5 (6)	3 (9)		0.106
	Moderate	77 (89)	26 (76)		
	Poor	3 (3)	4 (12)		
	NA	2 (2)	1 (3)		
Fibrosis stage* (%)	0	19 (22)	1 (3)		0.047
	1	23 (26)	7 (21)		
	2	10 (11)	8 (24)		
	3	8 (9)	5 (15)		
	4	24 (28)	8 (24)		

\*New Inuyama classification of chronic hepatitis. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ICG-R15, 15-minute retention rates of indocyanine green; IQR, interquartile range; NA, not available; NBNC, non-HBV non-HCV hepatitis; TACE, transcatheter arterial chemoembolization; y, year(s).

**Table 2. Patient background after propensity score matching**

		Control group (34)		TACE group (34)		P
		Mean, SD	Median [IQR]	Mean, SD	Median [IQR]	
Age (y)		71.8, <i>s</i> = 6.7	72.5 [68–75]	71.0, <i>s</i> = 8.5	72.5 [66.8–77.0]	0.647
Prior treatment (%)		11 (32)		8 (24)		0.588
Gender (male; %)		25 (74)		30 (88)		0.217
BMI (kg/m <sup>2</sup> )		23.6, <i>s</i> = 2.4	23.8 [22.2–25.2]	23.1, <i>s</i> = 2.8	24.2 [20.6–25.4]	0.457
Cause of hepatitis (%)	NBNC	8 (24)		4 (11)		0.171
	HBV	15 (38)		10 (29)		
	HCV	10 (29)		14 (41)		
	Alcohol	1 (3)		5 (15)		
	Other	1 (3)		3 (9)		
Child-Pugh score (%)	5	27 (79)		26 (76)		0.765
	6	6 (18)		8 (24)		
	8	1 (3)		0		
Comorbidity (%)	Cardio-vascular disease	5 (15)		5 (15)		1.000
	Diabetes	9 (26)		11 (32)		0.796
Creatinine (mg/dL)		0.80, <i>s</i> = 0.23	0.76 [0.68–0.92]	0.78, <i>s</i> = 0.13	0.8 [0.70–0.87]	0.626
Albumin (g/dL)		3.9, <i>s</i> = 0.4	4.0 [3.7–4.2]	3.9, <i>s</i> = 0.42	3.9 [3.7–4.2]	0.815
Bilirubin (mg/dL)		0.70, <i>s</i> = 0.28	0.60 [0.53–0.88]	0.68, <i>s</i> = 0.22	0.7 [0.5–0.8]	0.663
AST (IU/L)		40.1, <i>s</i> = 25.2	32 [26–48.3]	37.8, <i>s</i> = 21.9	33 [26.8–39.0]	0.602
ALT (IU/L)		34.4, <i>s</i> = 26.0	24 [20–40.1]	36.3, <i>s</i> = 24.7	30 [23.3–39.8]	0.753
Cholinesterase (IU/L)		205.1, <i>s</i> = 68.5	203.5 [146–250.5]	205.6, <i>s</i> = 80.0	191.5 [152.8–249.5]	0.979
AFP (ng/mL)		3342, <i>s</i> = 19120	5.8 [2.9–21.5]	1251.4, <i>s</i> = 4445.4	10.1 [4.3–110]	0.540
Platelet (/10 <sup>3</sup> μL)		181.1, <i>s</i> = 51.8	180.5 [143–217.8]	179.5, <i>s</i> = 80.7	172.5 [120.5–213]	0.923
Prothrombin time (%)		91.5, <i>s</i> = 14.6	91.4 [80.6–102]	88.8, <i>s</i> = 9.8	90 [81–97.6]	0.396
ICG-R15 (%)		16.4, <i>s</i> = 6.6	14 [12–19.5]	17.8, <i>s</i> = 13.9	15 [13–20]	0.596
Extent of hepatic resection (%)	Non-anatomic	15 (44)		17 (50)		0.724
	Segmentectomy	7 (21)		4 (12)		
	Sectorectomy	6 (18)		7 (21)		
	Lobe hepat-ectomy	5 (15)		8 (24)		
	Hemi-hepat-ectomy	5 (15)		3 (9)		
Number of tumor (%)	1	26 (76)		25 (74)		0.803
	2	6 (18)		8 (24)		
	3	2 (6)		1 (3)		
Maximum diameter (mm)		42.3, <i>s</i> = 35.7	27 [22–50]	40.8, <i>s</i> = 30.0	30 [21.3–48.8]	0.851
Histotype (%)	Well	1 (3)		3 (9)		0.138
	Moderate	32 (94)		26 (76)		
	Poor	0		4 (12)		
	NA	1 (3)		1 (3)		
Necrosis rate (%)	≥ 90%			12 (35)		
	89–50%			4 (12)		
	< 50%			18 (53)		
Fibrosis stage* (%)	0	4 (12)		1 (3)		0.515
	1	8 (24)		7 (21)		
	2	5 (15)		8 (24)		
	3	3 (9)		5 (15)		
	4	11 (32)		8 (24)		

