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Efficacy and safety of transarterial chemoembolisation with cone-beam CT in patients with hepatocellular carcinoma within the Milan criteria: a retrospective cohort study

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AIM: To compare the therapeutic efficacy and safety of transarterial chemoembolisation (TACE) for hepatocellular carcinoma (HCC) within the Milan criteria with or without the use of cone-beam computed tomography (CBCT).

MATERIALS AND METHODS: Patients with HCC within the Milan criteria who underwent conventional angiography-guided TACE (Angio-TACE group: 58 patients from January 2010 to December 2011) were compared with those who underwent CBCT-guided TACE (CBCT-TACE group: 55 patients from January 2013 to December 2014). Local progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS) were compared. Adverse events after TACE were also investigated.

RESULTS: Baseline characteristics were balanced between the two groups. LPFS was significantly longer in the CBCT-TACE group than in the Angio-TACE group (median: not reached for 36 versus 19.2 months, respectively; Log-rank p=0.029). In multivariable Cox regression analysis, CBCT guidance had a significantly lower risk of local progression or death (adjusted hazard ratio: 0.585; 95% confidence interval, 0.344–0.995; p=0.048); however, there was no significant difference in PFS (3-year PFS: 15.9% versus 26.8%, respectively; p=0.122) or OS (3-year OS: 85% versus 88.2%, respectively; p=0.761) between the Angio-TACE and CBCT-TACE groups. Post-embolisation syndrome occurred significantly less frequently in the CBCT-TACE group (p=0.002).

CONCLUSION: CBCT-guided TACE could improve local tumour control for HCC within Milan criteria and showed fewer cases of post-embolisation syndrome.

Introduction

Transarterial chemoembolisation (TACE) has been accepted as a standard locoregional therapy for unresectable hepatocellular carcinoma (HCC), especially for intermediate-stage HCCs.[1,2] For the treatment of early-stage

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HCCs, liver transplantation, surgical resection, or ablation are recommended as curative treatment options[1,2]; however, in an international multicentre study, chemoembolisation was also widely used for early-stage HCCs in the real world.[3] Possible reasons are as follows: although liver transplantation or surgical resection is recommended for patients within Milan criteria, liver transplantation is limited by a shortage of donors, and candidates for surgical resection are often restricted by low liver volume, portal hypertension, and serious postoperative complications such as hepatic dysfunction.[4] A number of early-stage HCC patients are not good candidates for ablation because of challenging anatomy and tumour location,[5] and potential risk of tract seeding after percutaneous approach exists.[6]

Recently, cone-beam computed tomography (CBCT) using a flat-panel detector system has been actively used during for TACE of HCC.[7,8] It can provide more accurate information on the detection of tumours and tumour feeding arteries than conventional angiography.[9,10] The application of CBCT guidance on TACE in patients within the Milan criteria might be able to improve clinical outcome over conventional chemoembolisation.[11]

Therefore, the purpose of this study was to compare the therapeutic efficacy and safety of TACE for HCCs within the Milan criteria with or without the use of CBCT.

Materials and methods

Patients

This retrospective study was performed with a cohort of prospectively collected data in single centre (National cancer centre, Goyang-si, South Korea). The institutional review board approved this study, and the requirement for informed consent was waived. Two-hundred and eight consecutive patients from January 2010 to December 2011, and 163 consecutive patients from January 2013 to December 2014 were initially treated by conventional angiography-guided TACE (Angio-TACE) and CBCT-guided TACE (CBCT-TACE) due to presumed HCC, respectively. The CBCT system was installed in 2012; therefore, patients who underwent TACE in 2012 were excluded to avoid interference of therapeutic effects between the two groups. After reviewing preprocedural CT or magnetic resonance imaging (MRI), 73 patients in the Angio-TACE group and 68 patients in the CBCT-TACE group were considered for possible inclusion based on the Milan criteria. Exclusion criteria were as follows[1]: history of previous or concomitant neoplastic disease other than HCC, and[2] no typical enhancing nodule (early enhancement on arterial phase and washout on portal/delayed phase) on CT or MRI. Finally, 58 patients with 71 tumours between January 2010 and December 2011 were enrolled in the Angio-TACE group, and 55 patients with 66 tumours between January 2013 and December 2014 under CBCT guidance were enrolled in the CBCT-TACE group (Fig 1).

Conventional TACE procedure

Conventional TACE was performed using doxorubicin (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Korea) and iodised oil (Lipiodol; Guerbet, Villepinte, France). After coeliac or common hepatic arteriography using a 5 F catheter (RH catheter; Cook, Bloomington, IN, USA) to evaluate vascular anatomy of the coeliac trunk and the hepatic artery, selective angiography was repeatedly performed to detect the target tumour and its tumour feeding artery using a 2 F microcatheter (Progreat α; Terumo, Tokyo, Japan). After confirming the tumour feeding artery, operators attempted to catheterise tumour feeding vessels as selectively as possible. After placement of the microcatheter tip in the proper position, 10–50 mg doxorubicin solution in non-ionic contrast medium (Visipaque 270; GE Healthcare Ireland, Cork, Ireland) was emulsified with iodised oil in a 1:4 (doxorubicin solution/iodised oil) volume ratio and then administered slowly. The amount of infused emulsion was determined by the operator based on the tumour size and

