Université de Poitiers
Faculté de Médecine et Pharmacie

Année 2017

THESE
POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(décret du 16 janvier 2004)

présentée et soutenue publiquement
le 25 septembre 2017 à Poitiers
par Monsieur Pierre Hestin

Facteurs associés à une réponse tumorale objective après première séance de chimio-embolisation intra artérielle sélective dans le carcinome hépatocellulaire : Impact des facteurs techniques

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REMERCIEMENTS :

A Monsieur le Professeur TASU,

Je vous remercie de m'avoir guidé tout au long de mon internat. Merci pour votre pédagogie et votre disponibilité en toutes circonstances. Recevez le témoignage de ma grande estime.

A Monsieur le Professeur GUILLEVIN,

Je vous remercie pour votre enseignement et votre accompagnement dispensés tout au long de mon internat. Recevez le témoignage de ma profonde reconnaissance.

A Madame le Professeur SILVAIN,

Je vous remercie d'avoir acceptée d'être membre de ce jury et de l'attention portée à mon travail. Je vous prie de croire en mes salutations distinguées.

A Monsieur le Docteur RONOT,

Je te remercie pour ton temps, ton expertise, ta rigueur et ta pédagogie. Reçois le témoignage de ma profonde reconnaissance.

A Monsieur le Docteur BOUCEBCI,

Je te remercie pour ton apprentissage, ta clairvoyance et ton esprit critique. Ta rigueur m'a permis d'évoluer tout au long de ma formation. C'est un honneur pour moi de t'avoir dans ce jury.

A Justine,
Tu es la plus belle chose qui me soit arrivée. Je suis très heureux de t'avoir chaque jour à mes côtés.

A mon père,
Merci pour ton éducation et ta rigueur qui ont fait de moi ce que je suis. Merci pour toutes les choses que tu m'as faites découvrir et pour tous ces moments que nous avons partagés et que nous continuerons de partager ensemble.

A Mamie,
Merci pour ton soutien, ta présence, ta bienveillance et ta compréhension. Attention aux fouines !

A Pascale,
Merci pour tes attentions et ta bienveillance durant toutes ces années.

A Olive, Mirza, Stepi, Vincent, Lolo, Rayman,
Merci pour tous ces moments que je partage avec vous et qui me font tout oublier, un peu trop peut être ;) au cercle des poètes disparus et pour la triste vie du bœuf et du canard quand on se voit.

A Maxime,
Tu as été un professeur de « la vie » pour moi bien avant dans avoir le titre. Merci pour tous ces moments dans le service de pointe de la radiologie suisse « Jésus !! look at this » et tous ces moments autour des Brooklyn « en cannette svp » Tu es la personne la plus extraordinaire que j'ai eu l'occasion de rencontrer.

A Arnaud,
Sans toi l'exil aurait pu être rapide durant ce semestre… bon ; on a bien rigolé au final !

A la famille Hadzic et aux bosniaques que je connais,
Merci pour votre générosité, votre gentillesse et pour vos enfants, ma vie aurait été bien plus triste sans eux. Vous aurez toujours une place chez moi.

A Stéphane Velasco et tous les chefs de vasculaire et un peu les manips,
Merci pour cette formation de grande qualité, cette rigueur et cette bonne ambiance. Ça change la vie d'un homme le vasculaire !

A Minus,
Il en aura fallu des années avant qu'on se parle ! Je suis très content que tu partages ma vie.

A Mirza, strong man, merci d'avoir toujours été là, on en a partagé des choses ! Merci de m'avoir suivi dans mes bêtises, qui au final étaient marrantes non ? je ne suis pas inquiet pour ton avenir, sauf peut-être financier monsieur Rockefeller ;)

Factors associated with an objective response after selective trans-arterial chemoembolization for hepatocellular carcinoma: focus on technical factors.

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Keywords : TACE. C-TACE. DEB-TACE. Chemoembolization. C-arm. CBCT.

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List of abbreviations

TACE: Transarterial chemoembolization
cTACE: Conventional transarterial chemo-embolization
DEB-TACE: Drug-eluding beads transarterial chemoembolization
HCC: Hepatocellular carcinoma
BCLC: Barcelona Clinical Liver Cancer

EASL: European Association for the Study of the Liver
AASLD: American Association for the Study of Liver Diseases
OR: Objective response
mRECIST: Modified Response Evaluation Criteria in Solid Tumors
CR: Complete response
PR: Partial response
SD: Stable disease
PD: Progressive disease
CBCT: Cone Beam Computed Tomography

Financial support: none
Competing Interests: none
Funding: None

ABSTRACT

Aim: To identify factors associated with an objective response according to the mRECIST criteria after a first session of selective transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC), with a focus on technical factors.

Methods: In this retrospective bicentric study, 385 patients (325 males, 84.4%) with 702 tumors (mean 40 ± 27mm), who underwent a first session of selective TACE for the treatment of HCC between January 2009 and January 2016 were included. Demographic, clinical, laboratory and technical factors associated with an objective response according to mRECIST criteria on the first follow up imaging were identified. Technical factors analyzed were; use of cone beam computed tomography (CBCT) for treatment guidance, and the type of TACE (i.e. Lipiodol-based conventional vs. drug-eluting beads). Objective response (OR) was defined as a complete or partial response, on a patient-based analysis

***Results*:** After one session of treatment, OR was observed in 66.9 % of patients. In univariate analysis, factors associated with OR were the use of embolic agent during TACE (69.4% vs. 46.3% p=0.010), absence of associated portal vein thrombosis (68.2% vs. 45.8%. p=0.041), and a total number of tumors <3 (69% vs. 55%. p=0.041), tumors not located in segment 1 or 4 (45% vs. 74% in other locations, p<0.001). Technical factors were not associated with OR (p=0.824 for the type of TACE, and p=0.451 for the use of CBCT).