\*New Inuyama classification of chronic hepatitis. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ICG-R15, 15-minute retention rates of indocyanine green; IQR, interquartile range; NA, not available; NBNC, non-HBV non-HCV hepatitis; TACE, transcatheter arterial chemoembolization; y, year(s).

**Table 3. Outcomes of clinical course**

	Control group (34)		TACE group (34)		<i>P</i>
	Mean, SD	Median [IQR]	Mean, SD	Median [IQR]	
Time from diagnosis to surgical resection (d)	66.2, <i>s</i> = 7.3	61.2 [33.8–75.5]	83.9, <i>s</i> = 35.0	87.5 [62.5–94.5]	0.134
Intraoperative hemorrhage volume (mL)	946.7, <i>s</i> = 1135.5	502.5 [197.5–976.2]	935.9, <i>s</i> = 1340.4	392.5 [258.8–995]	0.975
Operative duration (min)	437, <i>s</i> = 134.8	435 [324–515]	391, <i>s</i> = 150.9	378 [316–457]	0.197
Postoperative complication*	Any grade	16	13		0.624
	Grade ≥ 3	5	8		0.537
Hospital stay (d)	24.2, <i>s</i> = 19.7	19.5 [16–22]	20.5, <i>s</i> = 11.3	18 [14.3–22.3]	0.350

\*According to Clavien-Dindo classification. d, day(s); IQR, interquartile range; TACE, transcatheter arterial chemoembolization.

**Table 4. Detail of methodology for preoperative TACE**

		Prior term (17)	Latter term (17)	<i>P</i>
Selectivity of hepatic artery (%)	Lobe	2 (12)	3 (18)	0.617
	Segment	4 (24)	5 (29)	
	Subsegment or more	10 (59)	9 (53)	
	Other (1 <sup>st</sup> -branch of right inferior phrenic artery)	1 (6)	0	
Chemotherapeutic agent (%)	Epirubicin	2 (12)	3 (18)	0.153
	Epirubicin plus mitomycin C	5 (29)	10 (64)	
	Cisplatin	6 (35)	2 (6)	
	Miliplatin	0	1 (6)	
	NA	4	1	
Embolic agent (%)	Gelatin sponge	12 (71)	14 (82)	NA
	NA	5	3	

NA, not available; TACE, transcatheter arterial chemoembolization.

methodological homogeneity of preoperative TACE, survey period was divided into two terms. Details of preoperative TACE were shown separately depends on periods of study in table 4. We also confirmed no significant difference of surgical outcomes between first- and second- half period of this study.

