research article

Safety and efficacy of drug-eluting microspheres chemoembolization under cone beam computed tomography control in patients with early and intermediate stage hepatocellular carcinoma

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Background. Drug-eluting microsphere transarterial chemoembolization (DEM-TACE) is the standard of care in patients with intermediate-stage hepatocellular carcinoma and ensures targeted and controlled cytotoxic and ischemic effects. Proper patient selection and optimized treatment techniques are associated with longer median survival. The aim of this single-institution retrospective study was to evaluate safety and efficacy of DEM-TACE under cone beam computed tomography (CBCT) control in patients with early and intermediate stage hepatocellular carcinoma.

Patients and methods. A total of 144 patients (mean age 67.9 ± 8.0 years, 127 males and 17 females) between February 2010 and December 2018 were studied. Microparticles of different dimensions according to two manufacturers (diameter of 70–150 μm, 100–300 μm or 300–500 μm and 40-μm, 75-μm or 100-μm) were used and loaded with 50–150 mg of doxorubicin. The objective tumour response according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST), the time to progression, adverse events and overall survival were (OS) evaluated.

Results. In total, 452 procedures were performed (median, 3 per patient). Four (0.9% of all procedures) major complications were noted. Postembolization syndrome occurred after 35% of procedures. At the first imaging follow-up 2–3 months after first treatment, 91% of patients achieved an objective response. The median time to progression was 10.2 months (95% CI: 8.3-12.1 months). OS rates at 1, 2, 3, 4, and 5 years were 85%, 53%, 33%, 20% and 14%, respectively. The median survival time was 25.8 months (95% CI: 22.1–29.5 months).

Conclusions. DEM-TACE under CBCT control in patients with early and intermediate stage hepatocellular carcinoma is a safe and effective method of treatment with high objective tumour response and survival rates.

Key words: hepatocellular carcinoma; drug-eluting microspheres; doxorubicin; transarterial chemoembolization; cone beam computed tomography; safety; efficacy

Introduction

Hepatocellular carcinoma (HCC) accounts for most primary liver tumours and is the fourth most common cause of cancer-related death in the world.[1] The prognosis of the disease correlates strongly with liver function (defined by Child-Pugh's class, bilirubin, albumin, clinically relevant portal hyper-

tension, ascites), tumour status (defined by number and size of nodules, presence of vascular invasion, extrahepatic spread) and general tumour-related health status.[2] The Barcelona Clinic of Liver Cancer (BCLC) staging system divides patients into five groups to facilitate treatment selection and prognosis prediction.[2] According to the guidelines of the European Association for the Study of the Liver (EASL) and the European Society of Medical Oncology (ESMO), transarterial chemoembolization (TACE) is the standard treatment for HCC in patients with intermediate-stage disease, *i.e.*, BCLC stage B.[2,3] Furthermore, a clinical situation known as "treatment stage migration" has been introduced since not all patients with early-stage disease can be treated with surgery or ablation but may benefit from TACE.[4] The intention of treatment stage migration is to offer the next most suitable option within the same stage or the next prognostic stage to patients who do not respond to the recommended treatment or do not qualify for it, thus improving their outcomes.[4–6]

The principle of TACE is selective delivery of a high local concentration of a chemotherapeutic drug mixed with embolic material, which results in strong cytotoxic and ischemic effects.[2] Two techniques are currently recommended: conventional TACE (cTACE) and drug-eluting microsphere transarterial chemoembolization (DEM-TACE).[2,3] Conventional TACE (cTACE) uses a mixture of Lipiodol and chemotherapeutics, while DEM-TACE uses microparticles that can be loaded with a chemotherapeutic drug that is released in the target tissue slowly and in a controlled manner. The most frequently used drug in DEM-TACE is doxorubicin.[7]

Untreated patients with BCLC stage B disease have a median OS of 10 to 16 months after HCC diagnosis.[2,8] The median OS for patients treated with TACE is approximately 20 months after treatment initiation.[5,9] In well-selected patients, median OS can be prolonged to 30–50 months.[2,3] A difference in OS between patients treated with doxorubicin-loaded DEM-TACE and those treated with cTACE has not been observed.[10,11]

