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Transcatheter Arterial Chemoembolization for Treatment-Naive Hepatocellular Carcinoma Has Different Treatment Effects Depending on Central or Peripheral Tumor Location

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Keywords
Hepatocellular carcinoma · Transcatheter arterial chemoembolization · Systemic chemotherapy · Treatment response · Predictive factor

Abstract

Introduction: The purpose of this study was to evaluate the treatment efficacy of transcatheter arterial chemoembolization (TACE) for treatment-naive hepatocellular carcinoma (HCC) according to tumor location and burden. ***Methods:*** Between 2010 and 2019, consecutive patients who underwent TACE as the first treatment were enrolled. Tumors were classified into two categories based on their location, as central or peripheral tumors. Tumors in the central zone, which is within 1 cm of the main trunk or the first branch of the portal vein, were classified as central tumors, while those located in the peripheral zone were classified as peripheral tumors. Patients were grouped according to the HCC location and up-to-7 criteria. Patients with central tumors were classified into the central arm and those with only peripheral tumors were classified into the peripheral arm. Patients within and beyond the up-to-7 criteria were classified into the up-to-7 in and up-to-7 out-groups, respectively. Local recurrence-free survival (LRFS) and progression-free survival (PFS) were compared per nodule (central tumor vs. peripheral tumor) and per patient (central arm vs. peripheral arm), respectively. The prognostic factors of LRFS and PFS were analyzed by univariate and multivariate analyses. ***Results:*** A total of 174 treatment-naive patients with 352 HCCs were retrospectively enrolled. Ninety-six patients and 130 lesions were selected by propensity score matching. Median LRFS was longer for peripheral tumors than central tumors (not reached vs. 3.3 months, $p < 0.001$). Median PFS was 17.1 months (8.3–24.9) in the peripheral arm and up-to-7 in, 7.0 months (3.3–12.7) in the peripheral arm and up-to-7 out, 8.4 months (4.0–12.6) in the central arm and up-to-7 in, and 3.0 months (1.2–4.9) in the central arm and up-to-7 out-groups. The peripheral arm and up-to-7 in-groups had significantly longer PFS than the other three groups ($p = 0.013$, $p = 0.015$, $p < 0.001$, respectively). Multivariate analysis confirmed that the central zone and central arm

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were associated with high adjusted hazard ratios for tumor recurrence or death (2.87, $p < 0.001$; 2.89, $p < 0.001$, respectively). ***Conclusion:*** Treatment-naive HCCs in the peripheral zone had a longer LRFS and PFS following TACE compared to those in the central zone.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, the sixth most common cancer worldwide and the third leading cause of cancer-related death [1–3]. Treatment of HCC ranges from surgical resection to local ablation, transplantation, transcatheter arterial chemoembolization (TACE), and systemic treatments, such as molecular targeted agents (MTAs) that exhibit antitumor effects by blocking tumor angiogenesis, and immune checkpoint inhibitors, which exhibit an antitumor immune response [3–6].

Treatment of HCC is determined by the stage of HCC. Although the treatment of early stage HCC is generally surgery or local ablation, as recommended by the guidelines, these treatments are sometimes limited by several factors such as tumor location, comorbidities, liver function, age, and the patient's wish [3–5, 7]. For these patients, superselective conventional TACE is a potential treatment option [7, 8]. Conventional TACE is defined as a treatment that involves injection of a mixture of ethiodized oil and an anticancer drug, followed by embolization of the tumor-feeding artery with gelatin sponge particles. This method leads to the inflow of ethiodized oil not only into the supplying artery but also into both hepatic arterial branches and portal veins surrounding the tumors, through the vascular network of tumors, resulting in tumor necrosis [8, 9]. TACE and systemic therapies are generally recommended for patients with intermediate-stage and advanced-stage HCC, respectively [3–5, 10]. However, intermediate-stage HCC includes patients with a very wide range of tumor burden and liver function [3, 4]. There are several subclassifications of intermediate-stage HCC that are mainly based on Child-Pugh score and up-to-7 criteria (which indicates that the sum of the number and largest diameter (cm) of the tumors is within seven) [11–16]. Recently, the combination of systemic therapies and TACE has been introduced for patients with intermediate-stage HCC [10, 17–19]. However, some reports showed that the combination of MTAs and TACE is not effective [20–24]. Hence, the treatment strategy for patients with intermediate-stage HCC is still controversial. In order to choose an effective treatment strategy, it is necessary to identify the subset of patients that is likely to have good treatment outcomes after TACE.

Previously, several classifications of HCC were proposed to identify patient populations that would benefit from TACE [11–14]. In these studies, patients were mainly classified according to tumor burden and liver function, and reportedly, TACE was likely to be beneficial in patients with a lower tumor burden and better liver profile [11–14]. However, to the best of our knowledge, no studies have evaluated the long-term local and systemic prognosis of treatment-naive HCC with TACE depending on tumor location, whether central or peripheral. The purpose of this study was to evaluate the treatment efficacy of TACE for treatment-naive HCC according to tumor location and burden to investigate the appropriate treatment options available to HCC patients.

Materials and Methods

Patients and Tumors

From January 2010 to December 2019, patients who met the following criteria were included in this study: (1) diagnosis of treatment-naive HCC that fulfilled the criteria of the Japan Society of Hepatology Guidelines [10]; (2) conventional TACE as the initial treatment; (3) no local conversion therapy, such as ablation, surgical resection, or radiation therapy within 1 year after initial TACE; (4) no subsequent systemic therapy in those without tumor recurrence following initial TACE; (5) performance of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) following TACE; and (6) Barcelona Clinic Liver Cancer (BCLC) stage-0, A or B [4]. According to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, up to 5 tumors (>1 cm) in the liver per enrolled patient were identified as target lesions and included in this study [25]. Our Institutional Review Board approved this retrospective study and waived the requirement for patient consent for this retrospective review.

TACE Procedure

An interventional radiology CT system (Nexaris Angio-CT®; Siemens Healthcare GmbH, Forchheim, Germany) or a C-arm dual-phase cone-beam CT system (Artis zee BA Twin®; Siemens Healthcare) was used for the TACE procedure. Under local anesthesia, digital subtraction angiography was performed for the celiac artery and common hepatic artery using a 3- or 4-Fr catheter with a nonionic iodine contrast agent (iohexol, Omnipaque® 300 iodine, 300 mg I/mL; GE Healthcare, Tokyo, Japan). Then, CT during hepatic arteriography (CTHA) and CT during arterial portography images were obtained, and CT-maximum intensity projection images of the hepatic artery were created using a 3-D CT workstation (Synapse Vincent®; Fujifilm Corporation, Tokyo, Japan) to identify tumor-feeding arteries.

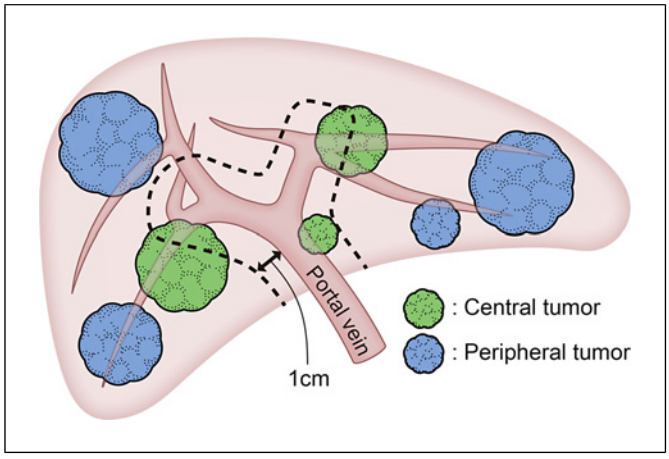

Fig. 1. Schema showing tumor location zones. Central tumor: tumors located even partially within 1 cm of the main trunk or first branch of the portal vein. Peripheral tumor: tumors located, even in part, more than 1 cm away from the main trunk or first branch of the portal vein.