#### Overall and recurrence free survival

Among the 68 patients evaluated by propensity score matching, tumor recurrence occurred in 37 (54.4%) and death from all causes occurred in 26 (38.2%). Figure 1 shows the overall survival rates in the two groups. The 1-, 3-, and 5-year overall survival rates were 97.0%, 93.9%, and 80.5%, respectively, in the control group and 87.5%, 62.3%, and 62.3%, respectively, in the TACE group; the difference was statistically significant ( $P = 0.014$ ). The 1-, 3-, and 5-year recurrence-free survival rates were 90.8%, 62.6%, and 49.4%, respectively, in the control group and 68.7%, 44.9%, and 44.9%, respectively, in the TACE group (Fig. 2;  $P = 0.043$ ). Furthermore,

recurrence free survival within less than 2 years was significantly worse in the TACE group than in the control group (Fig. 3;  $P = 0.035$ ). With regard to type of surgical procedures, there were no significant difference between anatomical or non-anatomical resection among each groups (Fig. 4).

#### DISCUSSION

Preoperative TACE has been used in the following ways: as neoadjuvant chemotherapy for resectable HCCs,<sup>13</sup> as a conversion therapy for unresectable HCC through down-staging,<sup>21</sup> to prepare for portal venous embolization to reduce the risk of rapid growth of HCC,<sup>26</sup> and with curative intent prior to salvaging surgical resection. In the current study, we evaluated the efficacy of TACE as a neoadjuvant therapy by comparing the prognosis of patients who underwent preoperative TACE and those who did not. The overall 5-year survival rate and the recurrence-free survival rate were significantly lower in the TACE group than in the control group. These findings clearly indicate that preoperative TACE negatively

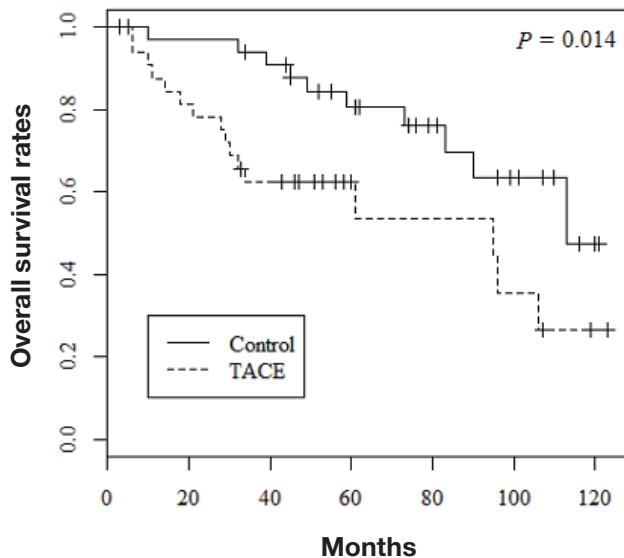
affects the prognosis of patients with potentially resectable HCC. Similar findings have been reported in previous studies.<sup>18, 20, 27–31</sup>

Several disadvantages of preoperative TACE have been postulated. First, it is likely that treatment with TACE delays surgical resection and that preoperative TACE renders surgical resection more difficult and delays the operation time, resulting in intraoperative tumor feeding through collateral vessels.<sup>20, 27</sup> Another possibility is that TACE mainly affects well-differentiated cells,

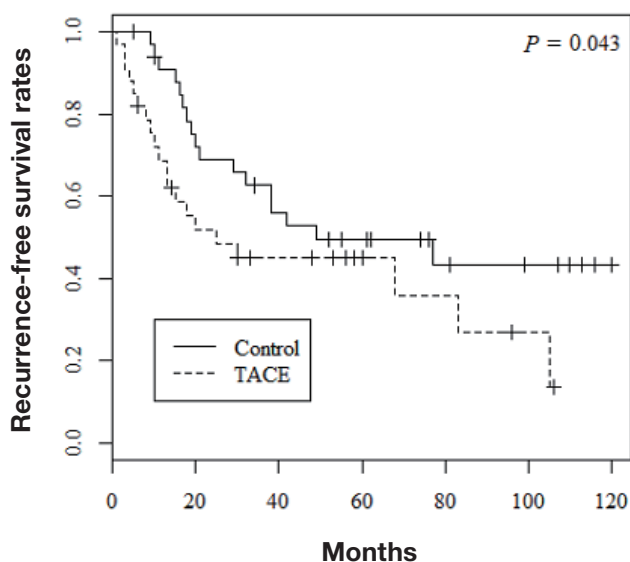
without completely killing poorly differentiated cells that are related to poor prognosis.<sup>28</sup> In the present study, however, such factors were unlikely to have influenced the poor prognosis observed in the TACE group because we performed statistical matching to reduce heterogeneity in patient profiles.

