Original article

Standardization of conventional chemoembolization for hepatocellular carcinoma

Matteo Renzulli [a,*], Giuliano Peta [a], Francesco Vasuri [b], Giovanni Marasco [c], Daniele Caretti [d], Laura Bartalena [a], Daniele Spinelli [a], Emanuela Giampalma [e], Antonietta D'Errico [b], Rita Golfieri [a]

[a] Department of Radiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna, Italy
[b] Pathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna, Italy
[c] Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna, Italy
[d] "Toso Montanari" Industrial Chemistry Department, University of Bologna, Bologna, Italy
[e] Radiology Unit, Bufalini Hospital, Cesena, Italy

A R T I C L E   I N F O

A B S T R A C T

Introduction and Objectives: Conventional transarterial chemoembolization (cTACE) has several limitations due to the lack of standardization. The aim of this study was to evaluate the chemical and physical characteristics and behaviors over time of emulsions for cTACE and to assess intra- and inter-operator variabilities in the preparation processes.
Materials and Methods: This *in vitro* study involved evaluation of emulsions for cTACE prepared using two methods: water-in-oil (WiO) and chemotherapeutic-in-oil (CiO). Three emulsions were prepared with each method and obtained after 20, 50, and 100 pumping exchanges. A drop from each final mixture was analyzed via light microscopy (time 1) and after 5, 10, 15, and 20 min since the end of preparation. After 20 min, all preparations were re-mixed and new drops were re-evaluated. The intra- and inter-operator variabilities were analyzed.
Results: The mean droplet diameter decreased non-significantly when the number of pumping exchanges increased and increased significantly over time for both WiO and CiO. The droplets returned to their initial diameters after re-mixing. There were no significant differences in the intra- and inter-operator variabilities ($P > 0.01$).
Conclusions: Any interventional radiologist, regardless of their experience, may prepare these emulsions. These data may represent a set of instructions to standardize cTACE.

1. Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing over the last decade, and HCC is now the fifth most common cancer and one of the most common causes of cancer-related deaths worldwide, with a low 5-year survival rate (10%–15%) [1–5]. Curative treatments for HCC can be applied only in very early/early stages of liver disease accounting for <20% cases at presentation [6,7]. Unfortunately, many patients with HCC are diagnosed at intermediate stage [5,7,8] in which trans-arterial chemoemboliza-tion (TACE) is usually indicated [6,9,10].

Currently, various chemoembolization regimens are available and applied worldwide. The two principal TACE techniques are conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE). In cTACE, a drug carried by lipiodol is administered as an arterial injection, followed by arterial embolization [11]. This technique has several limitations because of the lack of standardization at every step [12], starting from the choice of the drug (none is significantly more effective than the others) until the embolization endpoint [13]. This lack of standardization introduces many biases that limit comparisons of previously published series of patients treated with cTACE. Furthermore, patients with intermediate-stage HCC represented a markedly heterogenous population; in fact, a panel of experts proposed a sub-classification of this category in order to facilitate its clinical management [14]. Therefore, it is important

* Corresponding author at: Radiology Unit, Department of Experimental, Diagnostic and Speciality Medicine, Sant'Orsola Hospital, University of Bologna, Via Albertoni, 15, 40138, Bologna, Italy.
  E-mail address: matteo.renzulli@aosp.bo.it (M. Renzulli).

to not introduce another bias related to TACE procedure. Finally, a common and widely approved standard for chemoembolization is advocated.

The second chemoembolization modality, DEB-TACE, was introduced in interventional radiological practice to address the issue of standardization [15]. DEB-TACE is characterized by arterial injection of the drug directly loaded on embolization particles (microspheres) that function as drug carriers [16]. Standardization of this technique combining the cytotoxic and ischemic effects is ensured by calibrating the microspheres to load the same amount of drug. Moreover, these microspheres are commercially available in various diameters [17,18]. Small microspheres can run distally in the vessels, allowing the release of chemotherapeutic agents very close into the tumor. In fact, DEB-TACE appears to be more effective in terms of greater tumor response and less toxic effects when using small microspheres than when using large ones [17]. Nonetheless, the superiority of DEB-TACE over cTACE has never been confirmed [19]. In particular, DEB-TACE and cTACE were equally effective and safe, with the only advantage of DEB-TACE being less post-procedural abdominal pain [19]. Moreover, DEB-TACE has higher immediate costs than cTACE [20]. Therefore, many interventional radiology centers worldwide continue to use cTACE [21,22].