Selective catheterization of the tumor-feeding arteries was performed using a 3- or 4-Fr catheter and a 1.7–2.1-Fr microcatheter. Conventional TACE was performed using digital subtraction angiography, CTHA, and navigation images to avoid infusion into nontarget arteries as much as possible. An emulsion of epirubicin (Epirubicin®; Nippon Kayaku Co. Ltd., Tokyo, Japan) solution and ethiodized oil (Lipiodol®; Guerbet Japan Co. Ltd., Tokyo, Japan) was prepared with the aid of a three-way stopcock. For some patients, cisplatin (IA-call®; Nippon Kayaku Co. Ltd.) or miriplatin (Miripla®; Sumitomo Pharma Co. Ltd., Osaka, Japan) was used to make a suspension instead of an epirubicin emulsion. After injection of the emulsion or suspension into the feeding arteries, 1–2 mm gelatin sponge particles (Gelpart®; Nippon Kayaku Co. Ltd.) were injected until tumor staining disappeared. Doses of anticancer drugs and iodized oil were determined based on tumor size, tumor count, and liver function. The maximum dose of ethiodized oil, epirubicin, cisplatin, and miriplatin in a single TACE session was 10 mL, 50 mg, 100 mg, and 120 mg, respectively. If the tumor was too large to embolize all at once, the next TACE was scheduled within 1 month.

Follow-up and Evaluations

Tumor location, number, and size of tumors were assessed by preoperative CT or CTHA during TACE. Based on their location, tumors were classified as central or peripheral tumors. Tumors in the central zone meant that any portion of the tumors was present within 1 cm of the main trunk or first branch of the portal vein (central tumor), and tumors outside this zone were classified as being in the peripheral zone (peripheral tumor; Fig. 1). Patients with central tumors were classified into the central arm and those with only peripheral tumors were classified into the peripheral arm. Next, patients were classified into two groups based on up-to-7 criteria. Patients within the up-to-7 criteria were classified into the up-to-7 in-groups, and those exceeding the up-to-7 criteria were classified into the up-to-7 out-groups. Within a week after TACE, non-enhanced CT was performed to assess the safety margin of ethiodized oil. A positive safety margin was defined as at least 1-mm thick ethiodized oil accumulation surrounding the tumor [26]. The radiologic response was evaluated by contrast-enhanced CT or MRI within 1–3 months after TACE according to mRECIST [25]. Patients without viable lesions after TACE underwent tumor marker and contrast-enhanced CT or MRI screening every 3–12 months. If recurrence was confirmed, additional treatment was considered. Liver function was also evaluated according to Child-Pugh score and albumin-bilirubin (ALBI) score pretherapy and at 1, 3, and 6 months after TACE [27].

In this study, tumor prognosis was assessed in terms of local recurrence-free survival (LRFS) for each tumor and was defined as the time interval from the date of the initial TACE to the date local recurrence was identified by screening, i.e., no longer in a state of complete response (CR). We separately assessed patient prognosis in terms of progression-free survival (PFS), which was defined as the time from the date of the initial TACE to the date local recurrence was identified by screening, including recurrence of nontarget lesions, or the date of death from any cause. Response rate (RR) was defined as the percentage of patients with a CR or partial response.

Statistical Analysis

LRFS and PFS were both evaluated using the Kaplan-Meier method. The log-rank test was used to compare survival curves between tumor and patient groups. Fisher's exact test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables. Recurrence and prognostic factors of LRFS and PFS were both investigated using multivariate Cox regression analysis. Changes in ALBI scores before and after TACE were analyzed using the Wilcoxon signed-rank test. Statistical significance was determined by 2-tailed tests and considered significant at a p value of <0.05. The above analyses were performed using GraphPad Prism for Windows version 9.3.0 (GraphPad Software Inc., San Diego, CA, USA).

Propensity scores were calculated using a logistic regression model fit with the following variables: age, sex, etiology, tumor diameter, and feeding artery (single/multiple) as tumor factors, and age, sex, etiology, Child-Pugh score, ALBI score, BCLC stage (0, A/B), largest tumor diameter, tumor number, up-to-7 score, α-fetoprotein, and protein induced by vitamin K absence or antagonists-II (PIVKA-II) as patient factors. Propensity score matching was performed with a 1:1 ratio and a caliper width of 0.2. Propensity score calculation and matching were performed with EZR software version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) based on R software, version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) [28].

Results

Patient Characteristics

One thousand one hundred and seventy-one treatment-naive HCC patients who were treated at our facility were retrospectively reviewed. Among them, 357 patients who received conventional TACE as the initial treatment

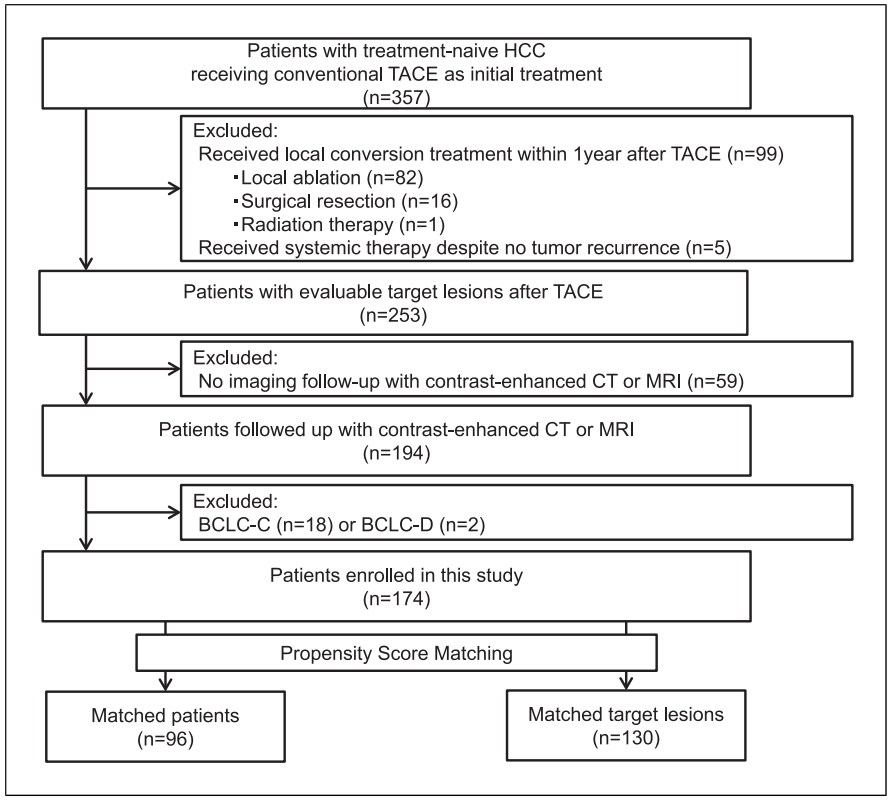

Fig. 2. Flow diagram of patient selection. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; CT, computed tomography; MRI, magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer.

were included. Of these, 183 patients were excluded for the following reasons: 99 patients received local conversion therapy within 1 year after TACE, 5 patients received systemic therapy after TACE despite no tumor recurrence, 59 patients had no imaging follow-up with contrast-enhanced CT or MRI, 18 patients were BCLC-C, and 2 patients were BCLC-D. Consequently, 174 patients with 352 target lesions were enrolled in this study, among which 96 patients and 130 lesions were selected using propensity score matching (Fig. 2). The characteristics of the tumors and patients are shown in Tables 1 and 2. Before matching, central tumors and patients in the central arm had significantly greater maximum tumor diameters (3.6 ± 2.6 vs. 2.3 ± 1.4 cm, $p < 0.001$; 4.5 ± 3.0 vs. 3.0 ± 1.3 cm, $p < 0.001$). PIVKA-II was also significantly higher in the central arm (mean 236 [range 10–238,237] vs. 120 [9–27,289] mAU/mL; $p = 0.011$). After matching, all the characteristics were comparable between the peripheral and central groups for both tumors and patients.