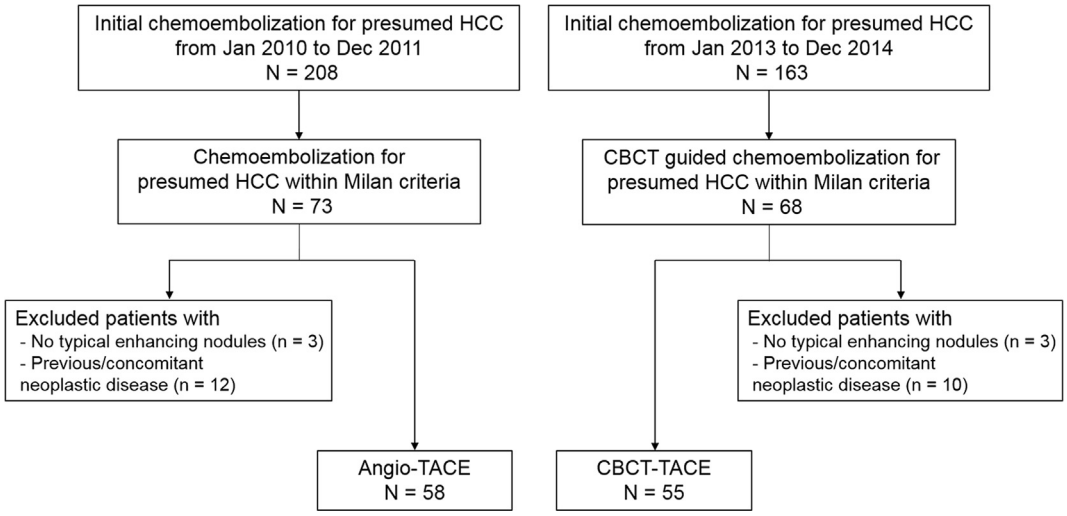

Figure 1 Flowchart of patient selection.

vascularity. After completing the administration, submillimetre-sized gelatin sponge particles were used for additional embolisation of feeding arteries. TACE was completed when tumour arterial enhancement disappeared and the tumour feeding artery was completely obstructed. Immediately after the TACE procedure, unenhanced liver CT was performed to confirm Lipiodol uptake of the tumour.

CBCT-guided TACE procedure

In 2013–2014, CBCT-guided TACE was performed with two angiography systems (AXIOM Artis Zee, Siemens, Erlangen, Germany; Allura Xper FD20, Philips Healthcare, Best, the Netherlands). To obtain whole-liver CBCT images, rotational hepatic arteriography and CBCT was performed at the common hepatic artery or proper hepatic artery with injection of undiluted (Artis Zee) or half-diluted (Allura Xper FD20) contrast media at a flow rate of 2–4 ml/s after 4–6 seconds of X-ray delay considering the flow rate of the hepatic artery and catheter used.[10] In case of the anatomical variation, additional scanning was performed at the right or left hepatic arteries if it was needed. The parameters were as follows: for dynaCT, rotational CBCT hepatic arteriography acquired during a single breath-hold for 8 seconds with 0.5° increment, 512×512 matrix in projections, total angle of 210° at approximately 26° per seconds, a system dose of approximately 0.36 Gy per frame, and a total of 419 projections; for XperCT, rotational CBCT hepatic arteriography acquired during a single breath-hold for 10.4 seconds with 0.5° increment, 512×512 matrix in projections, total angle of 240° at approximately 24° per second, a system dose of approximately 0.36 Gy per frame, and a total of 624 projections. The projection data were transferred to the assigned workstation (Leonardo with DynaCT, Siemens; XtraVision with XperCT, Philips), and multiplanar reconstruction images with 1-mm section thickness and maximum intensity projection images were reconstructed. After obtaining CBCT hepatic arteriography, superselective TACE was performed without additional angiography in most of the cases because CBCT image alone could be enough to depict the tumour feeding arteries.[10]

Repeated treatment and follow-up

Follow-up examinations were conducted including laboratory tests (liver function test and blood test), and dynamic CT or MRI 6–8 weeks after treatment and then once every 2–3 months thereafter. Subsequent TACE or other treatments were additionally performed on an "on-demand" basis at 2- to 3-month intervals when a residual viable tumour or new lesion was observed during the follow-up assessment. The number of additional treatment after initial TACE during the study period was also analysed.

Assessment of therapeutic efficacy

In the per-patient analysis, the modified Response Evaluation Criteria in Solid Tumours (mRECIST) were used with radiological imaging to evaluate treatment response.[12] Considering there was <4 mm section thickness in all preprocedural CT/MRI, the nodules that were ≥0.8 cm in size and that had a typical HCC enhancement pattern (enhancement during the hepatic arterial phase and the washout during portal/delayed phase) were allocated to a target lesion up to a maximum of two lesions per patient. Atypical enhancing nodules that could be diagnosed as HCC using follow-up imaging studies were allocated as a non-target lesion. Assessment of tumour response was performed by two interventional radiologists (I.J.L. and J.H.L.), and any inconsistency in assessment results was resolved by discussion. The response was determined based on the change in the sum of the maximum diameters of target lesions, the overall change in non-target lesions, and the presence of a new lesion. The overall response was categorised as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and objective response (OR) was defined as CR plus PR. When PD was present, the cause of progression was categorised as local tumour progression (LTP), intrahepatic distant recurrence (IDR), and other causes (vascular invasion, lymph node metastasis, or distant metastasis). Based on this analysis, time to local progression (TTLP), time to intrahepatic distant recurrence, and time to progression (TTP) were generated. In the tumour response analysis, time was censored at the date of the patient's death without progression, last follow-up in patients who were lost to follow-up, and conversion to other treatment without progression. In the survival analysis, local progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS) was evaluated. The time of OS was defined as the interval between the initial TACE of HCC and death or last follow-up. Time was censored at the date of liver transplantation and the date of last follow-up in patients whose survival status could not be confirmed.