Conclusion: This study reaffirms the high rate of OR after one session of selective TACE. Individual response seems to depend mainly on tumor location and burden. On contrary, technical factors such as the use of CBCT or the type of treatment delivery do not seem to affect overall response rate in patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a severe complication of chronic liver disease, and especially cirrhosis, with an estimated prevalence around 10000 new cases / year in France. It is the 5th most common cancer in the world in humans, and its incidence increases [1].

Transarterial chemoembolization (TACE) is the first-line treatment for intermediate stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) group classification (Appendix 1) [2–5]. It is also recommended by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [2, 3, 6].

There are two main techniques for the delivery of treatment during TACE. The first, referred to as conventional chemoembolization (cTACE), consists of the injection of chemotherapy (usually doxorubin) emulsified with poppy seed oil (Lipiodol) in vessels supplying the tumors. The second technique uses chemotherapy loaded in calibrated microbeads (drug-eluting beads, DEB-TACE). The objective of these two techniques is to administer high concentrations of chemotherapy in tumors by decreasing the systemic concentrations and thus the side effects compared to an intravenous drug injection. Both have proven their efficacy for the treatment of HCC [6–11] , with acceptable complication rates and tolerance.

During chemoembolization, and regardless of the technique used, detection of target lesions and catheterization of their feeder vessels may be difficult [12–15]. A recent volumic imaging technique, Cone Beam Computed Tomography (CBCT), is increasingly used as a complement or instead of the classical two-dimensional (2D) digital subtracted angiography (DSA). CBCT has shown to be superior to 2D imaging for the detection of tumors and tumor feeders [12, 16–20]. It is recommended by the Cardiovascular and Interventional Radiology Society of Europe (CIRCE) / Society of Interventional Radiology (SIR)[21]. However, there is currently no consensus on its use in the absence of good quality prospective data.

Although the efficacy of chemoembolization is now well demonstrated and recognized, the identification of individual predictive factors of response to treatment remains poorly known. Tumor size smaller than 5 cm, Lipiodol uptake during chemoembolization, tumor hypervascularity, a limited number of tumors have been shown to be associated with a good tumor response rate [22–27]. On the contrary, tumors located in segments I or IV, hypovascular tumor or the presence of associated portal vein thrombosis show lower response rate [22, 23, 26, 28, 29]. Importantly, most studies focus on individual tumor response. Yet, from an oncological point of view, the overall response rate of patients appears more clinically relevant. Indeed, after TACE, the decision to retreat is mainly based on imaging. Patients with remaining viable tumors will be recommended for treatment (either another TACE session or another treatment) even if one or several tumors show a complete response. From this perspective, the impact of technical factors is highly underestimated. It has been demonstrated that selectivity, i.e. the ability to catheterize and treat tumor feeders, leads to a higher rate of tumor necrosis [30]. Regarding treatment delivery, data from retrospective studies are contradictory as for the superiority of a technique in terms of tumor response [31–36]. Yet, prospective and randomized studies have not shown superiority of drug-eluting beads over conventional TACE [37–39]. Similarly, the influence of CBCT on tumor response is largely unknown. Recently, studies had shown a better sensitivity of CBCT than DSA to detect tumors, or tumor feeders, but not for the evaluation of tumor response [11, 12, 40, 41]

Thus, the aim of this study was to identify predictive factors of tumor response after a first session of selective chemoembolization in patients with hepatocellular carcinoma, with particular attention to technical factors.

MATERIALS AND METHODS

Patients and tumors

A bicentric retrospective study was performed in Beaujon University Hospital (Clichy, France – Center 1) and Milétrie University Hospital (Poitiers, France – Center 2). The protocol study was performed in accordance with the ethical principles originating from the Declaration of Helsinki 1975 and approved by local IRB with a waiver of informed consent.

Between 2009 to 2016, all patients treated by a first session of selective chemoembolization for HCC were identified. HCC were diagnosed by biopsy or non-invasive methods according to the recommendations of the European Association for the Study of the Liver (EASL) [3].

Tumors were staged in accordance with the BCLC system (29). A selective chemoembolization was defined by the ability to catheterize HCC feeder vessels.

Exclusion criteria were 1) history of chemoembolization, liver resection or thermoablation 2) severe liver dysfunction (Child score>10), 3) allergy or contraindication to doxorubicin or contrast medium injection 4) contraindication to arterial puncture (severe coagulation disorder), and 5) extrahepatic disease. Treatments were decided by multidisciplinary meeting discussion including hepatologists, hepatobiliary surgeons, and radiologists. Biological, demographic and clinical data were retrieved from medical charts.

Figure 1 shows the flow chart study.

Chemoembolization procedure

Patients were not receiving any additional treatment except for antiviral medication and symptomatic treatment of the post-TACE syndrome when present. Before undergoing TACE, all patients were informed of the side effects and risks of the procedure. Patients fasted overnight and were admitted to the hospital on the morning of the procedure. Hydration was

initiated (normal saline solution at a rate of 200–300 mL/h), and patients were given 12.5 mg of hydroxyzine, 20 mg of morphine sulphate, and 4 mg of ondansetron in center 1. No prophylactic antibiotic treatment was given prior to the procedure.