In general, preparation of the cTACE mixture involves two main possible modalities: (i) the water-in-oil (WiO) technique, in which the final emulsion contains a chemotherapeutic agent diluted with an aqueous solution (or contrast media) and subsequently mixed with lipiodol, and (ii) the chemotherapeutic-in-oil (CiO) technique, in which the final emulsion contains the drug mixed directly in lipiodol [23,24]. Although several studies have reported detailed preparations of these emulsions [23,24], many questions remain unanswered. The first question is what happens when the number of mixes is changed? The second question is what happens to the emulsions over time? Finally, the third question is what are the intra- and inter-operator variabilities in the preparation of emulsions using different methods?

In this context, the aims of this study were to evaluate *in vitro* chemical and physical characteristics and behaviors over time of emulsions for cTACE prepared using two different methods and to assess the intra- and inter-operator variabilities in the preparation processes.

2. Materials and methods

This study did not involve human or animal subjects or patients and, therefore, Institutional Review Board approval was not required.

2.1. cTACE emulsions

The *in vitro* study evaluated two different cTACE emulsions: WiO and CiO. All emulsions were prepared under a suction hood to avoid aerial toxicity of chemotherapeutic agents. The emulsions were prepared by two different operators, one (XX) with over 15 years of experience in interventional radiology and another (XX) with 5 years of experience in the same radiological field.

2.1.1. WiO preparation

The WiO preparation started with dilution of the chemotherapeutic agent with water. A non-ionic contrast agent was used instead of water for preparing an aqueous solution of epirubicin because it increases the density of the drug solution, which improves the stability of the final drug/lipiodol emulsion by lowering gravity-induced sedimentation [25]. To improve WiO emulsion, the volume of drug aqueous solution was kept lower than that of lipiodol: the ideal ratio is one volume of drug to two volumes of lipiodol [26]. For this, 5 mL of Iomeron 350® iodine contrast agent

(Bracco, Milan, Italy) and 10 mL of standard iodized oil (Lipiodol®; Guerbet, Milan, Italy) were aspirated using a 10-ml Luer lock syringe and added to a vial with epirubicin powder (50 mg; Farmorubicin; Pfizer, Latina, Italy); the mixture was shaken manually. Subsequently, when the epirubicin powder had dissolved in the contrast agent to form a homogenous solution, it was aspirated using a 20-ml Luer lock syringe. A three-way stopcock was used to mix the solution with 10 mL lipiodol already aspirated with an additional 20-ml Luer lock syringe. The contents of the syringe loaded with the drug were first pushed toward the syringe containing lipiodol to form the WiO emulsion with drops of the drug within lipiodol [27]. The chemotherapeutic aqueous solution and lipiodol were vigorously mixed using a three-way stopcock to generate sufficient energy to reduce droplet size [26].

2.1.2. CiO preparation

The CiO emulsion was obtained by directly mixing the chemotherapeutic agent with lipiodol. Specifically, 10 mL lipiodol was aspirated using a 10-ml Luer lock syringe and directly introduced in a vial of epirubicin powder (50 mg); the mixture was manually shaken. Subsequently, when epirubicin powder was mixed with lipiodol, the vial contents were aspirated using a 20-ml Luer lock syringe and mixed using a three-way stopcock and another 20-ml Luer lock syringe.

2.2. Droplet assessments

The most important investigation regarding WiO preparation has found that the smaller the particles, the better their ability to reach the smaller tumoral neovessels [18]. Based on this finding, at least 20 pumping exchanges through the stopcock are required to obtain an internal phase droplet size in the range of 70–100 μm [24].