A further improvement in TACE was the introduction of cone beam CT (CBCT) control during the procedure. CBCT is mounted on a C-arm fluoroscopy unit in the Institute of Radiology suite, allowing enhanced visibility in soft-tissue and vascular procedures. CBCT enables more precise implementation of TACE from planning to microcatheter positioning, which ensures visualization of the tumour-feeding vessels and parenchymal staining during TACE, achieving a detection accuracy significantly superior to that of standard 2D angiography.[12,13]

The aim of this single-institution retrospective study was to evaluate the safety and effectiveness of doxorubicin drug-eluting microsphere chemoembolization under CBCT control in patients with early and intermediate stage HCC.

Patients and methods

Patient selection

The present retrospective study included 144 patients with early and intermediate stage HCC who underwent doxorubicin-loaded DEM-TACE at our interventional oncology centre between February 2010 and December 2018. The last date for follow-up evaluation was 31 January 2020. Clinical examination, laboratory tests and contrast-enhanced four-phase computed tomography (CT) or magnetic resonance (MR) imaging with hepatobiliary contrast media (Primovist; Bayer HealthCare, Germany) were performed for each patient at baseline. A decision in favour of treatment with doxorubicin-loaded DEM-TACE was reached by consensus at a multidisciplinary hepatopancreatobilliary tumour board (MTB) at our institution, consisting of abdominal and interventional radiologist, gastroenterologist, hepatic surgeon, nuclear medicine physician, oncologist, and pathologist. The inclusion and exclusion criteria for the study are presented in Table 1.

Written informed consent for the procedure was obtained from all patients before each treatment. The need for informed consent for publication was waived by the national ethics committee due to the retrospective, anonymized study design. The study was performed in accordance with the Helsinki Declaration ethical standards for biomedical studies on humans and was approved by the Republic of Slovenia National Medical Ethics Committee on the 18th of April 2017 (decision number 60/04/17). All data were collected from patient charts held at the Clinical Institute of Radiology, Clinical Department of Gastroenterology and Clinical Department of Abdominal Surgery at University Medical Centre Ljubljana.

Treatment

The first treatment cycle was defined by at least two doxorubicin-loaded DEM-TACE procedures at intervals of 4–6 weeks (*i.e.* TACE 1a and 1b).

Additional procedures prior to the first dynamic contrast enhanced CT or MR evaluation were performed if the multifocality of the disease did not allow complete targeting of the tumours. All procedures were carried out under CBCT control (using Allura Xper FD20; Philips Healthcare and Artis Zee floor with DynaCT; Siemens, Forchheim, Germany). Typically, a 2.4-French microcatheter (Progreat®, Terumo Europe N. V, Belgium) was advanced into either a subsegmental or a segmental tumour-feeding artery depending on the location of the targeted tumour. CBCT was performed with the administration of a nonionic contrast agent (Ultravist 370®, Bayer HealthCare, Germany; Visipaque 320, GE Healthtcare, Norway) through a power injector (Avanta®, Medrad, Bayer HealthCare, Germany). The injection rate for the initial lesion visualization with catheter placed in main hepatic artery was typically 1 mL/s with a total injected volume of contrast agent of 10 mL and a delay time of 8–10 seconds.[13] For each CBCT scan, the area of interest was positioned in the system isocenter, and, over approximately 10 seconds, 310–321 projection images were acquired with the motorized C-arm. X-ray parameters of 51–120 kV and 101–125 mA, covering approximately 180–200° clockwise arc at a rotation speed of 20° per second were used. Multiple two-dimensional projections were acquired and reconstructed by using Feldkamp algorithm to generate three-dimensional volumetric images. The matrix size was 512 x 512, and the field of view (FOV) 38 x 38 cm.