Median ALBI scores of all the patients before and 1, 3, and 6 months after the first TACE were −2.33, −2.22, −2.36, and −2.46, respectively (online suppl. Fig. 1a; for all online suppl. material, see www.karger.com/doi/10.1159/000530441), with scores of −2.28, −2.25, −2.36, and −2.35, respectively, in the peripheral arm, and −2.37, −2.20, −2.36, and −2.61, respectively, in the central arm (online suppl. Fig. 1b, c). There were significant differences between ALBI scores pre-TACE and 1 month after TACE in all groups ($p = 0.003$, $p = 0.003$, $p = 0.001$, respectively), although no statistically significant differences in ALBI scores were observed between pre-TACE and 3 and 6 months after TACE.

Local Tumor Response

The LRFS rates of all the 352 lesions were 78.4% at 3 months, 67.6% at 6 months, and 54.8% at 1 year (Fig. 3a). In peripheral tumors, the percentages were 85.6%, 76.1%, and 62.9%, and in central tumors, they were 50.7%, 35.2%, and 23.2%, respectively, at these time periods (Fig. 3b). The LRFS rates of the 130 lesions selected by propensity score matching were 65.2% at 3 months, 51.7% at 6 months, and 42.1% at 1 year (Fig. 3c), those of peripheral tumors were 78.3%, 68.7%, and 60.9%, and those of central tumors were 52.3%, 34.9%, and 23.0%, respectively (Fig. 3d). The median LRFS of all the tumors before matching was 18.3 months (95% confidence interval [CI]: 11.3–69.8; Fig. 3a), that of peripheral tumors was 69.8 months (95% CI: 24.4-not available [NA]), and of central tumors was 3.1 months (95% CI: 2.6–5.4;

Table 1. Baseline characteristics of tumors before and after propensity score matching

Characteristics	Before matching			*p* value	After matching			*p* value
	overall (*n* = 352)	central tumor (*n* = 73)	peripheral tumor (*n* = 279)		overall (*n* = 130)	central tumor (*n* = 65)	peripheral tumor (*n* = 65)	
Age (mean ± SD), years	70.8±9.3	69.2±11.6	71.3±8.6	0.318	69.5±9.5	69.7±10.3	69.3±8.7	0.783
Sex (male/female)	258/94	54/19	204/75	0.883	98/32	47/18	51/14	0.415
Etiology (viral/nonviral)	254/98	46/27	208/71	0.050	90/40	44/21	46/19	0.704
Tumor diameter (mean ± SD), cm	2.6±1.8	3.6±2.6	2.3±1.4	<0.001*	3.1±1.9	3.2±1.9	3.0±1.9	0.429
Tumor diameter (≤5 cm/> 5 cm)	329/23	62/11	267/12	<0.001*	113/17	59/6	54/11	0.193
Feeding artery (single/ multiple)	230/122	24/49	206/73	<0.001*	44/86	24/41	20/45	0.458

*p value <0.05.

Fig. 3b). Median LRFS for the entire set of matched tumors was 6.3 months (95% CI: 4–13.3; Fig. 3c), it was not reached for peripheral tumors (95% CI: 10.3–NA), and it was 3.3 months for central tumors (95% CI: 2.6–5.4; Fig. 3d). Both before and after matching, LRFS was significantly more prolonged in peripheral tumors than central tumors ($p < 0.001$, $p < 0.001$, respectively). The rate of positive safety margins of ethiodized oil in each group was 80% among peripheral tumors and 56.9% among central tumors, indicating a significantly lower percentage in central tumors ($p = 0.005$).

Systemic Tumor Response

The RR for all 174 patients was 74.6% at 3 months, 57.1% at 6 months, and 36.7% at 1 year, with rates of 85%, 68.9%, and 48.1% in the peripheral arm, and 56.5%, 35.1%, and 14.8% in the central arm. The RR for the 96 matched patients was 73.4% at 3 months, 56.5% at 6 months, and 34.1% at 1 year, with rates of 89.4%, 72.3%, and 47.8% in the peripheral arm, and 57.4%, 40.0%, and 19.0% in the central arm. PFS for all the 96 matched patients was 80.2% at 3 months, 60.2% at 6 months, 39.3% at 1 year, 17.2% at 3 years, and 12.9% at 5 years (Fig. 4a). The median PFS for all matched patients was 8.0 months (95% CI: 6–10.3; Fig. 4a). PFS rates at these time periods were 89.6%, 72.9%, 51.5%, 25.8%, and 19.1% for the peripheral arm, and 70.8%, 47.4%, 25.7%, 6.8%, and not applicable (NA) for the central arm, respectively (Fig. 4b). The median PFS in the peripheral arm was 12.7 months (95% CI: 6.9–18.7), which was significantly longer than that of 5.4 months (95% CI: 3.6–8.3) in the central arm ($p = 0.001$; Fig. 4b). With classification of the matched patients into four groups based on up-to-7 criteria and tumor zone, PFS rates at 3, 6, 12, 36, and 60 months were 89.2%, 75.7%, 58.9%, 30.9%, and 27.0% in the peripheral arm and up-to-7 in, 90.9%, 63.6%, 27.3%, 9.1%, and 0% in the peripheral arm and up-to-7 out, 84.8%, 63.1%, 35.5%, 9.5%, and NA in the central arm and up-to-7 in, and 40.0%, 13.3%, 6.7%, NA, and NA in the central arm and up-to-7 out-groups (Fig. 4c). Median PFS in the four groups were, respectively, 17.1 months (95% CI: 8.3–24.9), 7.0 months (95% CI: 3.3–12.7), 8.4 months (95% CI: 4.0–12.6), and 3.0 months (95% CI: 1.2–4.9). The peripheral arm and up-to-7 in-groups had significantly longer PFS than the other three groups ($p = 0.013$, $p = 0.015$, $p < 0.001$, respectively; Fig. 4c), while the central arm and up-to-7 out-groups had significantly shorter PFS than the other three groups ($p < 0.001$, $p = 0.005$, $p < 0.001$, respectively; Fig. 4c). Differences between the peripheral arm and up-to-7 out-groups and central arm and up-to-7 in-groups were not significant ($p = 0.691$; Fig. 4c).