In normal pathophysiology, HCC vascularity results in microscopic arteriovenous shunting that bypasses the tumor capillaries and flows directly to the lung. Therefore, small particles can bypass the vascular microcirculation of the tumor and liver, causing non-target chemoembolization, which is the known risk of pulmonary and non-target chemoembolization. However, droplets or microspheres with a caliber of $\geq$50–70 μm cannot pass through any shunts because of their higher caliber, preventing the risk of pulmonary and non-target chemoembolization [28]. An internal phase droplet size in the range of 70–100 μm is obtained with at least 20 pumping exchanges through the stopcock [24]. To the best of authors' knowledge, there have been no quantitative investigations into the eventual internal phase droplet size after more than 20 vigorous pumping exchanges through the stopcock. Therefore, in this study, three emulsions with each technique, WiO and CiO, were prepared with 20, 50, and 100 vigorous pumping exchanges at a standard speed of 1 push/s using a three-way stopcock and two 20-ml Luer lock syringes. Furthermore, changes in different mixtures over time after preparation were determined. The procedure to track any changes was as follows. First, a drop was obtained from each of the six mixtures after preparation, was placed on a transparent slide, and immediately analyzed via light microscopy (time 1). A new drop from each preparation was obtained at 5 (time 2), 10 (time 3), 15 (time 4), and 20 (time 5) minutes after preparation without mixing again and analyzed via light microscopy. Finally, after 20 min, all preparations were re-mixed and a new drop was again evaluated via light microscopy (time of re-mix, TR).

The light microscope was connected to a digital camera, and preparations from each passage were photographed. The measurements were made using tools of ImageJ (National Institutes of Health, Bethesda, Maryland, USA). The preparations were qualitatively evaluated via light microscopy for droplet margins. For each

preparation, mean droplet diameter (± standard deviation [SD]) and droplet diameter range were evaluated.

The same operator prepared two emulsions after 20, two after 50 and two after 100 pumping exchanges at different times (time 1 and time 1 *bis*) to calculate the intra-operator variability in mean droplet diameter for both WiO and CiO. Thereafter, the inter-operator variability in mean droplet diameter was calculated under the same conditions.

2.3. Statistical analysis

The data collected during the study were summarized by groups and compared using descriptive statistical methods. Continuous variables were reported as mean and SD, while categorical variables as number and percentage. The normal distribution of droplets diameter among 10 evaluations performed by each operator at each time was checked with Shapiro-Wilk test. Variables with a normal distribution were compared using the *t*-test whereas variables without normal distribution were analyzed by the U-Mann-Whitney test or Kruskal Wallis test. Comparisons were made among two sets of pushing exchanges by the same operator (XX), at each number of pushing exchanges category (20, 50 or 100 pushing exchanges), among operators (XX vs XX) and at each time of droplet from preparation (times 1, 2, 3, 4, 5). The limit of statistical significance was set at $P < 0.05$. Statistical analyses were performed using Stata/SE (Version 14.2; Stata Corp, Texas, United States of America) for Windows.

3. Results

3.1. WiO preparation

The droplet margins of all WiO preparations appeared homogenously round regardless of their size. The mean droplet diameters (± SD) and the droplet diameter ranges of each WiO preparation (after 20, 50, and 100 pumping exchanges) at the different times (1, 2, 3, 4, 5, and TR) are presented in Table 1. The mean droplet diameter increased significantly over time (time 1 until 5) because the droplets tended to aggregate. The largest dimensional increase in droplet diameter occurred as early as 5 min after preparation (110 µm at time 1 vs. 1685 µm at time 2; $P < 0.001$) (Table 2) (Fig. 1). Conversely, mean droplet diameter did not increase significantly from time 2 until 5 ($P > 0.05$). Upon re-mixing the preparations after 20 min, droplet diameter returned to a value comparable to that at time 1. The mean droplet diameter decreased with increase in the number of pumping exchanges, although not significantly ($P = 0.436$) (Table 3). There were no significant differences in intra-operator (Table 3) and in inter-operator variabilities (Table 4).