Selective or superselective chemoembolization was performed with microparticles with varying diameters from different manufacturers loaded with 50–150 mg of doxorubicin: DC Beads (DC Bead®, Boston Scientific, Marlborough, Massachusetts) with a diameter of 70–150 μm, 100–300 μm or 300–500 μm; Tandem (Tandem®, Boston Scientific, Marlborough, Massachusetts) 2 ml or 3 ml of 40-μm, 75-μm and 100-μm, LifePearl microspheres (LifePearl®, Terumo Europe N. V, Belgium). The same size of the microparticles were then used for the following procedures in each patient. Since 2013, we have been using small microparticles (*i.e.* 70–150 μm) in all patients.

In patients with multifocal tumours, the position of the microcatheter was changed within the same session to ensure superselective delivery to each lesion.[13] Prior to microparticle delivery, CBCT was repeated to confirm the catheter position in feeding artery and complete coverage of the targeted lesions.

TABLE 1. Inclusion and exclusion criteria (Child-Pugh; CP)

Inclusion criteria	early-stage HCC patients ineligible for resection, transplantation or ablation; intermediate-stage HCC patients with a CP score of A or B (up to 7 points); treatment with DEM-TACE under cone beam CT control.
Exclusion criteria	DEM-TACE prior to liver transplantation; inability of regular follow-up.

DEM-TACE = drug-eluting microsphere transarterial chemoembolization; HCC = hepatocellular carcinoma

Treatment complications

Procedure-related complications were classified as complications occurring during the procedure or complications detected up to 1 month after the procedure. The complications were classified as minor and major according to the CIRSE Quality-Improvement Guidelines for Hepatic Transarterial Chemoembolization.[14] Postembolization syndrome (PES) was defined as fever, pain, nausea, elevation of liver transaminases (*i.e.* doubling of baseline value of aspartate aminotransferase (AST)) and an increased white blood cell (WBC) count that occur 24–72 hours after the procedure and was not considered a complication in accordance with the CIRSE guidelines.

Treatment response

Tumour treatment responses were evaluated with dynamic contrast-enhanced CT or dynamic MR imaging with hepatobiliary contrast media 2–3 months after the last doxorubicin-loaded DEM-TACE procedure according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST).[15] Patients with a complete response or a partial response were classified as having an objective response to treatment. In cases of an objective response to treatment, a radiological follow-up was performed every 3 months for the first 2 years, mostly with MRI of the liver. If no progression occurred after 2 years, follow-up imaging was then scheduled every 6 months. Doxorubicin-loaded DEM-TACE treatment was repeated when necessary in patients with residual or additional tumours observed on imaging, *i.e.* retreatment "on demand".[13] A decision for retreatment was again reached by MTB.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were

TABLE 2. Patient characteristics at baseline

Gender, number of patients (%)	
Male/Female	127 (88.2)/17 (11.8)
Age, years	
Mean ± SD	67.9 ± 8
Imaging characteristics	
Number of lesions per patient, median (range)	3 (1–10)
Bilobar, n. (%)	52 (36.1)
Unilobar, n. (%)	92 (63.9)
Right lobe, n. (%)	71 (49.3)
Left lobe, n. (%)	21 (14.6)
Signs of portal hypertension, n. (%)	
Yes/No	76 (52.8)/68 (47.2)
Ascites, n. (%)	
Yes/No	34 (23.6)/110 (76.4)
Cirrhosis, n. (%)	
Yes/No	120 (83.3)/24 (16.7)
Cirrhosis aetiology, n. (%)	
Alcohol	63 (52.5)
HBV	16 (13.3)
HCV	14 (11.6)
Primary biliary cirrhosis	2 (1.8)
Other	25 (20.8)
Child-Pugh score (avg. points ± SD)	5.7 ± 0.8
Child-Pugh class, n. (%)	
A/B	91 (75.8)/29 (24.2)
Barcelona Clinic of Liver Cancer stage, n. (%)	
A/B	50(34.7)/94 (65.3)
Laboratory characteristics, median (range)	
Albumin, [g/l]	39.5 (28–50)
Total bilirubin, [µmol/l]	18 (5–83)
AFP, [ng/ml]	14.4 (1.1–12809.8)
AST, [µkat/l]	0.82 (0.35–3.29)
GGT, [µkat/l]	1.77 (0.25–24.95)
Creatinine, [µmol/l]	78 (39.0–148.0)