Univariate and Multivariate Analyses of Nodules and Patients

The results of univariate and multivariate analyses are presented in Tables 3 and 4, respectively. Multivariate analyses confirmed that tumor location remained a significant prognostic factor associated with LRFS and PFS after TACE. The central zone and central arm were associated with higher adjusted hazard ratios (2.87, $p < 0.001$; 2.89, $p < 0.001$, respectively). BCLC classification,

Table 2. Baseline characteristics of patients before and after propensity score matching

Characteristics	Before matching			*p* value	After matching			*p* value
	overall (*n* = 174)	central arm (*n* = 64)	peripheral arm (*n* = 110)		overall (*n* = 96)	central arm (*n* = 48)	peripheral arm (*n* = 48)	
Age (mean±SD), years	71.2±9.8	70.2±11.5	71.8±8.5	0.688	70.3±9.5	71.2±10.6	69.4±8.1	0.231
Sex (male/female)	120/54	48/16	72/38	0.189	69/27	35/13	34/14	0.820
Etiology (viral/nonviral)	129/45	43/21	86/24	0.110	73/23	34/14	39/9	0.232
Child-Pugh score (mean±SD)	5.85±1.13	5.77±1.07	5.90±1.17	0.515	5.94±1.20	5.83±1.10	6.04±1.30	0.529
Child-Pugh (A/B)	130/44	49/15	81/29	0.669	71/25	36/12	35/13	0.816
ALBI score (mean±SD)	−2.37±0.52	−2.38±0.49	−2.36±0.54	0.870	−2.30±0.53	−2.35±0.48	−2.25±0.57	0.505
ALBI grade (1/2a/2b/3)	64/37/65/8	23/15/24/2	41/22/41/6	0.868	32/20/37/7	16/12/18/2	16/8/19/5	0.549
BCLC (0/A/B)	9/92/73	1/30/33	8/62/40	0.065	4/54/38	1/26/21	3/28/17	0.474
Largest tumor diameter (mean±SD), cm	3.5±2.2	4.5±3.0	3.0±1.3	<0.001*	3.4±1.5	3.4±1.5	3.3±1.5	0.538
Largest tumor diameter (*n*) (≤5 cm/>5 cm)	151/23	49/15	102/8	0.002*	85/11	44/4	41/7	0.336
Tumor number/patient (median, range)	2 (1–150)	2 (1–82)	2 (1–150)	0.132	2 (1–100)	2 (1–82)	1(1–100)	0.199
Tumor number (*n*) (<4/≥4)	123/51	40/24	83/27	0.070	70/26	31/17	39/9	0.066
Up-to-7 criteria (*n*) (in/out)	121/53	37/27	84/26	0.010*	70/26	33/15	37/11	0.358
AFP, ng/mL (median, range)	13.8 (2–1,039,586)	19.6 (2–1,039,586)	12.7 (2–5,732.5)	0.360	13.5(2–5,732.5)	11.5(2–3,479.1)	14.1(2–5,732.5)	0.287
AFP (*n*) (<400 ng/mL/≥400 ng/mL)	147/27	51/13	96/14	0.183	83/13	42/6	41/7	0.766
PIVKA-II, mAU/mL (median, range)	153 (9–238,237)	236 (10–238,237)	120 (9–27,289)	0.010*	142(10–34,603)	144(10–34,603)	133(12–19,441)	0.421
PIVKA-II (*n*) (<300 mAU/mL/≥300 mAU/mL)	108/66	35/29	73/37	0.126	62/34	32/16	30/18	0.670

ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonists-II. *p value <0.05.

up-to-7 criteria, and PIVKA-II also remained significant independent factors for PFS (Table 4).

Discussion

The present study demonstrated that both LRFS and PFS are significantly prolonged after TACE for treatment-naive HCC, more for peripheral tumors than central tumors, and in patients with only peripheral tumors than those with central tumors, respectively. Among them, patients within the up-to-7 criteria had a significantly better prognosis. Although the peripheral groups of both tumors and patients contained much smaller tumors, there were still significant differences in prognosis in terms of LRFS and PFS after adjusting for the size of tumors using propensity score matching.

Appropriate treatment selection is critical in the treatment of patients with HCC. The above results indicate that the ideal treatment selection should be considered separately for each of the four groups classified according to up-to-7 criteria and tumor location.

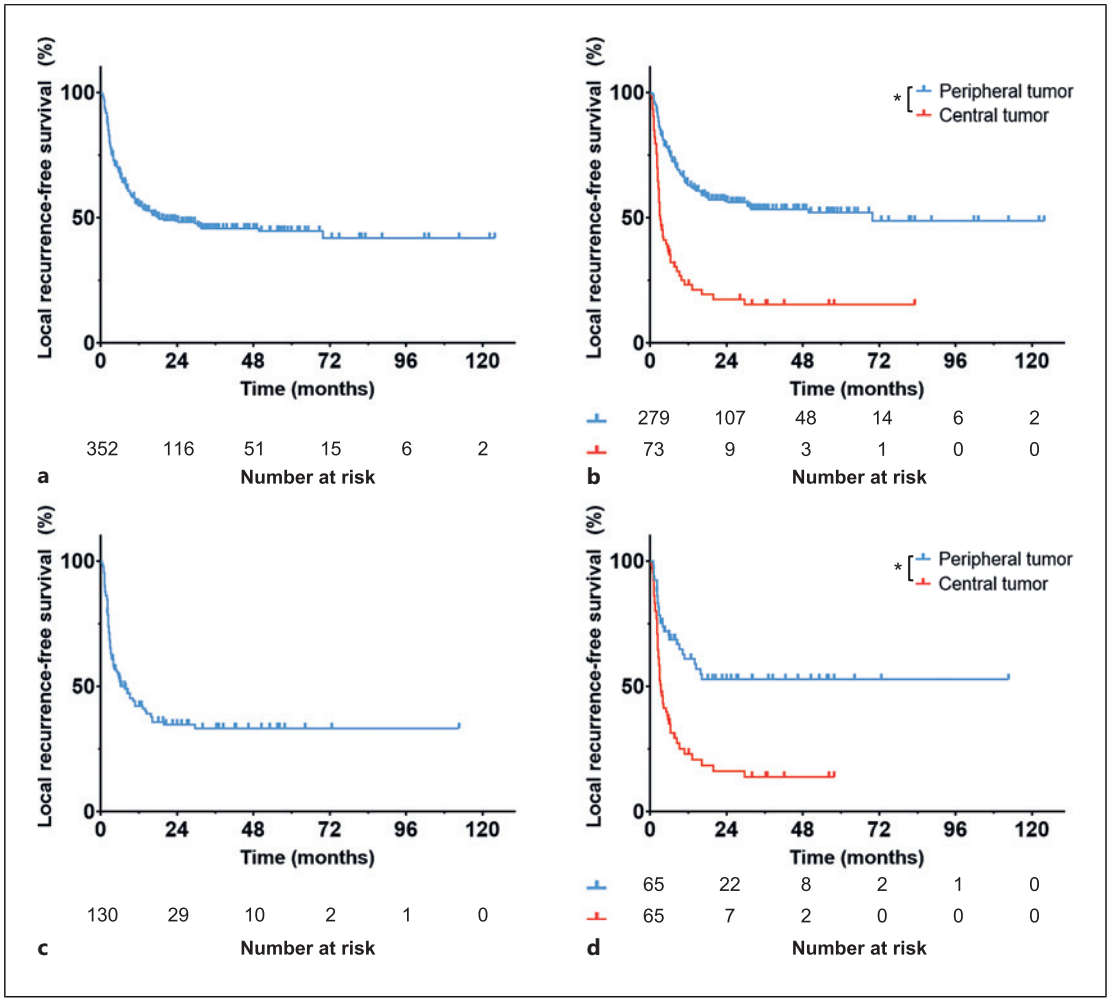

Fig. 3. Kaplan-Meier curves of LRFS before and after propensity score matching. **a** All the tumors before matching: Median LRFS 18.3 months (95% CI: 11.3–69.8). **b** Peripheral tumor versus central tumor before matching: Median LRFS 69.8 months (95% CI: 24.4–NA) versus 3.1 months (95% CI: 2.6–5.4); $p < 0.001$. **c** All the tumors after matching: Median LRFS 6.3 months (95% CI: 4.0–13.3). **d** Peripheral tumor versus Central tumor after matching: LRFS not reached (95% CI: 10.3–NA) versus 3.3 months (95% CI: 2.6–5.4); $p < 0.001$. LRFS, local recurrence-free survival; CI, confidence interval; NA, not available. *p value <0.05.