In the per-lesion analysis, time to target lesion progression was investigated. Size and location of the tumours were categorised and evaluated for subgroup analysis. Tumour location was defined as peripheral location (within 1 cm from liver margin) and otherwise, mid to central location. To evaluate the degree of selection and portal vein visualisation in TACE for the target lesions, all angiographic images in the TACE procedure were reviewed. The selectivity of tumour feeders at each TACE procedure was divided as lobar, sectional, segmental, subsegmental, and sub-subsegmental. Portal vein visualisation at spot radiography during chemoembolisation was graded as follows: 0 = not visualised, 1 = limited near the tumour, and 2 = whole or extended to the embolised area.[13]

Safety

All adverse events of chemoembolisation were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5). The presence of post-embolisation syndrome was assessed during the post-TACE hospital stay.[14] Serious adverse events were defined as any event resulting in death, any life-threatening consequences, persistent or significant disability/incapacity, unscheduled hospital visit, or prolongation of existing

hospitalisation. Prolongation of existing hospitalisation was defined as lasting >7 days. Laboratory test results at 1 month before the procedure and at 1 month after the procedure were analysed. For assessment of liver injury, clinical medical records and follow-up imaging studies were reviewed for the presence of liver abscess, bile duct dilatation, biloma, and liver infarction.[15] Bile duct dilatation was defined as present when it was visualised in segmental or wider distribution.

Statistical analysis

Categorical variables were reported in numbers and percentages, and continuous variables were reported in means and standard deviations. The patients were stratified by demographic variables, and comparisons between the two groups were performed using Fisher's exact test, chi-square test, or Student's t-test. Survival curves were analysed using the Kaplan–Meier method and were compared using the log-rank test. Univariate and multivariable Cox regression analyses were used to compare the treatment effects between the two groups adjusted for independent prognostic factors. All variables with $p<0.15$ in the univariate analysis were subjected to multivariable analysis. All statistical analysis was two-sided, and a difference was considered significant when $p<0.05$. All statistical analyses were performed using STATA 12.1 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics were balanced between the two groups, except for gender composition (Table 1). Size and location of the target lesions were not significantly different between the two groups (Table 2).

Table 2
Baseline characteristics of the target lesions.

Parameter	Angio-TACE (n=69)	CBCT-TACE (n=63)	p-Value
Tumour size (cm)	2.03±0.97	1.99±0.77	0.764
Tumour size			0.528
0.8–2 cm	38 (55.1)	36 (57.1)	
2.1–3 cm	20 (29)	21 (33.3)	
3.1–5 cm	11 (15.9)	6 (9.5)	
Tumour location			0.592
Peripheral	45 (65.2)	38 (60.3)	
Mid to central	24 (34.8)	25 (39.7)	

Values are presented as mean±standard deviation or n (%).
TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography.

Therapeutic efficacy: per-patient analysis

The tumour-response analysis of the patients is summarised in Table 3. After initial treatment, 52 of the 58 patients in the Angio-TACE group and 53 of the 55 in the CBCT-TACE group showed OR. At 36-month follow-up, CR was maintained in seven (13.5%) and 11 (25%) patients in the Angio- and CBCT-TACE groups, respectively. Forty-five (86.5%) patients in the Angio-TACE group and 33 (75%) in the CBCT-TACE group experienced PD at the 3-year follow-up. The most common causes of PD were LTP (23 patients, 51.1%) in the Angio-TACE group and IDR (20 patients, 60.6%) in the CBCT-TACE group. The TTLP was significantly longer in the CBCT-TACE group than in the Angio-TACE group (p=0.028; Fig 2a). The time to IDR was not significantly different between the two groups (p=0.996; Fig 2b). Although the median TTP was 14 months in the Angio-TACE group and 17 months in the CBCT-TACE group, the difference was not statistically significant (p=0.155; Fig 2c).

Thirty-eight (65.5%) patients in the Angio-TACE group and 22 (40%) in the CBCT-TACE group experienced LTP or death. The LPFS was significantly better in the CBCT-TACE group than in the Angio-TACE group (hazard ratio [HR],

Table 1
Baseline characteristics of the study patients.