TACE procedures were performed under local anesthesia by an experienced interventional radiologist (all with more than 5 years of practice in the field of interventional oncology). Diagnostic visceral arteriography was first performed by digital subtraction angiography (both centers) and/or 3D Cone beam CT (center 1) to determine arterial supply to the tumors. (figure 4)

Conventional TACE included an intra-arterial injection of a mixture of chemotherapy (60 mg of doxorubicin; Adriamycin; Pharmacia Upjohn, Kalamazoo, MI, USA), emulsified in poppy seed oil (Lipiodol, Guerbet, Aulnay-sous-bois, France). Embolization was achieved until near-stasis by injection of gelatin sponge (Gelitaspon, Gelita Medical BV, Amsterdam, Netherlands) or polyvinyl alcohol particles (Bead Block, Biocompatibles, Farnham, UK).

The drug-eluting beads procedure included 100–300 µm and/or 300–500 µm sized particles (Biocompatibles, Terumo), according to recent guidelines. Bead loading was performed with an intended dose of 150 mg/patient. Doxorubicin was not adjusted to body surface area or bilirubin levels. The beads were diluted in 20 ml of contrast material and slowly injected until flow stasis. No additional embolic particles were given. In center 2, if no blush tumor was identified, embolization was carried out according with pre-TACE CT.

In the absence of adverse effects or complications, patients were discharged 24-48 hours after the procedure.

Imaging Data and Analysis

All patients underwent contrast-enhanced abdominal CT, with the same protocol, at baseline and 4-8 weeks after treatment. CT scans were performed with a 64-slice multidetector scanner (LightSpeed VCT 64; GE Healthcare, Waukesha, Wi.) in center 1 and 40-slice multidetector scanner (Brilliance 40, Philips, Suresnes, France.) in center 2. Multiphase acquisitions were obtained following intravenous administration of 2mL/kg of a nonionic iodinated contrast medium (Iobitridol, Xenetix, 350 mg/mL, Guerbet, Aulnay-sous-bois, France) through a 16-18 gauge catheter via an antecubital vein at 4mL/s, by using a mechanical power injector (Medrad, Pittsburgh, PA, USA). Arterial, portal venous, and delayed-phase acquisitions were obtained 35, 70, and 180 seconds after the contrast medium had been injected (Show figures 3 and 6).

All CT scans were reviewed by a radiology resident (PH) and a senior abdominal radiologist with 10 years of experience in the field of liver oncology (MR), on a Picture Archive and Communication System (Carestream, Rochester, USA in center 1, and Mackesson Horizon Rad Station, Vancouver, Canada in center 2) and a consensus was reached. Radiologists were blinded to the clinical and biological data.

Baseline tumor characteristics were noted, including number and location (right, left or both livers and according to the Couinaud classification system), as well as infra-segmental portal venous thrombosis. The diameter of the largest tumor was noted for each patient. Treatment response was evaluated on follow-up CT 4-8 weeks after the treatment using the modified Response Evaluation Criteria in Solid Tumours (mRECIST) (Appendix 2) (figures 5 and 7). Objective response was defined as complete or partial response.

Statistical analysis

Values are expressed as means and standard deviations or medians and interquartile ranges (IQR) or percentages as appropriate unless specified otherwise. Factors associated with tumor response were assessed by Chi-square or Fisher exact tests for discrete variables, and the Student t-test or Mann-Whitney test for continuous variables. A *P*-value of .05 or lower was considered to be significant. Analyses were performed using SPSS software (v22.0; SPSS. Chicago. Il). Figures were created using Prism (v 7.0 GraphPad Inc. US).

RESULTS

Patient characteristics

Three hundred and eighty-five patients were included, 209 patients (54%) came from Center 1 and 176 patients (46%) from center 2. Table 1 shows baseline patient characteristics. Among these 385 patients; 325 (84.4%) were male, and the mean age was 67 ± 11.3 years. Three hundred and forty-eight patients (90.4%) had cirrhosis, including 103 (26.8%) due to excessive consumption of alcohol, and 86 patients (22.3%) due to mixed causes. A total of 284 patients (81.7%) had Child-Pugh A score, and 252 patients (65.5%) had HCC BCLC B. Only 24 patients (6.2%) had infra-segmental portal vein thrombosis.

Overall, 702 tumors were analyzed, corresponding to a mean of 1.83 tumors per patient. Mean tumor size was 40 ± 27mm and tumors were located in the right liver in most patients (n=257, 67%).

Chemoembolization

Table 2 and figure 2 show chemoembolization characteristics.

The mean time delay between diagnostic imaging and chemoembolization was 43 ± 38 days. The mean time delay between chemoembolization and follow up imaging was 38 ± 17 days.

Conventional chemoembolization was performed in 150 patient procedures (39%) and drug-eluting beads were used in 235 (61%). The mean dose of chemotherapy administered was 68 ± 18 mg. Overall, 95 patients (25%) had CBCT acquisition during chemoembolization.

Tumoral response

According to the mRECIST criteria, 257/385 patients (66.9%) had an objective response including 150/257 patients (58.4%) with a complete response and 107/257 patients (41.6%) with a partial response. The remaining patients had either stable disease (n=112, 87.5%) or progressive disease (n=16, 12.5%).

Factors associated with tumor response

The rate of tumor response did not significantly differ between centers (63.6 % vs. 70.9 % in center 1 and center 2, respectively, p=0.157).