AFP = alpha fetoprotein; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase); HBV = hepatitis B virus; HCV = hepatitis C virus; SD = standard deviation

expressed as the mean ± standard deviation or the median and range in case of skewed distributions. Survival rates and the time to progression (TTP) were calculated using the Kaplan–Meier method and compared using the log rank test. The limit of statistical significance was set at $p < 0.05$.

The follow-up time was determined as the number of months from the first doxorubicin-loaded DEM-TACE procedure until death or until 31 January 2020. The time to progression was calculated as the time until the date of imaging control showing progression or, in censored cases, until 31 January 2020, or patient death.

The analysis was performed using IBM® SPSS® Statistics 22 (International Business Machines Corp., Armonk, NY) for Windows.

Results

Patient characteristics

The baseline demographic, clinical, laboratory and imaging characteristics of 144 patients included in the analysis are summarized in Table 2. The mean patient age was 67.9 ± 8.0 years, and most patients were male (88.2%). The median number of lesions per patient was 3 (range, 1–10), and the median size of the largest lesion was 3.8 cm. Ninety-one patients were classified as Child-Pugh class A (75.8%), and the remaining 29 were classified as class B (24.2%). Twenty-four of the 144 (16.7%) patients were not cirrhotic. The most common aetiology of cirrhosis was alcohol abuse (52.5%, n = 63), followed by other (20.8%, n = 25), hepatitis B (13.3%, n = 16) and hepatitis C (11.6%, n = 14). Ninety-two (63.9%) patients had unilobar, predominantly right lobe, disease. Clinical signs of portal hypertension were observed in 76 (52.8%) patients, and ascites was observed in 34 (23.6%) patients. Sixty-eight of 101 (67.3%) patients with available AFP data had an elevated AFP level (> 7.5 ng/mL).

Procedure

Overall, 452 doxorubicin-loaded DEM-TACE procedures were performed in 144 patients. The median number of procedures per patient was 3 (range, 1–8). In 136 (94.4%) patients, at least two doxorubicin-loaded DEM-TACE procedures were performed. The remaining 8 (5.6%) patients had only one procedure at the time of their follow-up. Large microparticles (300–500 µm) were used in 16% of patients (n = 23), intermediate-size microparticles (100–300 µm) in 19.4% of patients (n = 28) and small microparticles (40–100 µm) in 64.6% of patients (n = 93) in the first doxorubicin-loaded DEM-TACE procedure. The maximum cumulative dose of doxorubicin per procedure was 150 mg (range 50–150 mg). Doxorubicin-loaded DEM-TACE was the primary treatment for 120 patients

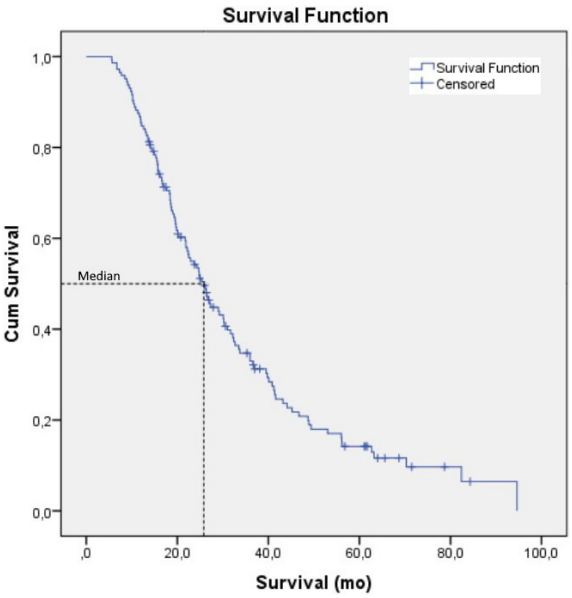

FIGURE 1. Kaplan-Meier curve of overall survival (entire study population).