Parameter	Angio-TACE (n=58)	CBCT-TACE (n=55)	p-Value
Age	60.02±11.11	60.53±9.75	0.796
Gender (male/female)	39 (67.2)/19 (32.8)	48 (87.3)/7 (12.7)	0.014
HBV surface antigen	44 (75.9)	38 (69.1)	0.420
Anti-HCV antibody	6 (10.3)	9 (16.4)	0.168
Serum albumin (g/dl)	3.96±0.44	4.00±0.59	0.644
Total bilirubin (mg/dl)	1.22±0.63	1.13±0.66	0.461
PT (INR)	1.18±0.15	1.20±0.21	0.528
Ascites (absent/present)	51 (87.9)/7 (12.1)	52 (94.5)/3 (5.5)	0.323
Portal hypertension (absent/present)	22 (37.9)/36 (62.1)	26 (47.3)/29 (52.7)	0.346
Child class (A/B)	51 (87.9)/7(12.1)	49 (89.1)/6(10.9)	1.000
Platelet (10^3/mm^3)	105.72±51.72	120.67±74.01	0.214
Creatinine (mg/dl)	0.95±0.13	0.90±0.21	0.147
AFP (≤200 ng/ml/>200 ng/ml)	48 (82.8)/10 (17.2)	50 (90.9)/5 (10.1)	0.201
Maximum tumours diameter (cm)	2.19±0.96	2.12±0.74	0.654
Number of tumours	1.40±0.65	1.47±0.72	0.554
Tumour multiplicity (single/multiple)	40 (69)/18 (31)	36 (65.5)/19 (34.5)	0.841
Tumour distribution (uni-lobar/bi-lobar)	50 (86.2)/8 (13.8)	48 (87.3)/7 (12.7)	1.000

Values are presented as mean±standard deviation or n (%).
TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography; PT (INR), prothrombin ratio (international normalised ratio); AST, aspartate transaminase; ALT, alanine transaminase.

Table 3
Tumour response analysis of the patients.

	Angio-TACE						CBCT-TACE					
	No. at risk	CR	OR	PD	Censored cases		No. at risk	CR	OR	PD	Censored cases	
					Treatment change	F/U loss					Treatment change	F/U loss
Best	58	46 (79.3)	52 (89.7)	2 (3.4)	—	—	55	45 (81.8)	53 (96.4)	2 (3.6)	—	—
Initial	58	38 (65.5)	49 (84.5)	2 (3.4)	—	—	55	42 (76.4)	53 (96.4)	2 (3.6)	—	—
6 M	54	28 (51.9)	33 (61.1)	19 (35.2)	4	0	45	37 (82.2)	40 (88.9)	5 (11.1)	6	4
12 M	53	24 (45.3)	25 (47.2)	27 (50.9)	5	0	45	26 (57.8)	26 (57.8)	19 (42.2)	6	4
18 M	52	16 (30.8)	16 (30.8)	36 (69.2)	5	1	44	17 (38.6)	17 (38.6)	27 (61.4)	6	5
24 M	52	12 (23.1)	12 (23.1)	40 (76.9)	5	1	44	15 (34.1)	15 (34.1)	29 (65.9)	6	5
36 M	52	7 (13.5)	7 (13.5)	45 (86.5)	5	1	44	11 (25)	11 (25)	33 (75)	6	5
Cause of PD	LTP: 23 (51.1) IDR: 15 (33.3), LTP&IDR: 5 (11.1), Other causes: metastasis in 2 (4.4)						LTP: 12 (36.4) IDR: 20 (60.6), LTP&IDR: 1 (3), Other causes: 0 (0)					

TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography; CR, complete response; OR, objective response; PD, progressive disease; F/U, follow-up; LT*p*=local tumour progression; IDR, intrahepatic distant recurrence.
Values are presented as n (%).

0.562; 95% confidence interval [CI], 0.331–0.954; log-rank p=0.029; Table 4, Fig 3a). Medial LPFS was 19.2 months in the Angio-TACE group and was not reached in the CBCT-TACE group. In multivariable analyses, CBCT guidance had a significantly lower risk of local progression or death (adjusted HR: 0.585; 95% CI, 0.344–0.995; p=0.048) after adjustment for maximum tumour size >2 cm and multiple tumours.

The PFS and OS were not significantly different between the Angio- and CBCT-TACE groups (55.5% versus 62%, 25.8%