In univariate analysis, an objective response was associated with the use of embolic agent during TACE (either drug-eluding beads [OR rate 69,1%] or gelatin sponge [OR rate 69,4%] versus no embolic agent [OR rate 46.3%], p=0.010), an absence of associated portal vein thrombosis (OR rates 68.2% vs. 45.8% in patients with a portal vein thrombosis, p=0.041), and the number of tumors (OR rate 69% vs. 55% in patients with 1-2 vs. ≥3 HCC respectively, p=0.041). Patients with tumors located in segment 1 or 4 had a lower OR rate (45% vs. 74 % in other locations, p<0.001).

Other factors such as the type of TACE (i.e. conventional or drug eluting beads, p=0.824), the use of CBCT or not (p=0.451), liver parenchyma status (p=0.353) or the etiology of liver disease (p=0.107) were not associated with tumor response. In center 1, the use of CBCT was associated with a higher rate of objective response (71% vs. 58%) but it did not reach the level of significance (p=0.062). It was also associated with a significantly higher rate of tumor response in patients with tumors located in segments 1 and 4 (58% vs. 39%, p=0.032).

DISCUSSION

The assessment of individual response to a given therapeutic option is becoming a major issue in patients affected by HCC. In this context, the main target of the present study was to identify HCC predictors of TACE response in order to improve management strategy of HCC patients potentially amenable to TACE. Indeed, a significant percentage of HCC patients treated with TACE (up to 60%) do not benefit from this treatment, and alternative therapies should thus be proposed. This study reaffirms the efficacy of selective TACE for the treatment of intermediate stage HCC, with a high rate of objective response. It showed that tumor location and number influence tumor response, together with the presence of portal vein thrombosis. As for the TACE technical factors, if the studies confirmed that the use of embolic agents leads to a better tumor response, it failed to demonstrate any influence of either the type of drug delivery platform, or the use of CBCT for treatment guidance.

Studies have identified two main groups of factors associated with tumor response: tumors features (including tumor vascularity, location or tumor burden), and laboratory tests (including those associated with tumor invasiveness such as alphafetoprotein rate, and those associated with liver function)[26, 28, 29, 42–44] (see Supplemental material 1). In the present study, tumor burden, and tumor location were also identified as patients with more than three

tumors, and those with tumors located in segments 1 or 4 showed a significantly lower objective response rate. Other factors, including laboratory tests, did not influence tumor response. Such discrepancies may be, at least partially, explained by the differences in chosen endpoints. While most studies focus on individual tumors, we chose to adopt a more oncological perspective by analyzing tumor response in patients. This is also why we did not analyze certain tumor features such as vascularity, because it was difficult to assess this in patients with more than one tumor. Yet, it is important to remember that, to date, possible predictive factors of tumor response are not used in clinical practice to preclude patients from TACE mainly because of the lack of alternative treatment in most patients, but also because tumor response remains very difficult – if not impossible – to predict on an individual basis.

Interestingly, technical factors of TACE, i.e. how the treatment is performed from planning to guidance and drug delivery, are poorly studied. This is the case for all interventional radiology treatments. It is problematic because treatment performances are in fact associated with a significant variability. One of the most important factors is vascular selectivity, i.e. the operator's ability to correctly identify and treat tumor feeders. It has become an essential concept and has been shown to be associated with a higher rate of tumor necrosis and better tolerance [30, 45]. In our study, all patients were treated by a first session of selective TACE, making it possible to identify the influence of other factors.

Drug eluting beads have been presented as a theoretically way of reducing variability, as suggested by recent publications on technical recommendations [46, 47]. Yet, the present study did not show any significant difference in objective response rate between patients treated with conventional or drug-eluding beads TACE. Data from retrospective studies are contradictory as to the superiority of one technique over the other in terms of tumor response, survival or time to progression [9, 31–39, 48–56] (Supplemental Material 2). Yet,

prospective and randomized trials did not show any difference between the two drug delivery techniques regarding tumor response, safety or patient survival [37–39, 48]. One may argue that Lipiodol deposition may bias tumor response evaluation in patients treated with conventional TACE, since hyperattenuation of iodine deposition may either mask underlying viable part of the tumor, or lead to response overestimation. Yet, Dioguardi Burgio et al. have shown that complete Lipiodol deposition was associated with complete or almost complete necrosis [57]. Takayasu et al have also reported a good correlation between tumoral necrosis on pathology and CT images if Lipiodol deposition was considered to be a necrotic portion [58]. Therefore, we strongly believe that such biases remain limited.

The added value of CBCT has been evaluated for the different steps of the procedure: detection and identification of liver tumors, identification of tumor vessels, intravascular guidance, and assessment of treatment [13, 40, 59](See Supplemental Material 3). A recent meta-analysis including 18 studies showed that the sensitivity of CBCT for detection HCC tumor was 90% versus 67% with digital subtraction. The sensitivity of CBCT for detection tumor feeding arteries was 93% versus 55% [12]. This resulted in substantial changes in the treatment procedure in 28% of the cases [15]. Yet, published data regarding the oncological benefit are scarce. It has been suggested that patients who undergo chemoembolization with CBCT have a better overall and progression-free survival than those treated with DSA alone [11, 60].Yet, these studies were not randomized and included small populations. Regarding tumor response, data are even scarcer. Miyayama et al have shown that the rate of tumor response with CBCT is better than with conventional 2D-guided treatment[41]. Recently, Cornelis et al. showed that patients treated with a dedicated tumor feeding vessel detection software based on CBCT images had better response than patients treated with conventional 2D imaging [61]. Yet, CBCT was not associated with OR in the present study. This may be