In patients with very early and early stage HCC defined according to BCLC stage, the recommended treatment is curative treatment, such as ablation and resection [4]. Previous papers have reported a median time to tumor recurrence of 18 (IQR: 7–42) months, and 3- and 5-year cumulative incidences of first recurrence of 70.8% and 81.7%, respectively [29]. In the current study, median PFS was 17.1 months in the peripheral arm and up-to-7 in-groups, and the overall 1-, 3-, and 5-year PFS rates were 58.9%, 30.9%, and 27.0%, respectively, which were comparable to the results of most previous radiofrequency ablation (RFA) studies in the literature [29, 30]. However, curative treatments might not be available even in the very early and early stages of HCC in some cases, for reasons such as patient refusal, status after biliary surgery, or the presence of other serious comorbidities. In such cases, TACE can be regarded as an alternative to curative treatment in the peripheral arm and up-to-7 in-groups. On the other hand, according to the recommendation by the Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Statement, drug treatments, such as MTA or immune checkpoint inhibitor, which can lead to a high RR, are preferred in patients beyond the up-to-7 criteria [11]. In the central arm and up-to-7 out-groups in our study, median PFS was just 3.0 months. This result supports the fact that TACE is not indicated as the first-line therapy in TACE-unsuitable patients, as suggested by the APPLE

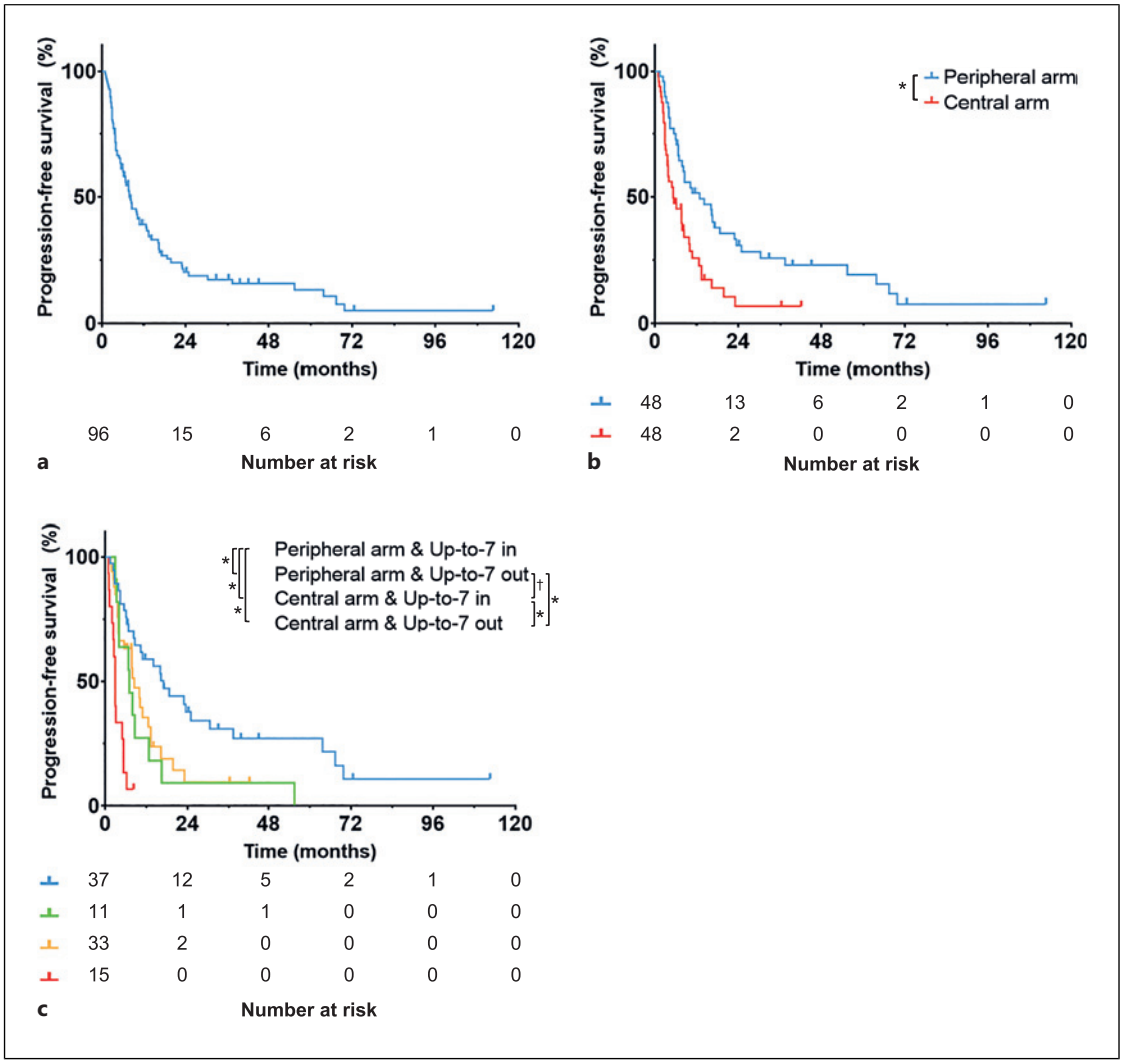

Fig. 4. Kaplan-Meier curves of PFS after propensity score matching. **a** All the patients: median PFS 8.0 months (95% CI: 6.0–10.3). **b** Peripheral arm versus central arm: median PFS 12.7 months (95% CI: 6.9–18.7) versus 5.4 months (95% CI: 3.6–8.3); $p = 0.001$. **c** Peripheral arm and up-to-7 in versus peripheral arm and up-to-7 out versus central arm and up-to-7 in versus central arm and up-to-7 out: median PFS 17.1 months (95% CI: 8.3–24.9) versus 7.0 months (95% CI: 3.3–12.7) versus 8.4 months (95% CI: 4.0–12.6) versus 3.0 months (95% CI: 1.2–4.9). The peripheral arm and up-to-7 in-groups had significantly longer PFS than the other three groups ($p = 0.013$, $p = 0.015$, $p < 0.001$, respectively); the central arm and up-to-7 out-groups had significantly shorter PFS than the other three groups ($p < 0.001$, $p = 0.005$, $p < 0.001$, respectively). PFS, progression-free survival; CI, confidence interval. *p value <0.05. †p value ≥0.05.

Consensus Statement [11]. In the peripheral arm and up-to-7 out-groups and central arm and up-to-7 in-groups in this study, median PFS were 7.0 and 8.4 months, respectively, which were significantly longer than those in the central arm and up-to-7 out-groups, suggesting that these two groups might be candidates for TACE. However, in both of these groups, TACE might not play a sufficient role as curative treatment, since both groups had a relatively high recurrence rate, suggesting the need for careful follow-up.