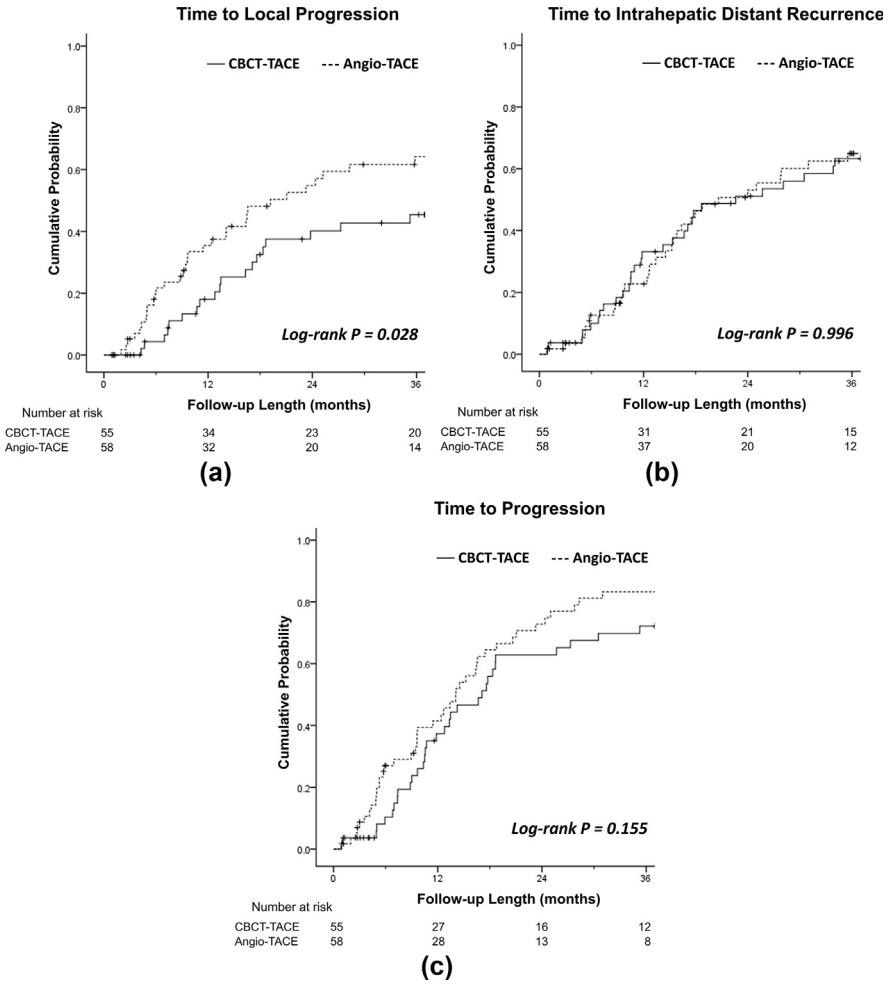

Figure 2 Therapeutic efficacy: (a) time to local progression; (b) time to intrahepatic distant recurrence; (c) time to progression.

Table 4
Univariate and multivariable analysis of prognostic factors for local tumour progression-free survival.

Parameter	Univariate analysis			Multivariable analysis		
	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Group (Angio- versus CBCT-TACE)	0.562	0.331–0.954	0.033	0.585	0.344–0.995	0.048
Age (≤60 versus >60)	0.693	0.417–1.154	0.159			
Gender (F versus M)	0.847	0.477–1.503	0.570			
HBsAg (absent versus present)	0.673	0.337–1.343	0.261			
Anti-HCV Ab (absent versus present)	1.007	0.457–2.218	0.986			
Serum albumin (>3.5 versus ≤3.5 mg/dl)	0.912	0.474–1.755	0.783			
Total bilirubin (≤2 versus >2.0 mg/dl)	1.523	0.690–3.360	0.298			
PT (INR; ≤1.2 versus >1.2)	0.686	0.404–1.165	0.163			
Ascites (absent versus present)	1.549	0.665–3.610	0.311			
Portal hypertension (absent versus present)	1.367	0.813–2.297	0.238			
Child class (A versus B)	1.432	0.704–2.913	0.322			
Platelet (10^3/mm^3)	0.998	0.993–1.002	0.377			
Creatinine (mg/dl)	0.699	0.171–2.856	0.619			
Portal hypertension (absent versus present)	1.367	0.813–2.297	0.238			
AFP (≤200 versus >200 ng/ml)	1.120	0.593–2.115	0.727			
Maximum tumour size (≤2 versus >2 cm)	1.873	1.117–3.139	0.017	2.209	1.290–3.781	0.004
Tumour multiplicity (single versus multiple)	1.793	1.067–3.015	0.028	2.128	1.239–3.655	0.006
Bi-lobar involvement (absent versus present)	1.307	0.660–2.587	0.443			

TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography; F, female; M, male; HBsAg, hepatitis B virus surface antigen; anti-HCV Ab, anti hepatitis C virus antibody; AFP, alpha-fetoprotein; PT (INR), prothrombin ratio (international normalised ratio).