explained by a center effect, since only one of the two centers did perform CBCT. Yet, if the use of CBCT was associated with a higher rate of objective response according to mRECIST in center 1, it did not reach the level of significance. These results suggest that if the use of CBCT leads to better detection of HCC (seeing) and better detection of tumors feeding arteries (reaching) this does not necessarily lead to a better tumor response. Here again, most studies evaluated the use of CBCT focus on treated tumor response and not on patients. As stated above, we strongly believe that patients are more important than tumors from an oncological point of view. Overall, this should not be held against the use of CBCT during TACE, given its many advantages in terms of treatment planning and guidance, but also in terms of tumor response prediction by evaluating the retention pattern of iodized oil (after conventional TACE) or the contrast saturation (after DEB-TACE) [17, 40, 62–66].

Aside from its retrospective design, this study suffers from several limitations. First, it includes patients over several years, during which expertise of operator may have evolved. Moreover, despite standardized procedures, TACE procedures were different in the two centers. Overall, this may have led to different response rates. Yet, habits did not change in neither center during the study period, and the observed response rate was not different between them, thus limiting the possible bias. Second, several factors associated with response were not included in the present study such as tumor vascularity, or C-reactive protein. Regarding the former, and as stated above, this was intentional because this feature is difficult to assess in patients with more than one tumor. Regarding the latter, it was not available for the majority of patients. This is also why we did not analyze several indexes such as the STATE score. Yet, studies have shown that this score showed disappointing results when externally validated [67]. Finally, we did not analyze long-term outcome.

In conclusion, this study reaffirms the high rate of OR after one session of selective TACE. Individual response remains difficult to predict. Technical factors such as the use of CBCT or the type of treatment delivery do not seem to affect overall response rate in patients.

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TABLES

Table 1: Patient and tumor characteristics at baseline.

Patients	**N = 385**
Mean age (years)	67.0 ± 11.39
Gender	
Male	325 (84.4)
Female	60 (15.6)
Cirrhosis	
No	37 (9.8)
Yes	348 (90.4)
Etiology of liver disease	
No liver disease	23 (6)
Excessive alcohol consumption	103 (26.8)
HBV	41 (10.6)
HCV	88 (22.9)
NAFLD	32 (8.3)
Mixed causes	86 (22.3)
Other causes*	12 (3.1)
Child class**	
A	284 (81.7)
B	63 (18)
C	1 (0.3)
Number of lesions per patient	
One	219 (56.9)
Two	111 (28.8)
Three and more	55 (14.3)
BCLC stage	
A	133 (34.5)
B	252 (65.5)
Portal vein thrombosis	24 (6.2)
Largest tumor diameter (mm)	39.29 ± 27
Lobe (%)	
Right	257 (67)
Left	50 (13)
Bilobar	78 (20)
Location in segment 1 or 4	65 (17)
Baseline alphafetoprotein (ng/mL)†	12. IQR 5-104

Values are presented as mean and standard deviation.
BCLC = Barcelona Clinic Liver Cancer. HBV = hepatitis B virus. HCC = hepatocellular carcinoma. HCV = hepatitis C virus. NAFLD = nonalcoholic fatty liver disease
* Other underlying liver diseases were: hemochromatosis in seven patients. Budd-Chiari syndrome in two patients. Malignant transformation of liver adenomatosis in one patient and cirrhosis of unknown origin in one patient. Co infection VHB-VHD in one patient.
** Child classes are defined for the 348 patients presenting chronic liver disease
† values are expressed as median with interquartile range (IQR)

Table 2: Chemoembolization characteristics (n=385).

Type of chemoembolization	
Conventional chemoembolization	150 (39)
Drug-eluting beads	235 (61)
Complementary embolization	
Gelfoam	149 (36) *
None	39 (44) *
Doxorubicin dose mg	67.7 ± 28
3D CBCT guidance	95 (24.7)

* The sum exceeds 100% because some patients received both gelfoam and PVA particles

Table 3: Factors associated with objective tumor response.

		Objective response according to mRECIST		
		Yes (N = 257)	No (N = 128)	P- value Univariate
Patients	N = 385	257 (66.9)	128 (39.1)	
Centre 1	209 (54.3)	133 (51.8)	76 (59.4)	0.157
Centre 2	176 (45.7)	124 (48.2)	52 (40.6)	
Age (years)	67± 11	67± 12	67± 11	0.940
Gender				0.371
Male	325 (84.4)	220 (85.6)	104 (88.1)	
Female	60 (15.6)	37 (14.4)	24 (11.9)	
Cirrhosis				
No	37 (9.8)	27 (10.5)	10 (7.8)	0.353
Yes	348 (90.4)	230 (89.5)	118 (92.2)	
Etiology of liver disease				0.107
No liver disease	23 (6)	18 (7)	4 (3.1)	
Alcohol consumption	103 (26.8)	69 (26.7)	35 (27.3)	
HBV	41 (10.6)	31 (12.1)	10 (7.8)	
HCV	88 (22.9)	54 (21.2)	34 (26.6)	
NAFLD	32 (8.3)	25 (9.7)	7 (5.5)	
Mixed causes	86 (22.3)	55 (21.4)	31 (24.2)	
Other causes*	12 (3.1)	5 (1.9)	7 (5.5)	
Child class**				0.771
A	284 (81.7)	188 (81.8)	97 (82.4)	
B	63 (18)	41 (17.8)	22 (18.6)	
C	1 (0.3)	1 (0.4)	0 (0)	
Chemoembolization				0.824
Conventional	150 (39)	99 (38.5)	51 (39.8)	
drug eluting beads	235 (61)	158 (61.5)	77 (60.2)	
Type Embolization				**0.010**
None	41 (10.7)	19 (7.4)	22 (17.2)	
Gelfoam	124 (32.2)	86 (33.4)	38 (29.7)	
Beads	220 (57.1)	152 (59.2)	68 (53.1)	
CBCT				0.451
yes	95 (24.7)	67 (26.1)	28 (21.8)	
no	290 (75.3)	190 (73.9)	100 (78.2)	