3.2. CiO preparation

The droplet margins of all CiO preparations appeared homogenously round regardless of their size. The mean droplet diameters (± SD) and the droplet diameter ranges for each CiO preparation (after 20, 50, and 100 pumping exchanges) at the different times (1, 2, 3, 4, 5, and TR) are presented in Table 1. The mean droplet diameter increased significantly over time (time 1 until 5). The most significant aggregation occurred as early as 5 min after preparation (120 µm at time 1 vs. 1757 µm at time 2; $P < 0.001$) (Table 2). Conversely, mean droplet diameter did not increase significantly from time 2 until 5 ($P > 0.05$). Upon re-mixing of preparations after 20 min, droplet diameter returned to a value comparable to that at time 1. The mean droplet diameter decreased with increase in the number of pumping exchanges, although not significantly

Table 1
Characteristics of droplets in water-in-oil and chemotherapeutic-in-oil emulsions after different pumping exchanges and at different times after preparation for the leading operator (XX).

Number of pushing exchanges	T1 MD±SD (µm)	T1 Range of droplet diameters (µm)	T2 MD±SD (µm)	T2 Range of droplet diameters (µm)	T3 MD±SD (µm)	T3 Range of droplet diameters (µm)	T4 MD±SD (µm)	T4 Range of droplet diameters (µm)	T5 MD±SD (µm)	T5 Range of droplet diameters (µm)	TR MD±SD (µm)	TR Range of droplet diameters (µm)
WiO												
20	110±33.9	32–155	1685±458	48–2220	1742±475	54–2530	1843±466	56–2233	1950±485	61–2522	108±51	34–159
50	108±35.3	30–153	1673±532	46–2214	1732±456	49–2528	1820±473	53–2232	1948±503	55–2515	100±52	31–155
100	94±35.9	27–150	1654±486	42–2209	1703±482	45–2511	1789±469	47–2216	1923±493	49–2504	93±48	29–153
CiO												
20	120±29.7	56–175	1757±468	69–2418	1782±464	71–2555	1866±451	71–2556	1996±494	79–2718	125±49	57–176
50	115±31.7	53–173	1744±452	64–2412	1779±459	69–2552	1844±438	71–2554	1994±483	73–2711	122±45	50–171
100	102±33	50–170	1739±434	58–2408	1774±432	62–2548	1837±425	63–2550	1963±455	65–2702	118±56	49–168

WiO: water-in-oil emulsion; *CiO*: chemotherapeutic-in-oil emulsion; *MD*: mean diameter; *SD*: standard deviation; *T1*: time 1, immediately after preparation; *T2*: time 2, 5 min after preparation; *T3*: time 3, 10 min after preparation; *T4*: time 4, 15 min after preparation; *T5*: time 5, 20 min after preparation; *TR*: time of re-mix.

Table 2
Comparison of droplets diameter in water-in-oil and chemotherapeutic-in-oil emulsions after different pumping exchanges and at different times after preparation for the leading operator (XX).

N° of pushing exchanges	T1 mean (SD)	T2 mean (SD)	P	T3 mean (SD)	P (T1 vs T3)	P (T2 vs T3)	T4 mean (SD)	P (T1 vs T4)	P (T2 vs T4)	P (T3 vs T4)	T5 mean (SD)	P (T1 vs T5)	P (T2 vs T5)	P (T3 vs T5)	P (T4 vs T5)
WIO															
20	110 (33.9)	1685 (458)	<0.001	1742 (475)	<0.001	0.788	1843 (466)	<0.001	0.454	0.637	1950 (485)	<0.001	0.225	0.354	0.621
50	108 (35.3)	1673 (532)	<0.001	1732 (456)	<0.001	0.793	1820 (473)	<0.001	0.522	0.677	1948 (503)	<0.001	0.250	0.328	0.565
100	94 (35.9)	1654 (486)	<0.001	1703 (482)	<0.001	0.824	1789 (469)	<0.001	0.535	0.691	1923 (493)	<0.001	0.235	0.326	0.541
CiO															
20	120 (29.7)	1757 (468)	<0.001	1782 (464)	<0.001	0.906	1866 (451)	<0.001	0.602	0.686	1996 (494)	<0.001	0.281	0.331	0.547
50	115 (31.7)	1744 (452)	<0.001	1779 (459)	<0.001	0.866	1844 (438)	<0.001	0.622	0.750	1994 (483)	<0.001	0.248	0.444	0.774
100	102 (33)	1739 (434)	<0.001	1774 (432)	<0.001	0.859	1837 (425)	<0.001	0.616	0.746	1963 (455)	<0.001	0.275	0.353	0.530

N°: number; WiO: water-in-oil emulsion; CiO: chemotherapeutic-in-oil emulsion; SD: standard deviation; T1: time 1, immediately after preparation; T2: time 2, 5 min after preparation; T3: time 3, 10 min after preparation; T4: time 4, 15 min after preparation; T5: time 5, 20 min after preparation.