As previously mentioned, there are two types of intrahepatic recurrence after resection, namely metastasis of the primary tumor and secondary de novo tumor formation. Recurrence rates also peak twice after resection—recurrence in the early phase (< 2 years) is mainly the result of metastases, whereas recurrence in the late phase (≥ 2 years) is attributable to new lesions.<sup>2, 32</sup> Several studies have demonstrated a higher recurrence rate and lower overall survival in patients who underwent preoperative TACE.<sup>18, 29–31</sup> In the present study, recurrence free survival within less than 2 years was significantly worse in the TACE group than in the control group, indicating the possibility that intrahepatic metastasis occurred more frequently in the TACE group than in the control group. Therefore, it is possible that increased early recurrence is related to the poor overall survival observed in the TACE group in the current study.

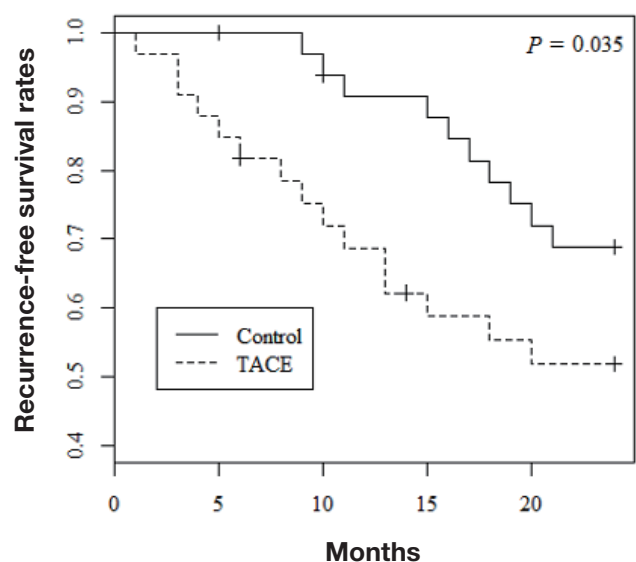
Recent studies have revealed that preoperative TACE may enhance the expression of vascular endothelial growth factor protein, which encourages angiogenesis and results in metastasis.<sup>33</sup> TACE may also increase the expression of a hypoxia-inducible factor that is related to hepatic damage, resulting in carcinogenesis.<sup>34–36</sup> These molecular alterations might also be responsible for the low overall survival and high early-phase recur-