The effect of combination therapy with TACE and systemic therapy is still controversial. Several large studies showed no significant differences in local recurrence or survival between the combination of TACE with multi-kinase inhibitors like sorafenib, brivanib, or orantinib versus TACE alone [20–24]. In particular, from the results of two of the studies, the author concluded that there were definitive evidences that combined therapy of drug-eluting beads TACE and sorafenib does not improve outcomes [22, 23]. However, in certain patients

Table 3. Results of univariate and multivariate Cox regression analyses of local recurrence-free survival in matched tumors

	Survival time (median, month) (95% CI)	Univariate analysis	Multivariate analysis	
		p value	hazard ratio (95% CI)	*p* value
Sex				
Male	5.7 (3.3–10.9)			
Female	13.3 (2.7–NA)	0.163	0.64 (0.35–1.08)	0.109
Age				
<75 years	6.0 (3–14.1)			
≥75 years	8.3 (3.3–19.8)	0.564	0.84 (0.5–1.35)	0.477
Etiology				
Viral	9.2 (3.6–15.8)			
Nonviral	4.6 (2.1–10.9)	0.208	1.33 (0.82–2.11)	0.237
Tumor diameter				
<5 cm	8.4 (4.2–14.4)			
≥5 cm	3.3 (2.4–NA)	0.611	1.15 (0.56–2.15)	0.677
Feeding artery				
Single	10.3 (3.9–NA)			
Multiple	5.6 (3.1–10.9)	0.169	1.4 (0.86–2.33)	0.182
Safety margin of ethiodized oil				
Positive	13.3 (5.4–NA)			
Negative	3.3 (2.4–6. 3)	<0.001*	1.55 (0.96–2.48)	0.072
Tumor location				
Peripheral	Not reached (10.3–NA)			
Central	3.3 (2.6–5.4)	<0.001*	2.87 (1.75–4.78)	<0.001*

CI, confidence interval; NA, not available. *p value <0.05.

with intermediate-stage HCC, favorable results have recently been reported with the combination and switching of TACE and systemic therapy [17, 18, 31, 32]. Incomplete TACE for HCC with a high tumor burden has been reported to increase the expression of hypoxia-inducible factor 1-α in the tumor, leading to upregulation of vascular endothelial growth factor (VEGF) and angiopoietin-2 [33, 34]. These phenomena result in increased angiogenesis, vascular invasion, and metastasis [34]. Blocking these receptors might prevent this negative feedback. MTAs have also been reported to improve the delivery and distribution of anticancer drugs within the tumor [35, 36]. In fact, it has been reported that combination adjuvant treatment using MTAs with anti-VEGF effects and TACE is beneficial for improving PFS and OS [17, 18]. In a previous study, median PFS was significantly longer in the TACE plus sorafenib group than in the TACE alone group (25.2 vs. 13.5 months; $p = 0.006$) [17]. Moreover, combination therapy of TACE and lenvatinib in patients with unresectable HCC has been reported to produce estimated median PFS, OS, and time to untreatable progression of at least 2 years [18]. Hence, introduction of adjuvant treatment with MTAs before TACE is considered as one of the treatment options not only for patients beyond the up-to-7 criteria but also for patients within the up-to-7 criteria with central tumors.

The present study showed that tumor location is particularly important from the perspective of local and systemic control of HCCs. There have been various reports on prognostic factors for local tumor control and survival after TACE [9, 26, 37–44]. However, only few prognostic factors related to location have been reported. In previous reports, tumors in the segmental border zone and in the median liver (Couinaud's segments 1 or 4) had a poor prognosis [40–42]. Another report showed that contact with the liver surface was a significant risk factor for local recurrence [43]. It has also been reported that tumors abutting the hepatic capsule, within 1 cm of the capsule, or adjacent to visible (>1-mm diameter) blood vessels did not have a significantly different prognosis [41, 42]. Bryant et al. reported that tumor location was a predictive factor for local recurrence during short-term follow-up [44]. They showed that central tumors (defined as less than 4 cm from the portal vein bifurcation) had a very low rate of complete or >90% tumor necrosis (23%). However, the report had some limitations: it did not demonstrate long-term results, such as LRFS or PFS according to tumor location, it included partial response as local control, it did not

Table 4. Results of univariate and multivariate Cox analyses of progression-free survival in matched patients

	Survival time (median, month) (95% CI)	Univariate analysis	Multivariate analysis	
		p value	hazard ratio (95% CI)	*p* value
Sex				
Male	6.5 (4.1–8.3)			
Female	13.3 (8.4–63.7)	0.001*	0.65 (0.34–1.20)	0.183
Age				
<75 years	6.9(3.9–10.3)			
≥75 years	8.6 (6.3–19.8)	0.050	0.62 (0.37–1.04)	0.069
Etiology				
Viral	8.6 (6.5–14)			
Nonviral	5.6 (3.9–8.3)	0.007*	1.43 (0.78–2.56)	0.229
Child-Pugh				
A	7.9 (5.6–10.2)			
B	10.9 (3.9–16.4)	0.822	1.08 (0.56–2.05)	0.819
ALBI				
1	8.6 (4.9–14)			
2, 3	7.8 (5.3–10.9)	0.108	1.65 (0.94–2.93)	0.084
BCLC				
0, A	13.3 (8.4–17.1)			
B	4.2 (3.1–6.3)	<0.001*	3.38 (1.55–7.08)	0.002*
Tumor diameter				
<5 cm	8.0 (6–10.9)			
≥5 cm	6.3 (2.7–16.4)	0.348	0.43 (0.16–1.07)	0.076
Tumor number				
<4	10.3 (7.7–16.1)			
≥4	3.9 (2.9–6.8)	<0.001*	0.50 (0.10–1.24)	0.127
Up-to-7 criteria				
Within	10.9 (7.8–16.2)			
Beyond	4.0 (3–6.3)	<0.001*	3.37 (1.38–8.47)	0.008*
AFP				
<400	7.9 (6–10.2)			
≥400	13.3 (4.4–55.6)	0.262	0.70 (0.31–1.43)	0.349
PIVKA-II				
<300	8.7 (6.8–13.3)			
≥300	4.9 (3.3–7.9)	0.004*	1.69 (1.01–2.80)	0.041*
Tumor location				
Peripheral	12.7 (6.9–18.7)			
Central	5.4 (3.6–8.3)	0.001*	2.89 (1.75–4.82)	<0.001*

CI, confidence interval; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonists-II. *p value <0.05.

consider tumor diameters between central and peripheral locations, and TACE was not an initial treatment. The classification method used in our study was different from the above report. Selective or superselective TACE is used to enhance treatment efficacy of peripheral tumors [8, 45]. Intrahepatic arteries generally accompany portal veins. Portal veins are more discernable than the intrahepatic arteries in contrast-enhanced CT and MRI images. Segmental branches of intrahepatic arteries, which are the targets of selective TACE, are generally located less than 1 cm away from the main trunk or first branch of the portal vein [46, 47]. Consequently, we considered it appropriate to use the boundary of 1 cm away from the main portal trunk or 1st branch of the portal vein to differentiate between central and peripheral tumors in this study. Compared to peripheral tumors, since central tumors require more extensive treatment from the central side of the feeder, they might be more difficult to treat completely. Generally, obtaining safety margins in TACE is an important technical factor for improving local tumor control [7]. Our study demonstrated that there was a significant difference

in the percentage of positive safety margin of ethiodized oil between peripheral and central tumors. The difference in the positive safety margin might also support the idea that treatment is difficult for the central tumors.