Table 3
Characteristics of droplets in water-in-oil and chemotherapeutic-in-oil emulsions after different pumping exchanges at T1 after two different preparations performed by the same Operator (XX).

Number of pushing exchanges	Operator 1 T1 mean (SD)	Operator 1 T1 *bis* mean (SD)	P
WiO			
20	110 (33.9)	107 (35.4)	0.910
50	108 (35.3)	106 (37.3)	0.970
100	94 (35.9)	94 (35.9)	1
P (kruswal wallis test)	0.436	0.423	
CiO			
20	120 (29.7)	116 (35)	0.850
50	115 (31.7)	115 (30.5)	0.940
100	102 (33)	108 (28.8)	0.710
P (kruswal wallis test)	0.178	0.468	

WiO: water-in-oil emulsion; CiO: chemotherapeutic-in-oil emulsion; SD: standard deviation; T1: time 1, immediately after preparation.

Table 4
Characteristics of droplets in water-in-oil and chemotherapeutic-in-oil emulsions after different pumping exchanges, immediately after preparation by each operator.
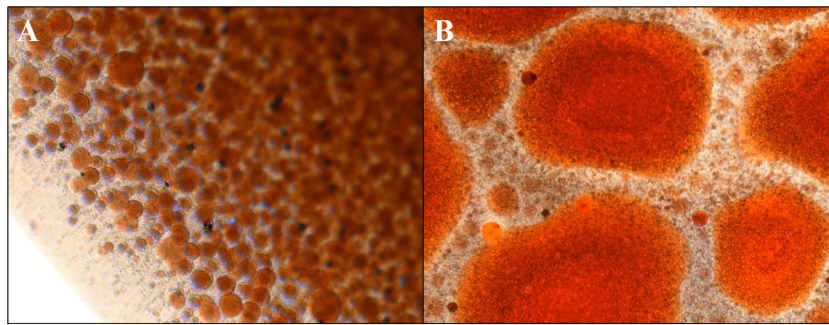
Number of pushing exchanges	Operator *1* T1 mean (SD)	Operator *2* T1 mean (SD)	P
WiO			
20	110 (33.9)	113 (33.5)	0.791
50	108 (35.3)	109 (34.4)	0.910
100	94 (35.9)	99 (32.1)	0.596
CiO			
20	120 (29.7)	117 (31.1)	0.821
50	115 (31.7)	112.2 (36.1)	1
100	102 (33)	100 (35.2)	0.734

WiO: water-in-oil emulsion; CiO: chemotherapeutic-in-oil emulsion; SD: standard deviation; T1: time 1, immediately after preparation.

($P = 0.178$) (Table 3). There were no significant differences in intra-operator (Table 3) and in inter-operator variabilities (Table 4).

4. Discussion

Since the first suggestions regarding the preparation of cTACE emulsions, which dates back to the early 1980–90 s, it has been accepted that 20 pumping exchanges of the lipiodol and drug mixture produce large droplets (diameter range, 30–160 μm). However, to the best of authors' knowledge, no study has investigated changes in droplet parameters with increasing number of mixes. The present study demonstrated that there were no significant changes in mean diameter of droplets produced by 20, 50, or 100 pumping exchanges. Interestingly, the droplet mean diameter and the diameter range of droplets produced with these three different number of pumping exchanges remained unaltered for both WiO and CiO preparations. The diameter range of droplets are comparable to that reported by de Baere et al. [24]. Moreover, our results of mean droplet diameter and standard deviations, which were not previously reported in literature, suggest that the obtained droplet diameter is not too small to facilitate extrahepatic chemoembolization via the possible presence of extrahepatic shunts. Conversely, through quantitative analysis, this study demonstrated for the first time that 20 pumping exchanges of lipiodol and drug are sufficient to produce small drops that can reach tumors distally; therefore, these data are crucial for cTACE standardization. Moreover, these results have other implications. First, the data demonstrate that it is not possible to manually produce very small droplets. It is necessary to use blenders for obtaining very small droplets (10–40 μm), such as that in another study [24]. Second, the droplet size range in this study was wide, consistent with that in other studies [23,24], and did not vary with increase in the number of pumping exchanges. To homogenize the droplet size, it is necessary to use modified stop-