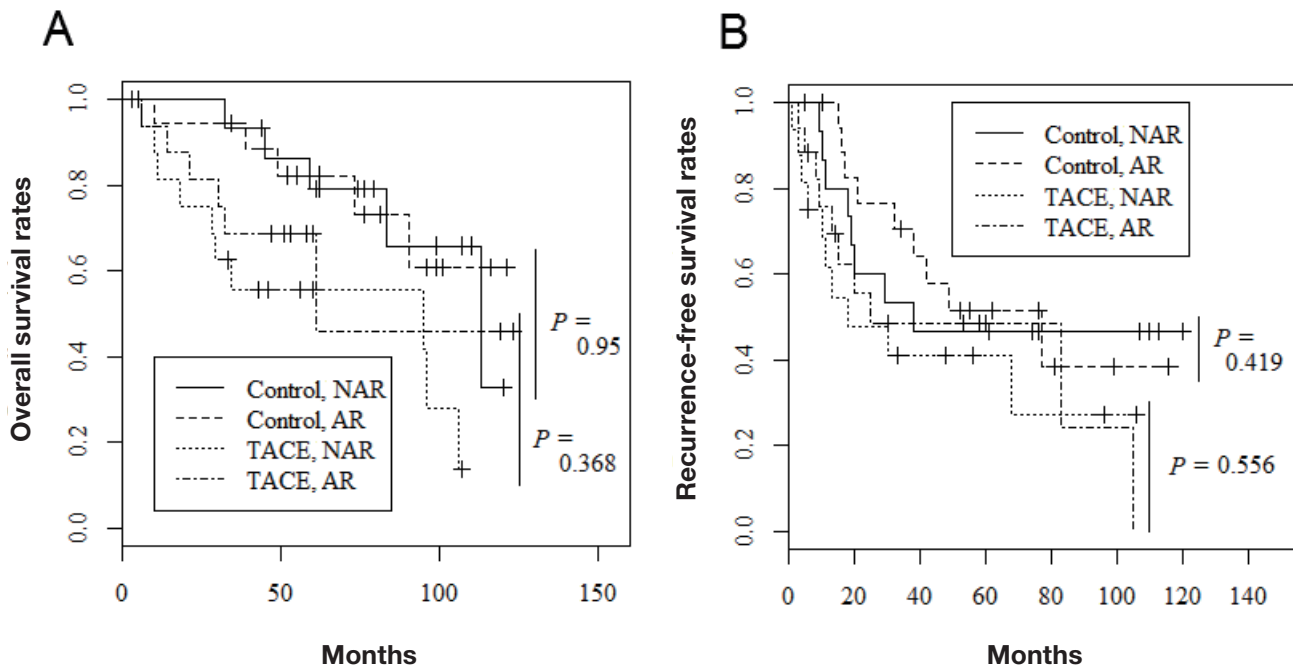
**Fig. 1.** Overall survival rates of the TACE and control groups. TACE, transcatheter arterial chemoembolization.



**Fig. 2.** Recurrence-free survival rates of the TACE and control groups. TACE, transcatheter arterial chemoembolization.



**Fig. 3.** Recurrence-free survival rates within less than 2 years after resection. TACE, transcatheter arterial chemoembolization.



**Fig. 4.** Long-term outcomes in both TACE and control group according to operative procedure. **A:** Overall survival rates. **B:** Recurrence-free survival rates. AR, anatomical resection; NAR, non-anatomical resection; TACE, transcatheter arterial chemoembolization.

rence rate observed in the TACE group in the current study.

This study had several limitations. First, histopathological analysis could not be conducted prior to the interventions; therefore, the two groups could not be matched for histopathological characteristics, which may have been a confounding factor. Second, the study was retrospective in design, meaning that there were missing values for several variables. Finally, the sample size may have limited the statistical robustness of the results to some extent. However, consistent results were obtained in previous studies that support our current findings. With regard to survival rates in previous reports, 5-year overall and recurrence-free survival rates in patients with preoperative TACE were similar to our results.<sup>29</sup> Moreover, Roayaie et al reported outcomes of treatments other than resection among patients who were candidate for resection.<sup>37</sup> Comparing our result to their results, resection with preoperative TACE may be superior to radiofrequency ablation or TACE but inferior to resection, so that our result seem plausible.

In conclusion, our results indicated that preoperative TACE seems to adversely affect the long-term outcomes of patients who underwent surgical resection to treat resectable HCC. Ischemic stimulation of resectable HCC induced by preoperative TACE might worsen the post-operative clinical course, especially in the early phase. Therefore, preoperative TACE should not be considered

as a standard therapy for patients with potentially resectable HCC.

*The authors declare no conflict of interest.*

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