Delay diagnosis-TACE (days)	43 ± 38	44 ± 37	40 ± 39	0.400
Delay TACE-follow up (days)	38 ± 16.6	39 ± 18	35 ± 12	0.367
Dose of doxorubicin (mg)	67.7 ± 27.9	66 ± 27	70 ± 29	0.250
Number of HCC				
1	219 (56.9)	143 (56.0)	76 (58.8)	
2	111 (28.8)	84 (32.5)	27 (22.9)	0.070
3	30 (7.8)	17 (6.5)	13 (10.2)	
>3	25 (6.5)	13 (5.0)	12 (8.1)	
1 or 2	330 (85.7)	227 (88.3)	103 (80.5)	**0.043**
3 or more	55 (14.3)	30 (11.7)	25 (19.5)	
BCLC stage				0.253
A	133 (34.5)	94 (36.6)	38 (29.6)	
B	252 (65.5)	163 (63.4)	89 (69.4)	
Portal vein thrombosis				**0.040**
yes	24 (6.2)	11 (4.3)	13 (10.2)	
no	361 (93.8)	246 (95.7)	115 (89.8)	
Largest tumor diameter (mm)	39 ± 27	45 ± 25	51 ± 35	
Location (%)				0.800
Right liver	257 (67)	169 (65.8)	88 (67.2)	
Left liver	50 (13)	33 (12.8)	17 (13.3)	
Bilobar	78 (20)	55 (21.4)	23 (18)	
Location in segments 1/4	65 (16.8)	29 (11.3)	36 (28)	**0.001**
Baseline Prothrombin Ratio (%)†	77.4 ± 15.8	77.3 ± 15.5	77.5 ± 16.6	0.876
Baseline Total serum bilirubin (mg/dL)	18.8 ± 19.0	18.5 ± 21.2	19.4 ± 13.5	0.765
Baseline alphafetoprotein (ng/mL)	12. IQR 5-104	12. IQR 5-104	11. IQR 5-58	0.713

Values are presented as mean and standard deviation or as values (percentages).
BCLC = Barcelona Clinic Liver Cancer. HBV = hepatitis B virus. HCV = hepatitis C virus. NAFLD = nonalcoholic fatty liver disease. α-FP = alpha foetoproteïn. 3D = three-dimensional.
* Statistically significant result ($p < 0.05$).
** Child classes were analyzed for patients presenting chronic liver disease.
Doxorubicin dose injected is expressed as a fraction of chemotherapy dose (150mg for drug-eluting beads procedure and 60mg for conventional chemoembolization).
† expressed as median and interquartile range (IQR).

Supplemental material 1: Factors associated with tumor response during TACE in recent literature.

Article	Date	Predictive factors identified	OR and P-value***
Ebied et al [22]	2003	Hypervascular vs. hypovascular for tumor response and survival	p=0.002
O'Suilleabhain et al [23]	2003	to better response: Female gender Absence of portal vein thrombosis Albumin greater than 35g/L Absence of ascite AFP below 1000ng/L* Unilobar tumor Fewer than 3 tumors Tumor size < 8cm	 p=0.037 p=0.011 p=0.040 p=0.028 p=0.007 p=0.027 p=0.015 p=0.021
Hiraoka et al (28)	2009	For poor response: Bilobar tumor Tumor size >10cm AFP> 400ng/ml* Portal vein thrombosis	
Riaz et al [68]	2010	Correlation between EASL criteria response after TACE and histopathologic response	
Yand et al [69]	2010	Higher hepatic arterial perfusion was correlated with better Lipiodol deposition	p=0.01
Hong Tao hu et al [43]	2011	For poor response: Portal vein thrombosis Tumor size > 4cm Tumor vascularity AFP > 83ng/ml*	 4.24 p<0.01 2.85 p=0.02 11.97 p<0.01 p=0.03
Tsai YJ et al [29]	2011	For poor response: AFP> 40ng/mL* Score Child-Pugh B Performance Status 1 Volume tumor > 65cm3 Vascular invasion	 p=0.024 p=0.011 p<0.001 p=0.01 p=0.05
Sawhney et al (42)	2011	AFP>200 ng/mL*	
Lee et al [70]	2012	For better response: Size of drug eluding Beads < 90 µm	 p=0.07
Kwan et al [71]	2012	For better response: Avid lesion enhancement Presence of feeding vessel larger than 0.9mm Extensive accumulation of Lipiodol during TACE	 p=0.03 p=0.01 p=0.04