Fig. 1. Light microscopic findings of the water-in-oil emulsion showing small droplets after 20 pumping exchanges at time 1 (A) and larger droplets 5 min after preparation (time 2) (B).

cocks with porous filters that produce particles with even more homogenous diameters, specifically 50 and 100 μm, which cannot easily be done manually [29].

The study demonstrated that there were no significant differences in intra- and inter-operator variabilities in droplet diameters of WiO and CiO emulsions. These results, which have not been previously demonstrated, are very important for use in a potential standardization protocol. In fact, these data show that the preparation process does not depend on the time of preparation (intra-operator variability) and degree of expertise of the operator (inter-operator variability).

Conventionally, it is believed that the mixture of lipiodol and drug must be prepared at the time of administration and promptly used after preparation [24]. Additionally, it has previously been proposed that mixtures should be re-homogenized, if necessary, during the same treatment session [26]. Neither of these two recommendations was based on quantitative analyss. Our data demonstrate for the first time that over time, the droplets in WiO and CiO emulsions tend to aggregate equally, ultimately increasing the droplet diameter. Interestingly, the maximum increase in droplet diameter was achieved as early as 5 min after preparation regardless of the number of pumping exchanges. Specifically, droplet diameter increased by more than 10 times after 5 min (>1500 μm) and then more slowly up to 20 min independent of the number of pumping exchanges and type of preparation (WiO or CiO). These aggregated droplets appear to be too large to be effective because they can occlude vessels proximally. Moreover, upon re-mixing the emulsions after just 20 min, the droplet diameter returned to the initial values, which allowed them to be used effectively again. These data should be considered in any potential standardization of the emulsion process in clinical practice. In fact, in recent years, superselective catheterization has been shown to be associated with favorable outcomes of patients treated for HCC [30]. However, superselective catheterization needs time, and these data demonstrated that it is necessary to mix the emulsion immediately before the next injection, with no time limits.

In the near future, the use of different surveillance programs for patients with a high risk of developing HCC and a wide diffusion of magnetic resonance imaging performed using hepatospecific contrast media will probably allow HCC diagnosis in many patients and identification of some aggressive features [31–33]. Furthermore, advances in imaging techniques have enabled identification of aspects such as microvascular invasion [34]. Finally, cTACE represents one of the most used treatments for patients with HCC and may be the most effective therapeutic option for recurrent HCC in patients with microvascular invasion [10,35]. Therefore, it would be very useful to standardize the technique. Moreover, it is well known that the treatment choice is an independent prognostic factor in BCLC-B patients and curative options (that actually do not represent the standard of care for BCLC-B patients) offer a better patients' outcome. Therefore, TACE (retained the standard of care for BCLC-B patients) could probably be replaced by other curative therapies, especially in patients with poor liver function [36]. Probably, this process is also due to the absence of a standardization of cTACE procedure. Results of the present study can be used to develop a protocol for cTACE standardization.

The standardization of TACE procedure allows to achieve another important advantage. It is well known that the doses delivered in the interventional radiological procedures are much higher than those in diagnostic imaging: therefore, efforts for dose optimization nowadays should be made mainly for interventional radiological procedures [37]. The standardization of TACE procedure allows to go through this direction. In fact, the emulsion if not re-mixed every five minutes could produce an increase of the angiographic time for example due to a blockage of microcatheters since the droplets tend to agglomerate.

An important limitation of this study is that only one chemotherapeutic agent, epirubicin, was tested in this analysis. However, epirubicin is the most commonly used agent in cTACE worldwide [38]; thus, these results can be used to standardize cTACE using this drug at the least.