In previous reports, other prognostic factors for local tumor control included tumor size, number, markers, and vascularity, accumulation of ethiodized oil, safety margin of ethiodized oil, type of TACE, and number of TACEs [9, 26, 37–42]. Systemic prognostic factors included all of these factors except type and number of TACE, plus liver function, portal vein thrombus, achievement of CR after the first TACE, early local recurrence within 1 year, performance status, BCLC stage, and C-reactive protein level [26, 38–40, 48–58]. Tumor size, number, and markers, and liver function have been frequently reported and are widely accepted as prognostic factors of HCC [37–41, 50–59]. There are many scoring systems and models that employ the above factors, such as the subclassification of BCLC B HCC, hepatic arterial embolization prognostic (HAP) score, modified HAP score, modified HAP-II score, modified HAP-III score, SANCOR model, the prognostic nomogram, the ALBI-TAE model, the seven-eleven criteria, the six-and-twelve score, the pre-TACE-predict, and the post-TACE-predict [12, 38, 50–59]. However, some of these might be difficult to use practically because of the complexity of cutoff values and calculations. On the other hand, the classification according to tumor location and the up-to-7 criteria used in this paper can be easily performed using only CT or MRI and is intuitive to use. In particular, classification according to tumor location determined using preoperative contrast-enhanced CT or MRI is simple and easy to understand and can be used in combination with other subclassifications.

In this study, large tumor diameter was not found to be a significant factor for local recurrence in both univariate and multivariate analyses. The study also showed that patients with high AFP levels tended to have a better prognosis (Tables 3, 4). These results are contrary to those of other studies that showed that large tumor size was a significant factor for local recurrence, and that high AFP level was a worse prognostic factor [37, 40, 51, 53, 54]. Further analysis of tumor diameter ≥5 cm and <5 cm groups in this study showed that the large-size tumor group had fewer coexisting tumors and tended to present as a single nodule. Conversely, the small-size tumor group tended to have multiple tumors (data not shown). Similarly, analysis of the AFP ≥400 and <400 groups showed a trend toward fewer tumors in the high AFP group and more tumors in the low AFP group (data not shown). We considered that these are the reasons why the present study results were inconsistent with previous papers about tumor size and AFP. Some previous reports have also suggested that tumor number is a more significant prognostic factor than tumor size in relation to prognosis after TACE [60, 61]. Hence, tumor number might have affected LRFS and PFS in this study.

The effect of TACE on liver function is still controversial. In previous studies, patients who continued to receive TACE despite TACE refractoriness or high tumor burden had a poor prognosis in terms of liver function [31, 62]. In another study, the deterioration ratios of liver function did not increase with repeated TACE [60]. In this study, long-term deterioration of liver function was not observed in either the peripheral or central arms. However, a further large cohort study is needed to confirm the long-term safety of TACE in treatment-naive HCC patients.

There are several limitations in the present study. This was a single-center retrospective study with propensity score matching. Further, large-scale prospective studies are required to enhance the validity of our results. In addition, since the study only included patients with treatment-naive HCCs, it is not clear whether similar results would be obtained in patients with previously treated HCCs.

Conclusion

TACE for treatment-naive HCCs in the peripheral zone was associated with prolonged LRFS and PFS compared to those in the central zone. Alternative therapies with a combination of TACE and systemic therapy should be considered in patients with central tumors or a high tumor burden.

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Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Osaka City University Graduate School of

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.A., K.K., and A.Y. conceived and designed the study. K.A., K.K., A.Y., A.J., S.U.-K., E.S., and K.M. acquired and processed the data. K.A., K.K., and A.Y. analyzed and interpreted the data, and drafted the manuscript. All authors including N.K. and Y.M. critically revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: cancer today [Internet]. 2020 [cited 2022 Sep 14]; Available from: https://gco.iarc.fr/today.
2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.
3 European Association for the Study of the Liver Electronic address easloffice@easloffi-ceeuEuropean Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182–236.
4 Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022 Mar;76(3):681–93.
5 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018 Jan;67(1):358–80.
6 Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology. 1983 Aug;148(2):397–401.
7 Charoenvisal C, Tanaka T, Nishiofuku H, Anai H, Sato T, Matsumoto T, et al. Feasibility and techniques of securing 3D-safety margin in superselective transarterial chemoembolization to improve local tumor control for small hepatocellular carcinoma: an intend-to-treat analysis. Liver Cancer. 2021 Feb;10(1):63–71.
8 Miyayama S, Matsui O. Applying superselective conventional TACE. Endovascular Today. 2017 Apr;16(4):52–6.
9 Ikeda M, Arai Y, Inaba Y, Tanaka T, Sugawara S, Kodama Y, et al. Conventional or drug-eluting beads? Randomized controlled study of chemoembolization for hepatocellular carcinoma: jivrosg-1302. Liver Cancer. 2022 Sep;11(5):440–50.
10 Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of hepatocellular carcinoma in Japan: JSH Consensus statements and recommendations 2021 update. Liver Cancer. 2021 Jun;10(3):181–223.
11 Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: asia-pacific primary liver cancer Expert Consensus statements. Liver Cancer. 2020 Jun;9(3):245–60.
12 Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis. 2012 Nov;32(4):348–59.
13 Kudo M. Extremely high objective response rate of lenvatinib: its clinical relevance and changing the treatment paradigm in hepatocellular carcinoma. Liver Cancer. 2018 Sep;7(3):215–24.
14 Yamakado K, Hirota S. Sub-classification of intermediate-stage (Barcelona clinic liver cancer stage-B) hepatocellular carcinomas. World J Gastroenterol. 2015 Oct 7;21(37):10604–8.
15 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35–43.
16 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973 Aug;60(8):646–9.
17 Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. 2020 Aug;69(8):1492–501.
18 Ueshima K, Ishikawa T, Saeki I, Morimoto N, Aikata H, Tanabe N, et al. Transcatheter arterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable hepatocellular carcinoma (TACTICS-L) in Japan: final analysis. J Clin Oncol. 2022;40(4_Suppl l):417–7.
19 Kudo M. New treatment paradigm with systemic therapy in intermediate-stage hepatocellular carcinoma. Int J Clin Oncol. 2022 May 8;27(7):1110–9.
20 Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer. 2011 Sep;47(14):2117–27.
21 Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology. 2014 Nov;60(5):1697–707.
22 Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol. 2016 May;64(5):1090–8.
23 Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol. 2017 Aug;2(8):565–75.