Kawaguchi et al (72)	2012	Lipiodol accumulation pattern evaluated by CT immediately after TACE was a good indicator of tumor response	p=0.01
Miyayama et al [41]	2014	Using CBCT during TACE	p<0.001
Odisio BC et al (72)	2014	Correlation between mRECIST and histopathology Encapsulate lesion	p=0.001 p=0.002
Suk Oh et al [65]	2014	Contrast saturation with DEB evaluated by CBCT after TACE was a good correlation with response	p<0.001
Kim et al [17]	2015	For poor response: Tumor size >5cm AFP>200ng/mL*	
Park et al [72]	2015	For better response: Tumor size <5cm Presence of feeding arteries	 p=0.047 p=0.043
Vesselle et al (24)	2015	For better response: Tumor size < 5 cm Location in median liver was associated with lower response than location in right liver Total extinction blush immediately after TACE	 p=0.001 p=0.003 OR 3.57 p=0.009
Chen et al [44]	2016	Tumor size Deposition of Lipiodol AFP*	p=0.017 p=0.024 p=0.041
Schicho et al (73)	2016	Conventional TACE vs microsphere and DEB-TACE induce better elevated of VEGF** after 1month	p=0.04
Jeong et al [26]	2017	For poor response: one tumor with size > 5cm AFP>20ng/mL* Portal vein thrombosis	 p=0.02 p=0.026 p=0.013

* Alphafetoprotein (ng/mL).
** Vascular endothelial growth factor.
*** Statistically significant result ($p < 0.05$).

Supplemental material 2: Comparison between DEB-TACE and cTACE for the treatment of hepatocellular carcinoma.

Reference	Date	Type of TACE	P-value *
Scartozzi et al (31)	2010	cTACE > DEB-TACE for survival	p=0.03
Lammer et al [37]	2010	DEB-TACE= cTACE for response but better tolerance	P=0.11 p<0.001
Dhanasekaran et al [32]	2010	DEB-TACE > cTACE for survival	p=0.03
Van Malestein et al (38)	2011	DEB-TACE less plasma concentration of chemotherapy than cTACE DEB-TACE= cTACE for tumor response	p<0.001 p=0.54
Sacco et al [48]	2011	cTACE=DEB-TACE	
Ferrer et al (33)	2011	DEB-TACE = cTACE for response and survival Better tolerance of DEB-TACE	 p<0.001
Wiggermann et al [34]	2011	DEB-TACE > cTACE	p=0.01
Song et all [9]	2012	DEB-TACE> cTACE for response and TTP+	p<0.001
Recchia et al (49)	2012	Low toxicity DEB-TACE	p<0.001
Nicolini et al [50]	2013	DEB-TACE> cTACE for survival after liver transplantation	p=0.049
Jia-Yan et al (51)	2014	DEB-TACE > cTACE for survival (meta-analysis).	
Huang et al [73]	2014	DEB-TACE> cTACE for response and survival (meta-analysis).	
Facciorusso et al (53)	2015	Response cTACE> DEB-TACE Same for survival.	p<0.039 p=0.10
Arabi et al [35]	2015	DEB TACE less adverse effect vs cTACE. DEB-TACE=cTACE for survival.	p=0.01 p=0.4
Golfieri et al (39)	2015	cTACE = DEB-TACE for safety, efficacy and survival. More pain for cTACE.	p=0.949
Kloeckner et al [54]	2015	Survival DEB-TACE=cTACE.	p=0.76
Xie et al [36]	2015	DEB-TACE=cTACE for survival. DEB-TACE>cTACE for response (meta-analysis).	
Zou et al [55]	2016	DEB-TACE > cTACE for response and survival (meta-analysis).	
Baur et al [56]	2016	DEB-TACE=cTACE for time to progression	p=0.02
Lee et al [27]	2017	DEB-TACE=cTACE for time to progression	p=0.02

cTACE: Conventional chemoembolization.
DEB-TACE: Drug-eluding Beads chemoembolization.
*Statistically significant result ($p < 0.05$).

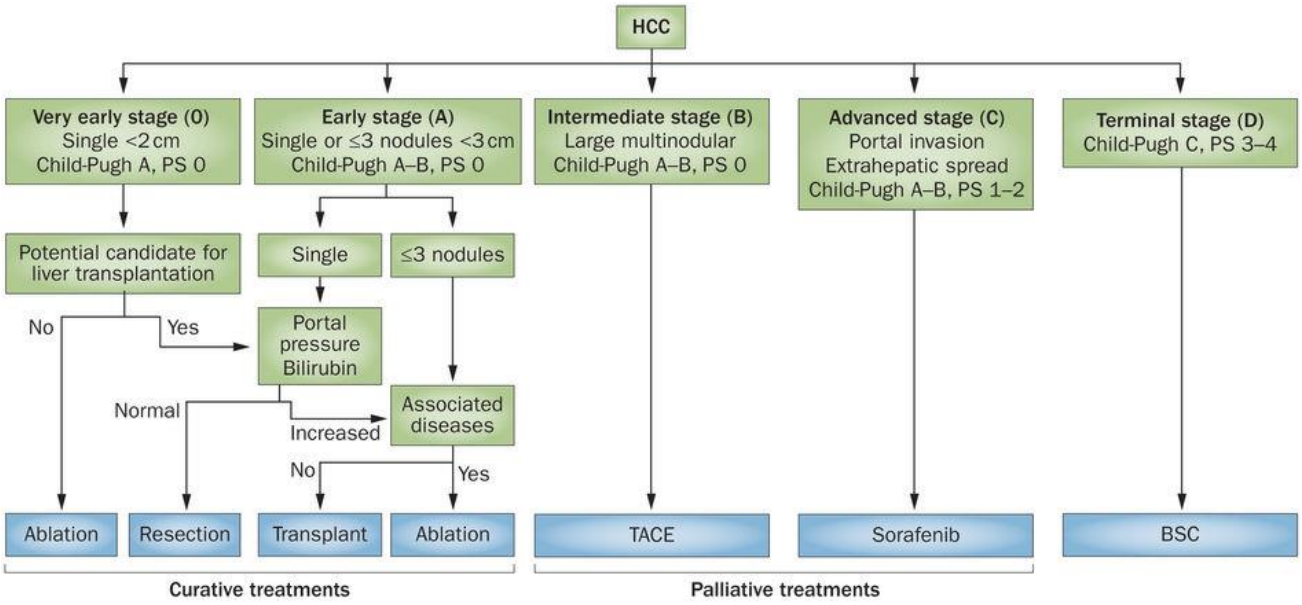
Supplemental material 3: Recent studies showing the value of CBCT during TACE.