5. Conclusion

This study demonstrated that 20 pumping exchanges are sufficient to prepare WiO or CiO emulsions for cTACE. Re-mixing of the emulsion is needed every 5 min to avoid aggregation into larger droplets in cases of highly lengthy infusions (i.e., large tumors) or multiple superselective catheterizations. Any interventional radiologist may prepare these emulsions regardless of their experience. These study results may represent a set of instructions for cTACE standardization.AbbreviationsHCChepatocellular carcinomaTACEtrans-arterial chemoembolizationcTACEconventional trans-arterial chemoembolizationDEB-TACEdrug-eluting bead trans-arterial chemoembolizationWiOwater-in-oilCiOchemotherapeutic-in-oilSDstandard deviationTRtime of re-mix

Abbreviations

HCC	hepatocellular carcinoma
TACE	trans-arterial chemoembolization
cTACE	conventional trans-arterial chemoembolization
DEB-TACE	drug-eluting bead trans-arterial chemoembolization
WiO	water-in-oil
CiO	chemotherapeutic-in-oil
SD	standard deviation
TR	time of re-mix

Declarations of interest

None.

References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
[2] Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–6.
[3] Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004;127:S5–16.
[4] American Cancer Society Cancer facts and figures 2015. Atlanta, GA: American Cancer Society, 2015. Available online at http://www.cancer.org/acs.
[5] Cucchetti A, Trevisani F, Cescon M, Ercolani G, Farinati F, Del Poggio P, et al. Cost-effectiveness of semi-annual surveillance for hepatocellular carcinoma in cirrhotic patients of the Italian liver cancer population. J Hepatol 2012;56:1089–96.
[6] European Association for the Study of the Liver. European association for the study of the liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[7] Forner A, Real MI, Varela M, Bruix J. Transarterial chemoembolization for patients with hepatocellular carcinoma. Hepatol Res 2007;37. S230-S7.
[8] Brown DB, Cardella JF, Sacks D, Goldberg SN, Gervais DA, Rajan DK, et al. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2006;17:225–32.
[9] Bruix J, Sherman M. Practice guidelines committee, american association for the study of liver diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–36.
[10] Varela M, Reig M, de la Mata M, Matilla A, Bustamante J, Pascual S, et al. Treatment approach of hepatocellular carcinoma in Spain. Analysis of 705 patients from 62 centers. Med Clin (Barc) 2010;134:569–76.
[11] Terzi E, Terenzi L, Venerandi L, Croci L, Renzulli M, Mosconi C, et al. The ART score is not effective to select patients for transarterial chemoembolization retreatment in an Italian series. Dig Dis 2014;32:711–6.
[12] Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007;30:6–25.
[13] Jin B, Wang D, Lewandowski RJ, Riaz A, Ryu RK, Sato KT, et al. Chemoembolization endpoints: effect on survival among patients with hepatocellular carcinoma. AJR Am J Roentgenol 2011;196:919–28.
[14] Giannini EG, Moscatelli A, Pellegatta G, Vitale A, Farinati F, Ciccarese F, et al. Application of the intermediate-stage subclassification to patients with untreated hepatocellular carcinoma. Am J Gastroenterol 2016;111:70–7.
[15] Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474–81.
[16] Poon RT, Tso WK, Pang RWC, Ng KKC, Woo R, Shing KKC, et al. A Phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007;5:1100–8.
[17] Prajapati HJ, Xing M, Spivey JR, Hanish SI, El-Rayes BF, Kauh JS, et al. Survival, efficacy, and safety of small versus large doxorubicin drug-eluting beads TACE chemoembolization in patients with unresectable HCC. AJR Am J Roentgenol 2014;203. W706-W14.
[18] Padia SA, Shivaram G, Bastawrous S, Bhargava P, Vo NJ, Vaidya S, et al. Safety and efficacy of drug-eluting bead chemoembolization for hepatocellular carcinoma: comparison of small versus medium-size particles. J Vasc Interv Radiol 2013;24:301–6.