(83.0%). Other treatments for HCC preceding the first doxorubicin-loaded DEM-TACE are presented in Table 3.

Procedure complications

PES occurred in 158 procedures (35.0%). All PES cases were managed medically and did not prolong hospitalization. In addition to PES, eleven (2.4% of all procedures) minor complications occurred and are presented in Table 4. Gastric erosions in symptomatic patients were detected by gastroscopy and treated medically. Intraprocedural small arterial branch rupture was immediately successfully treated with coil embolization.

Four (0.9% of all procedures) major complications were noted: ischemic cerebrovascular insult to the cerebellum, radial artery thrombosis following a transradial approach, variceal bleeding resulting from emesis after the procedure and infection of the necrotic tumour, which resolved after antibiotic treatment.

Overall survival

After a median follow-up of 23.8 months (range, 5.6–94.6), 115 patients had died. The one-, two-, three-, four- and five-year survival rates were 85%, 53%, 33%, 20% and 14%, respectively (Figure 1). The median OS was 25.8 months (95% CI: 22.1–29.5 months).

TABLE 3. Hepatocellular carcinoma (HCC) treatment prior to initial doxorubicin-loaded drug-eluting microsphere transarterial chemoembolization (DEM-TACE)

Treatment	Number of patients (%)
No previous treatment	120 (83.0)
cTACE	2 (1.4)
Surgical resection	13 (9.3)
Transplantation	1 (0.7)
Surgical resection and RFA	1 (0.7)
Surgical resection and cTACE	1 (0.7)
RFA	2 (1.4)
MWA	1 (0.7)
ECT	3 (2.1)

cTACE = conventional TACE; ECT = electrochemotherapy; MWA = microwave ablation; RFA = radiofrequency ablation

TABLE 4. Minor complications after drug-eluting microsphere transarterial chemoembolization (DEM-TACE) in the study population

Complications	Number of procedures (%)
Chest pain	4 (0.9)
Pain in the right shoulder	1 (0.2)
Hematoma at the puncture site	3 (0.7)
Gastric erosions	2 (0.4)
Intraprocedural small arterial branch rupture	1 (0.2)

Child-Pugh class, ascites and portal hypertension showed statistically significant differences with respect to OS on univariate analysis (Table 5) ($p = 0.008$; $p = 0.001$; $p = 0.016$).

No statistically significant difference was observed between unilobar and bilobar disease ($p = 0.609$).

Treatment response and time to progression

An objective response was achieved in 131 (91%) of 144 patients at the first dynamic contrast enhanced imaging follow-up. A complete response was achieved in 72 of 131 patients (55.0%) patients, and a partial response was achieved in 59 (45.0%) patients.

Progression was observed at the first imaging follow-up in 13 of 144 patients. Eight patients had target lesion progression, 3 patients had a new

TABLE 5. Overall survival after DEM-TACE in the study population Senči polja med vrsticami

Factor	Number of patients	Median survival	95% CI	*p* value
Child-Pugh A	91	26.6	17.7–35.5	0.008
Child-Pugh B	29	19.6	18.4–20.8	
Portal hypertension	76	20.2	14.7–25.7	0.001
No portal hypertension	68	32.4	24.0–40.8	
Ascites	34	19.6	15.3–23.9	0.016
No ascites	110	29	23.0–35.0	
Unilobar disease	92	24.9	21.0–28.8	0.609
Bilobar disease	52	26.3	21.5–31.1	

intrahepatic lesion, and 2 developed extrahepatic lesions. Further decisions were based on clinical evaluations, laboratory values and imaging data. Patients with target lesion progression were further treated with doxorubicin-loaded DEM-TACE (37.5%, n = 3) or systemic chemotherapy (25%, n = 2) or received best supportive care (37.5%, n = 3). Patients with new intrahepatic lesions were further treated with doxorubicin-loaded DEM-TACE (n = 1), systemic chemotherapy (n = 1), or both (n = 1). Both patients with extrahepatic lesions received systemic chemotherapy.