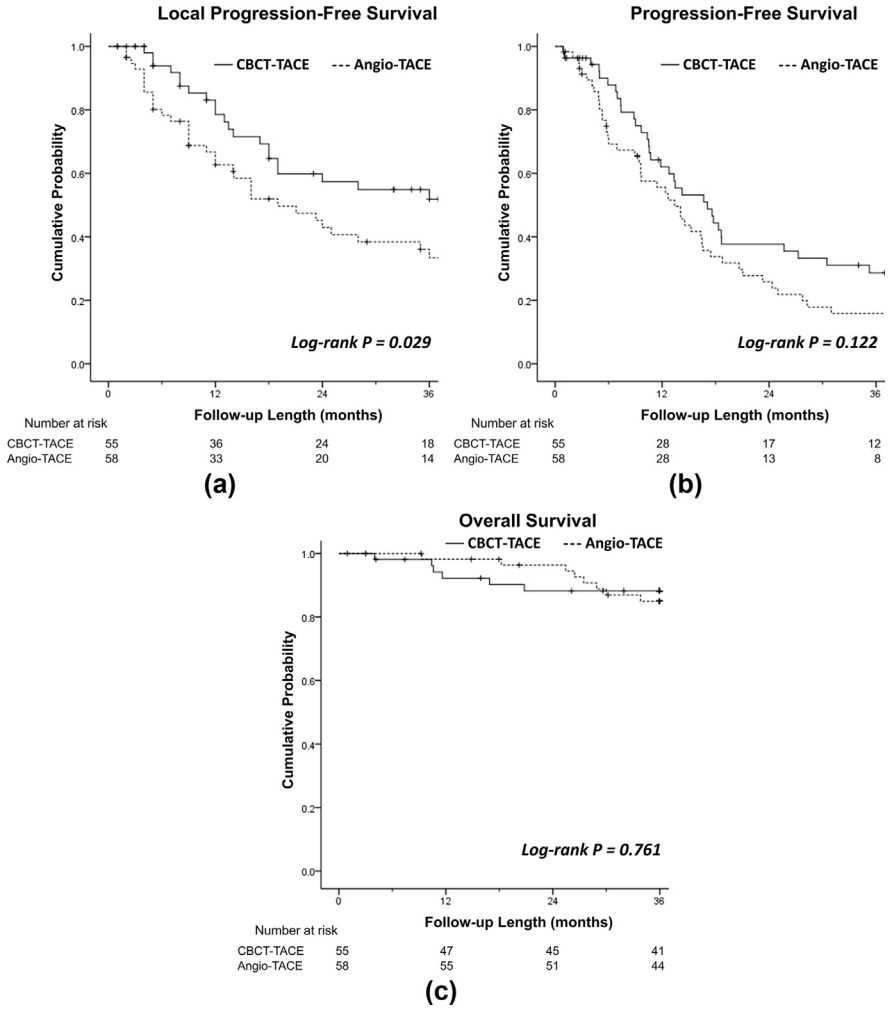

Figure 3 Survival analysis: (a) local progression-free survival; (b) progression free-survival; (c) overall survival.

versus 37.7%, and 15.9% versus 28.6% at 1, 2, and 3 years, respectively, p=0.122; 98.2% versus 92.2%, 96.4% versus 88.2%, and 85% versus 88.2% at 1, 2, and 3 years, respectively, p=0.761; Fig 3b and 3c).

Therapeutic efficacy: per-lesion analysis

Time to target lesion progression was significantly longer in the CBCT-TACE group than in the Angio-TACE group (p=0.003; Fig 4a). In the case of tumours in size ≤2 cm and with a peripheral location, the CBCT-TACE group showed significantly decreased tumour progression than the Angio-TACE group (p=0.002, and p=0.003, respectively; Fig. 4b–e).

TACE with subsegmental or sub-subsegmental fashion could be achieved in 59 of 63 tumours (93.6%) in the CBCT-TACE group, but in only 16 of 69 tumours (23.1%) in the Angio-TACE group (p<0.001; Table 5). The degree of portal vein visualisation after TACE was significantly higher in the CBCT-TACE group than in the Angio-TACE group (p<0.001).

Safety assessment

The incidence of adverse events is summarised in Table 6. Post-embolisation syndrome occurred less frequently in the CBCT-TACE group (p=0.002). There was no significant difference in hospital stay or unscheduled hospital visits between the two groups. In terms of laboratory toxicity after 1 month, serum aspartate aminotransferase and alanine aminotransferase levels increased more frequently in the CBCT-TACE group than in the Angio-TACE group (p=0.005 and p=0.007, respectively). Other laboratory findings and an increase in Child–Pugh score were not significantly different between the two groups. Bile duct dilatation was found in six patients (10.3 %) in the Angio-TACE group, and one patient (1.8%) in the CBCT-TACE group, but the difference was not statistically significant. No biloma formation or liver infarction was found in either group.

Additional treatment after first chemoembolisation

Seven patients in the Angio-TACE group and three patients in CBCT-TACE group underwent liver transplantation and were excluded from the analysis of additional treatment. The patients in the Angio-TACE group more frequently underwent additional treatments/chemoembolisation than those in the CBCT-TACE group (2.04±1.66 versus 1.44±1.27; 1.71±1.64 versus 0.88±1.08; p=0.043 and p=0.003, respectively; Table 7).

Discussion

In the present study, local tumour control for the patients with HCCs within the Milan criteria by TACE was improved after installing the CBCT system. Previous studies reported that selective TACE facilitated tumour necrosis and enhanced local tumour control.[16,17] Because CBCT identified tumour feeding arteries more effectively than conventional angiography, the CBCT-TACE group in the present study had an enhanced degree of selectivity of tumour feeder and peritumoural portal vein visualisation over the Angio-TACE group, which might contribute to longer LPFS.

The beneficial effect of CBCT-guided TACE was maximised in peripherally located or small tumours (≤2 cm). The diameter of the tumour feeding artery is significantly correlated with tumour size.[18] Because the feeding artery of small tumours is not yet hypertrophied and arterial flow to the tumour is not sufficiently developed, small tumours would be limited in the therapeutic effect of non-selective TACE. Moreover, it is difficult to identify fine tumour feeding arteries on angiography; however, if TACE is selectively performed through fine tumour feeding arteries as visualised on CBCT, it could be easier to achieve complete Lipiodol retention at the tumour and around the tumour with a safety margin similar to that achieved with a large tumour. In peripherally located tumours, high-grade wedge-shaped Lipiodol retention at the tumour and peritumoural portal veins can be more easily achieved by using an angiographic subsegmentectomy technique through the tumour feeding artery compared with centrally located tumours,[19] which can reduce local tumour recurrence.[13,20]

The OS and PFS were not significantly different between the two groups. IDR, vascular invasion, and metastasis were almost identical between the two groups, and the impact of the difference in local tumour control was diluted. When tumour recurrence was detected, additional treatment with multidisciplinary approaches was also performed, which might improve overall survival of patients.[21,22] Moreover, the present study involved only patients with HCC within the Milan criteria, well-preserve liver function, and without severe chronic comorbidities. As a result, 3-year OS exceeded 80% in both groups, which is comparable to outcome of surgical resection or TACE plus RFA.[23] Therefore, the number of deaths might have been too small to show a statistical difference.