[19] Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255–64.
[20] Cucchetti A, Trevisani F, Cappelli A, Mosconi C, Renzulli M, Pinna AD, et al. Cost-effectiveness of doxorubicin-eluting beads versus conventional transarterial chemo-embolization for hepatocellular carcinoma. Dig Liver Dis 2016;48:798–805.
[21] Luedemann WM, Geisel D, Gebauer B, Schnapauff D, Chapiro J, Wieners G, et al. Comparing HCC arterial tumour vascularisation on baseline imaging and after lipiodol cTACE: how do estimations of enhancing tumour volumes differ on contrast-enhanced MR and CT? Eur Radiol 2020;30:1601–8.
[22] 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 Interv Radiol 2020;43:423–33.
[23] de Baere T, Zhang X, Aubert B, Harry G, Lagrange C, Ropers J, et al. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. Radiology 1996;201:731–5.
[24] de Baere T, Dufaux J, Roche A, Counnord JL, Berthault MF, Denys A, et al. Circulatory alterations induced by intra-arterial injection of iodized oil and emulsions of iodized oil and doxorubicin: experimental study. Radiology 1995;194:165–70.
[25] Tzeng WS, Wu RH, Chang SC, Chou CK, Lin CY, Chen JJ, et al. Ionic versus nonionic contrast media solvents used with an epirubicin-based agent for transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2008;19:342–50.
[26] Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1989;170:783–6.
[27] de Baere T, Arai Y, Lencioni R, Geschwind JF, Rilling W, Salem R, et al. Treatment of liver tumors with lipiodol TACE: technical recommendations from experts opinion. Cardiovasc Intervent Radiol 2016;39:334–43.
[28] Gabr A, Ranganathan S, Mouli SK, Riaz A, Gates VL, Kulik L, et al. Streamlining radioembolization in UNOS T1/T2 hepatocellular carcinoma by eliminating the lung shunt study. J Hepatol 2020;8278:30122–7.
[29] Tanaka T, Nishiofuku H, Masada T, Fukuoka Y, Sato T, Tatsumoto S, et al. Drug release property of lipiodol emulsion formed by glass membrane emulsification device for transarterial chemoembolization. Cardiovasc Intervent Radiol 2020;43:135–9.
[30] 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;24:509–17.
[31] Renzulli M, Golfieri R, Bologna Liver Oncology Group (BLOG). Proposal of a new diagnostic algorithm for hepatocellular carcinoma based on the Japanese guidelines but adapted to the Western world for patients under surveillance for chronic liver disease. J Gastroenterol Hepatol 2016;31:69–80.
[32] Golfieri R, Garzillo G, Ascanio S, Renzulli M. Focal lesions in the cirrhotic liver: their pivotal role in gadoxetic acid-enhanced MRI and recognition by the Western guidelines. Dig Dis 2014;32:696–704.
[33] Vasuri F, Golfieri R, Fiorentino M, Capizzi E, Renzulli M, Pinna AD, et al. OATP 1B1/1B3 expression in hepatocellular carcinomas treated with orthotopic liver transplantation. Virchows Arch 2011;459:141–6.
[34] Renzulli M, Buonfiglioli F, Conti F, Brocchi S, Serio I, Foschi FG, et al. Imaging features of microvascular invasion in hepatocellular carcinoma developed after direct-acting antiviral therapy in HCV-related cirrhosis. Eur Radiol 2018;28, 506–13.
[35] Jin YJ, Lee JW, Lee OH, Chung HJ, Kim YS, Lee JWI, et al. Transarterial chemoembolization versus surgery/radiofrequency ablation for recurrent hepatocellular carcinoma with or without microvascular invasion. J Gastroenterol Hepatol 2014;29:1056–64.
[36] Pecorelli A, Lenzi B, Gramenzi A, Garuti F, Farinati F, Giannini EG, et al. Curative therapies are superior to standard of care (Transarterial chemoembolization) for intermediate stage hepatocellular carcinoma. Liver Int 2017;37:423–33.
[37] Compagnone G, Giampalma E, Domenichelli S, Renzulli M, Golfieri R. Calculation of conversion factors for effective dose for various interventional radiology procedures. Med Phys 2012;39:2491–8.
[38] Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016;64:106–16.