24 Kudo M, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol. 2018 Jan;3(1):37–46.
25 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52–60.
26 Kattipatanapong T, Nishiofuku H, Tanaka T, Sato T, Masada T, Tatsumoto S, et al. Improved local tumor control and survival rates by obtaining a 3D-safety margin in superselective transarterial chemoembolization for small hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2020 Mar;43(3):423–33.
27 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015 Feb 20;33(6):550–8.
28 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452–8.
29 Rossi S, Ravetta V, Rosa L, Ghittoni G, Viera FT, Garbagnati F, et al. Repeated radiofrequency ablation for management of patients with cirrhosis with small hepatocellular carcinomas: a long-term cohort study. Hepatology. 2011 Jan;53(1):136–47.
30 Francica G, Saviano A, De Sio I, De Matthaeis N, Brunello F, Cantamessa A, et al. Long-term effectiveness of radiofrequency ablation for solitary small hepatocellular carcinoma: a retrospective analysis of 363 patients. Dig Liver Dis. 2013 Apr;45(4):336–41.
31 Arizumi T, Ueshima K, Minami T, Kono M, Chishina H, Takita M, et al. Effectiveness of sorafenib in patients with transcatheter arterial chemoembolization (TACE) refractory and intermediate-stage hepatocellular carcinoma. Liver Cancer. 2015 Dec;4(4):253–62.
32 Shimose S, Kawaguchi T, Tanaka M, Iwamoto H, Miyazaki K, Moriyama E, et al. Lenvatinib prolongs the progression-free survival time of patients with intermediate-stage hepatocellular carcinoma refractory to transarterial chemoembolization: a multicenter cohort study using data mining analysis. Oncol Lett. 2020 Sep;20(3):2257–65.
33 Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. World J Gastroenterol. 2004 Oct 1;10(19):2878–82.
34 Wang HM, Lo GH, Hsu PI, Lin CK, Chan HH, Chen WC, et al. Nodular regenerative hyperplasia of the liver. Acta Radiol. 2008 Jun;71(10):523–7.
35 Kano MR, Komuta Y, Iwata C, Oka M, Shirai YT, Morishita Y, et al. Comparison of the effects of the kinase inhibitors imatinib, sorafenib, and transforming growth factor-beta receptor inhibitor on extravasation of nanoparticles from neovasculature. Cancer Sci. 2009 Jan;100(1):173–80.
36 Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005 Jan 7;307(5706):58–62.
37 Golfieri R, Renzulli M, Mosconi C, Forlani L, Giampalma E, Piscaglia F, et al. Hepatocellular carcinoma responding to superselective transarterial chemoembolization: an issue of nodule dimension? J Vasc Interv Radiol. 2013 Apr;24(4):509–17.
38 Hung YW, Lee IC, Chi CT, Lee RC, Liu CA, Chiu NC, et al. Redefining tumor burden in patients with intermediate-stage hepatocellular carcinoma: the seven-eleven criteria. Liver Cancer. 2021 Nov;10(6):629–40.
39 Jin YJ, Chung YH, Kim JA, Park W, Lee D, Shim JH, et al. Predisposing factors of hepatocellular carcinoma recurrence following complete remission in response to transarterial chemoembolization. Dig Dis Sci. 2013 Jun;58(6):1758–65.
40 Chen M, Cao J, Hu J, Topatana W, Li S, Juengpanich S, et al. Clinical-radiomic analysis for pretreatment prediction of objective response to first transarterial chemoembolization in hepatocellular carcinoma. Liver Cancer. 2021 Feb;10(1):38–51.
41 Vesselle G, Quirier-Leleu C, Velasco S, Charier F, Silvain C, Boucebci S, et al. Predictive factors for complete response of chemoembolization with drug-eluting beads (DEB-TACE) for hepatocellular carcinoma. Eur Radiol. 2016 Jun;26(6):1640–8.
42 Park SH, Cho YK, Ahn YS, Park YO, Kim JK, Chung JW. Local recurrence of hepatocellular carcinoma after segmental transarterial chemoembolization: risk estimates based on multiple prognostic factors. Korean J Radiol. 2007 Mar–Apr;8(2):111–9.
43 Nakano MM, Yamamoto A, Nishida N, Hamuro M, Hamamoto S, Jogo A, et al. Risk factors for local recurrence of hepatocellular carcinoma after transcatheter arterial chemoembolization with drug-eluting beads (DEB-TACE). Jpn J Radiol. 2019 Jul;37(7):543–8.
44 Bryant MK, Dorn DP, Zarzour J, Smith JK, Redden DT, Saddekni S, et al. Computed tomography predictors of hepatocellular carcinoma tumour necrosis after chemoembolization. HPB. 2014 Apr;16(4):327–35.
45 Golfieri R, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology. 2011 May;53(5):1580–9.
46 Ibukuro K, Takeguchi T, Fukuda H, Abe S, Tobe K, Tanaka R, et al. Spatial relationship between intrahepatic artery and portal vein based on the fusion image of CT-arterial portography (CTAP) and CT-angiography (CTA): new classification for hepatic artery at hepatic hilum and the segmentation of right anterior section of the liver. Eur J Radiol. 2012 Feb;81(2):e158–65.
47 Ibukuro K, Takeguchi T, Fukuda H, Abe S, Tobe K, Tagawa K. Spatial relationship between the hepatic artery and portal vein based on the fusion image of CT angiography and CT arterial portography: the left hemiliver. AJR Am J Roentgenol. 2013 May;200(5):1160–6.
48 Jeong SO, Kim EB, Jeong SW, Jang JY, Lee SH, Kim SG, et al. Predictive factors for complete response and recurrence after transarterial chemoembolization in hepatocellular carcinoma. Gut Liver. 2017 May 15;11(3):409–16.
49 Hucke F, Pinter M, Graziadei I, Bota S, Vogel W, Muller C, et al. How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol. 2014 Dec;61(6):1287–96.
50 Kim JH, Shim JH, Lee HC, Sung KB, Ko HK, Ko GY, et al. New intermediate-stage subclassification for patients with hepatocellular carcinoma treated with transarterial chemoembolization. Liver Int. 2017 Dec;37(12):1861–8.
51 Kadalayil L, Benini R, Pallan L, O'Beirne J, Marelli L, Yu D, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol. 2013 Oct;24(10):2565–70.
52 Pinato DJ, Arizumi T, Allara E, Jang JW, Smirne C, Kim YW, et al. Validation of the hepatoma arterial embolization prognostic score in European and Asian populations and proposed modification. Clin Gastroenterol Hepatol. 2015 Jun;13(6):1204–8.e2.
53 Park Y, Kim SU, Kim BK, Park JY, Kim DY, Ahn SH, et al. Addition of tumor multiplicity improves the prognostic performance of the hepatoma arterial-embolization prognostic score. Liver Int. 2016 Jan;36(1):100–7.
54 Cappelli A, Cucchetti A, Cabibbo G, Mosconi C, Maida M, Attardo S, et al. Refining prognosis after trans-arterial chemo-embolization for hepatocellular carcinoma. Liver Int. 2016 May;36(5):729–36.
55 Kim BK, Shim JH, Kim SU, Park JY, Kim DY, Ahn SH, et al. Risk prediction for patients with hepatocellular carcinoma undergoing chemoembolization: development of a prediction model. Liver Int. 2016 Jan;36(1):92–9.
56 Lee IC, Hung YW, Liu CA, Lee RC, Su CW, Huo TI, et al. A new ALBI-based model to predict survival after transarterial chemoembolization for BCLC stage B hepatocellular carcinoma. Liver Int. 2019 Sep;39(9):1704–12.

57 Wang Q, Xia D, Bai W, Wang E, Sun J, Huang M, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: a multicentre observational study. J Hepatol. 2019 May;70(5):893–903.
58 Han G, Berhane S, Toyoda H, Bettinger D, Elshaarawy O, Chan AWH, et al. Prediction of survival among patients receiving transarterial chemoembolization for hepatocellular carcinoma: a response-based approach. Hepatology. 2020 Jul;72(1):198–212.
59 Xu L, Peng ZW, Chen MS, Shi M, Zhang YJ, Guo RP, et al. Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. J Hepatol. 2015 Jul;63(1):122–30.
60 Saito N, Tanaka T, Nishiohuku H, Sato T, Masada T, Matsumoto T, et al. Transarterial-chemoembolization remains an effective therapy for intermediate-stage hepatocellular carcinoma with preserved liver function. Hepatol Res. 2020 Oct;50(10):1176–85.
61 Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, et al. A prognostic score for patients with intermediate-stage hepatocellular carcinoma treated with transarterial chemoembolization. PLoS One. 2015;10(4):e0125244.
62 Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child-pugh A liver function: a proof-of-concept study. Cancers. 2019 Jul 31;11(8):1084.