CBCT-guided TACE caused significantly less post-embolisation syndrome including abdominal pain, nausea, and vomiting. This is possibly because as more sub-subsegmental TACE was available on the guidance of CBCT, incidental infusion to normal parenchyma or an adjacent organ such as gallbladder could be minimised.[14] Although an increase in the level of aspartate transaminase/alanine transaminase, which suggested acute liver injury, was more frequently observed in the CBCT-TACE group, other laboratory results regarding liver function were not significantly different. The frequency of the increase in Child–Pugh score was nearly identical between both groups. Although a stronger ischaemic attack by more selective catheterisation was applied to the tumours and adjacent peritumoural liver tissue, liver function was not as significantly decreased because CBCT-guided TACE could restrict the area that suffered from ischaemic injury.

The need for additional treatment after initial TACE was significantly decreased in the CBCT-TACE group compared with the Angio-TACE group, probably because of improvement in local tumour control through the use of CBCT. This suggested the strength of Therefore CBCT-guided chemoembolisation is cost-effective in terms of treatment and life

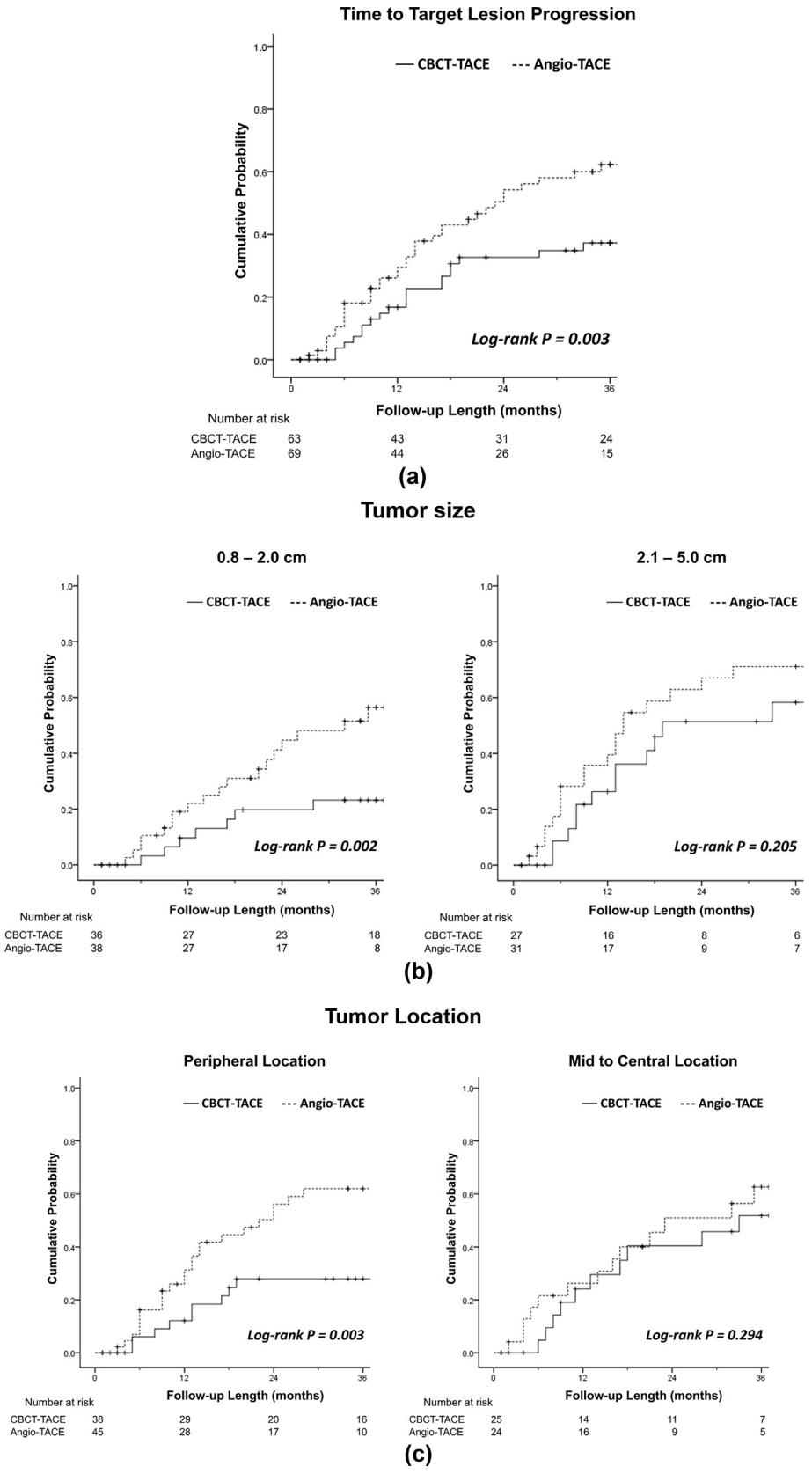

Figure 4 Time to progression of the target lesions: (a) total; (b) 0.8–2 cm tumours; (c) 2.1–5 cm; (d) peripheral located tumours; (e), mid to centrally located tumours.