During the follow-up, progression was observed in 115 patients (79.9%). Of these, 27 patients (23.5%) had target lesion progression. The median time to progression was 10.2 months (95% CI: 8.3–12.1 months). Overall, further HCC treatment after progression was performed in 93 patients. Doxorubicin-loaded DEM-TACE was performed in 66 patients, MWA in 2 patients and both in 1 patient. Twenty-one patients were treated with systemic therapy alone, and 3 were treated with systemic therapy and doxorubicin-loaded DEM-TACE. The remaining 22 patients received best supportive care.

Discussion

The purpose of this retrospective study was to evaluate the safety and effectiveness of DEM-TACE in patients with early and intermediate stage HCC. TACE is the standard of care for HCC patients with intermediate-stage disease. Moreover, for patients who are ineligible for surgical resection or percutaneous ablation, TACE is also considered a first-line treatment option in the early stage.[16,17] However, intermediate HCC corresponds to a highly heterogeneous group of patients with significant variations in number and size of tumour, patient performance status and liver function, resulting in variable survival rates.[18] The median OS for patients treated with TACE is reported to range from approximately 19 months to 40–50 months in well-selected patients[2,3,9], which is consistent with our results. The median OS in our study was 25.8 months, with a range from 5.6 months to more than 7 years. A multicentric study by Han *et al*. in 2019 showed a median OS of 19.9 months with a range from 7 months to more than 4 years.[19] A study by Burrel *et al.* showed that the median OS can be prolonged up to 48.6 months with careful patient selection.[4] Several prognostic factors, such as Child Pugh class and tumour number, have been linked to higher survival rates and can be used to select ideal candidates for TACE.[19,20] The Child Pugh score is a valuable tool for assessing liver function, and our results support its correlation with survival. However, this score does not consider some events that may indicate end-stage liver disease (*e.g.*, renal failure, spontaneous bacterial peritonitis, hyponatremia, recurrent encephalopathy, and malnutrition) and may be replaced by other selection criteria in the future.[16] Another factor that may lead to better survival rates in some studies is treatment stage migration, as the survival of BCLC-A patients is expected to be better than that of BCLC-B patients.[6] Treatment stage migration also applies to BCLC stage B. Although most patients achieve an objective response after treatment, they can present with new tumour sites during their follow-up and thus qualify as having disease progression. Intrahepatic treatable progression can be treated with repeat TACE. On the other hand, the untreatable progression may necessitate initiation of systemic therapy. In this study, migration to systemic therapy was recorded in 24 patients.

Higher OS may be related to the high objective response rates achievable with TACE, which is supported by the fact that an objective response to treatment measured by mRECIST correlates with prolonged OS.[21,22] According to the European Association for the Study of the Liver mRECIST represents the gold standard for radiologically evaluating tumour response during HCC locoregional treatment.[2] Previously used EASL criteria express the change in the two dimensions of hyperenhancing tumour and therefore also reflect the extent of necrosis caused by the treatment. mRECIST criteria adopted a single long-axis measurement and are simplified objective measure of treatment response, especially with the use of su-

perselective approach where little or no viable tumour is expected. An objective response to TACE is achieved in approximately 50% of patients, with the lowest rate reported to be approximately 16% and the highest reported to be approximately 85.6%.[16,17,23] A prospective, randomized phase II study comparing doxorubicin-loaded DEM-TACE with cTACE showed higher objective response rates in the doxorubicin-loaded DEM-TACE group – 51.6% *vs*. 43.5%, respectively.[11] In a study by Suk *et al*. assessing CBCT after doxorubicin-loaded DEM-TACE, an objective response was achieved in 85.6% of patients (63.8% complete response, 21.8% partial response).[23] Our results exceed those of the above studies, showing a 91% rate of an objective response defined according to the mRECIST.