Table 5
Details of chemoembolisation procedures for target lesions.

Parameter	Angio-TACE (n=69)	CBCT-TACE (n=63)	p-Value
Selectivity of tumour feeder			< 0.001
Lobar	4 (5.8)	0 (0)	
Sectional	10 (14.5)	1 (1.6)	
Segmental	39 (56.5)	3 (4.8)	
Subsegmental	13 (18.8)	14 (22.2)	
Superselective	3 (4.3)	45 (71.4)	
Portal vein uptake			< 0.001
Grade 0	15 (21.7)	6 (9.5)	
Grade 1	40 (58)	16 (25.4)	
Grade 2	14 (20.3)	41 (65.1)	

Values are presented as n (%).
TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography.

Table 7
Additional treatment after first treatment.

Parameters	Angio-TACE (n=51)	CBCT-TACE (n=52)	p-Value
No. of additional treatments			
Mean±SD	2.04±1.66	1.44±1.27	0.043
0	7 (13.7)	15 (28.8)	
1	17 (33.3)	14 (26.9)	
2	11 (21.6)	12 (23.1)	
3	6 (11.8)	8 (15.4)	
≥4	10 (19.6)	3 (5.8)	
No. of additional TACE			
Mean±SD	1.71±1.64	0.88±1.08	0.003
0	13 (25.5)	26 (50)	
1	15 (29.4)	13 (25)	
2	9 (17.6)	6 (11.5)	
3	7 (13.7)	7 (13.5)	
≥4	7 (13.7)	0 (0)	

Seven patients in the Angio-TACE group and three patients in the CBCT-TACE group underwent liver transplantation and were excluded from this analysis.
Values in parentheses are percentages.
TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography.

quality of patients by reducing the number of readmissions.[24] Even locoregional therapy can gradually deteriorate normal liver parenchyma; therefore, decreasing LTP by CBCT-TACE is potentially advantageous for the preservation of liver function.

This study has some limitations. First, the investigation was a retrospective study, which could not avoid a selection bias; however, baseline demographics of the two groups were well balanced, and some bias could be solved with the multivariable Cox proportional hazards model. Second, there might be a chance that some patients in the Angio-TACE group might undergo additional TACE using CBCT during the follow-up period. To minimise this bias, a 1-year period of discontinuation was set between the enrolment point of both groups. Third, tumour-response evaluation was performed retrospectively. When tumour recurrence was detected, previous follow-up images were sought to search for the beginning of the tumour recurrence. Because this process was more sensitive than the usual clinical situation, TTP in this study was shorter than the real time point for additional treatment in many cases. Fourth, there was difficulty in determining whether tumour recurrence was present near the Lipiodolised lesion followed by CT rather than MRI. In this case, tumour recurrence was evaluated in consensus referring to a serial review of the follow-up images (CT or MRI).

In conclusion, CBCT-guided TACE could improve local tumour control for HCC within the Milan criteria and showed fewer cases of post-embolisation syndrome.

Table 6
Adverse events and toxicities according to the treatment group.

Parameter	Angio-TACE (n=58)	CBCT-TACE (n=55)	p-Value
Post-embolisation syndrome	41 (64.1)	23 (35.9)	0.002
Fever	12 (20.7)	11 (20)	1.000
Nausea	30 (51.7)	5 (9.1)	<0.001
Vomiting	14 (24.1)	0 (0)	<0.001
Anorexia	9 (15.5)	3 (5.5)	0.126
Abdominal pain	32 (55.2)	17 (30.9)	0.009
Hospitalisation (days)	2.31±2.07[a]	2.33±1.38[a]	0.959
Prolonged hospitalisation (>7 days)	2 (3.4)	0 (0)	0.495
Unscheduled hospital visit	1 (1.7)	1 (1.8)	1.000
Increased Child–Pugh score after 1 month	6 (10.3)	5 (9.1)	1.000
Laboratory toxicity after 1 month			
PT (INR; grade 0/1/2)	45/11/2 (77.6/18.9/3.5)	37/13/5 (67.3/23.6/9.1)	0.340
Albumin (grade 0/1/2)	25/33/0 (43.1/56.9/0)	12/41/2 (21.8/74.5/3.7)	0.502
Total bilirubin (grade 0/1/2)	50/2/6 (86.2/3.5/10.3)	41/9/5 (74.5/16.3/9.2)	0.068
AST (grade 0/1/2/3)	32/10/5/11 (55.2/17.3/8.6/18.9)	13/16/12/14 (23.6/29.1/21.8/25.5)	0.005
ALT (grade 0/1/2/3)	34/9/5/10 (58.7/15.5/8.6/17.2)	16/22/6/11 (29.0/40/10.0/20)	0.007
Bile duct dilatation	6 (10.3)	1 (1.8)	0.060

Values in parentheses are percentages.
TACE, transarterial chemoembolisation; CBCT, cone-beam computed tomography; PT (INR), prothrombin ratio (international normalised ratio); AST, aspartate transaminase; ALT, alanine transaminase.
[a] Values are mean±SD.

Conflict of interest

J.-W.P. received lecture fees from Bayer Healthcare, Eisai, and Ono-BMS; serves as a consultant to Ono-BMS, Eisai, Midatech, Roche, Bayer Healthcare, Cue, and Genetech. Otherwise all other authors including corresponding author state that there is no conflict of interests.

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