The benefits of CBCT for intra-arterial liver procedures are now well established and documented. The detection accuracy of CBCT for HCC lesions is equivalent to those of multidetector CT and MRI and superior to that of angiography. CBCT is the most accurate imaging technique to identify tumour-feeding arteries and can be used to rule out nontarget embolization of nontumour-feeding extrahepatic arteries. These advantages of CBCT can result in better treatment efficacy of DEM-TACE and other intra-arterial therapies.[13]

DEM-TACE has been demonstrated to result in fewer complications than cTACE.[24] In a systematic review of cTACE by Lencioni *et al*., 274 articles with a total of 34,137 patients were analyzed and adverse events were observed in 15,351 patients in a total of 217 selected studies.[9] The most common procedure-related complication was PES, with the incidence of 47.7%. Other studies describe an even higher incidence of PES, with an estimated rate of 48%.[9] According to the CIRSE guidelines, PES by itself is considered an expected outcome of the procedure rather than a complication.[14,25] Procedural complications, including intraprocedural small arterial branch rupture, hematoma at the puncture site, cerebellar stroke and radial artery thrombosis following a transradial approach, occurred in 1.1% of our cases. Eosophageal variceal bleeding was managed with endoscopic variceal banding. To our knowledge there is no known mechanism through which TACE could facilitate variceal bleeding. Since the bleeding occurred only once in otherwise large cohort of patients with high risk for variceal bleeding, we believe that this was probably a coincidental event. Other complications are all recognized although extremely rare following TACE procedures and all of them were one-time events.[26-28] Intraprocedural small arterial branch rupture was managed with endovascular coil embolization and this complication didn't prolong the patient's hospital stay. Ischemic stroke is an extremely rare, but recognized event.[27] A recent literature review describes twelve cases in patients undergoing DEB-TACE or cTACE with mechanisms including intrahepatic arteriovenous shunts, hepatopulmonary shunts and intracardiac shunts. The presence of arteriovenous shunting to hepatic or pulmonary veins is routinely checked for at intraprocedural angiography and is a well-known contraindication to performing TACE, while checking for intracardiac shunts is not routinely performed in these patients. The patient in our cohort had a cerebellar stroke, which occurred after the procedure being performed via the right internal mamarian artery. Due to the cerebellar location, we hypothesize this non-target embolization was the result of the reflux of the embolic agent into the vertebral artery. In our patient the symptoms of ischemic insult resolved spontaneously, and no specific treatment was applied. Thrombosis of the radial artery was a result of transradial approach in a patient with a severe stenosis of iliac arteries preventing transfemoral approach. Radial artery occlusion is not a TACE specific complication and it occurs in 1 – 10% of patients following transradial interventions with lower numbers of complications occurring in experienced centers.[26] Our patient was managed conservatively while hospitalized but was then lost to angiological follow-up.

Our study has some limitations. This was a retrospective study including only a limited number of patients and no control group. A standard treatment methodology and patient selection criteria for TACE are lacking due to the heterogeneity of the HCC patient population with BCLC stages A and B. Therefore, patient selection should be carefully considered to achieve the best outcomes. Subsequent studies should include a larger group of patients. Other medical centres should also be included since the results of this single-centre study may not be applicable to other centres and geographic regions. Furthermore, although four interventional radiologists performed DEM-TACE according to uniform protocols, minor variations, such as in catheterization selectivity, were inevitable. Finally, the treatment effect of DEM-TACE may also be significantly influenced by multimodality treatment; thus, the long-term outcomes might not be representative.

In conclusion, DEM-TACE under CBCT control in patients with early and intermediate stage HCC is a safe and effective method of care. The results

of this study are consistent with that in our study from 2016, confirming that proper patient selection, routine utilization of CBCT control for superselective TACE guidance, regular treatment response evaluation and liver function tests, together with retreatment "on demand" results in high objective tumour response and survival rates.

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