Reference	Date	Advantage of CBCT vs DSA	P value*
Kakeda et al (20)	2007	Better HCC detection	
Meyer et al [74]	2008	Biphasic injection for see hypervascular tumor during TACE	p=0.019
Miyayama et al [75]	2009	Detecting and treating small HCC 1.3 +/- 0.3cm	
Tognolini et al [15]	2010	Detection tumors change treatment planning and see residual tumor after TACE	
Iwazawa et al [76]	2010	CBCT >MDCT biphasic for detecting HCC<1cm CBCT =MDCT for HCC=1cm CBCT >MDCT for HCC < 20mm	p<0.001 p<0.001
Miyayama et al (19)	2011	CBCT+ provides useful information that helps perform for TACE CBCT dual phase for depicted corona enhancement in HCC	
Iwazawa et al (60)	2012	Survival Local progression free Using CBCT was an independant factor of survival (multivariate analysis)	p=0.005 p=0.003 p=0.033
Loffroy et al [77]	2012	Detectability of HCC is the same with CBCT biphasic or MRI	
Higashihara et al [78]	2012	CBCT=MDCT dual phase for sensitivity and specificity for detection HCC	p=0.32
Loffroy et al (66)	2013	CBCT dual phase immediately after DEB-TACE to predict response tumor at 1 month	p<0.001
Yu et al [79]	2013	Detection HCC<1cm vs MRI	p=0.023
Suk Oh et al [65]	2013	Evaluation of contrast saturation immediately after DEB-TACE by CBCT to predict tumor response	p<0.001
Miyayama et al (18)	2013	Detectability of tumors and tumors feeding branches	p<0.001
Zheng et al [16]	2013	CBCT was better to detecting HCC< 3cm than CT or DSA	P<0.001
Tacher et al (59)	2013	CBCT dual phase for see tumor Reach tumor Evaluate treatment success	
Choi et al [80]	2014	Most tumor feeding arteries supplying HCC's in the caudate lobe	p=0.011
Minami et al (81)	2014	Feeding tumor vessels	p<0.001

Kim et al [17]	2015	Visualization off smal HCC<1cm and tumors feeders Presence of extra hepatic collateral arteries Assurance of completeness of chemoembolization	p<0.001
Jian-Jun Li et al (64)	2015	C-arm Lipiodol immediately after TACE detecting more small tumors	
Lee et al [81]	2015	Add MIP and MPR during CBCT is better than CBCT alone	p<0.001
Popovic et al (11)	2016	Safety and survival after TACE using CBCT	Mean overall survival was 33.9 months (95% CI; 28.9 – 38.9 months)
Bapst et al [13]	2016	CBCT produces additional information for TACE	
Ishikawa et al (63)	2016	Conventional CT=CBCT for evaluated deposition and concentration of Lipiodol after TACE	p<0.001
Pung et al [12]	2017	Detection tumors and see tumors feeding arteries (meta-analysis)	
Minami et al (62)	2017	Predicting tumor response by retention pattern of iodized oil (density and homogeneity) in HCC evaluate by CBCT	p=0.019
Gutierrez et al [82]	2017	CBCT= MDCT for detecting tumors >1cm MDCT had superior image quality than CBCT	p<0.001 p<0.001
Wang et al (14)	2017	Dual phase CBCT is more sensitive to detect HCC<3cm	p<0.001

HCC: Hepatocellular carcinoma.
CBCT: Cone beam computed tomography.
MDCT: Multidetector computed tomography.
DSA: Digital substraction angiography.
TACE: Transarterial chemoembolization.
* Statistically significant result ($p < 0.05$).

Appendix 1: BCLC staging system and treatment strategy: reproduced from Nature review clinical oncology.



Appendix 2: Modified Response Evaluation Criteria in Solid Tumours (mRECIST): Reproduced from Imaging criteria for assessing tumor response Fournier et al.

Complete response (CR)	Disappearance of any intratumoral arterial enhancement in all target lesions (up to two measurable liver lesions)
Partial response (PR)	Al least a 30% decrease of the sum of unidimensional diameters of viable (enhancement in the arterial phase) target lesions. Taking as reference the baseline sum of the diameters of target lesions
Stable disease (SD)	Any cases that do not qualify for either partial response or progressive disease
Progressive disease (PD)	An increase of at least 20% in the sum of diameters of viable (enhancing) target lesions. Taking as reference the smallest sum of the diameters viable (enhancing) target lesions recorded since treatment started (nadir)

Figure 1: Flow chart of the study.

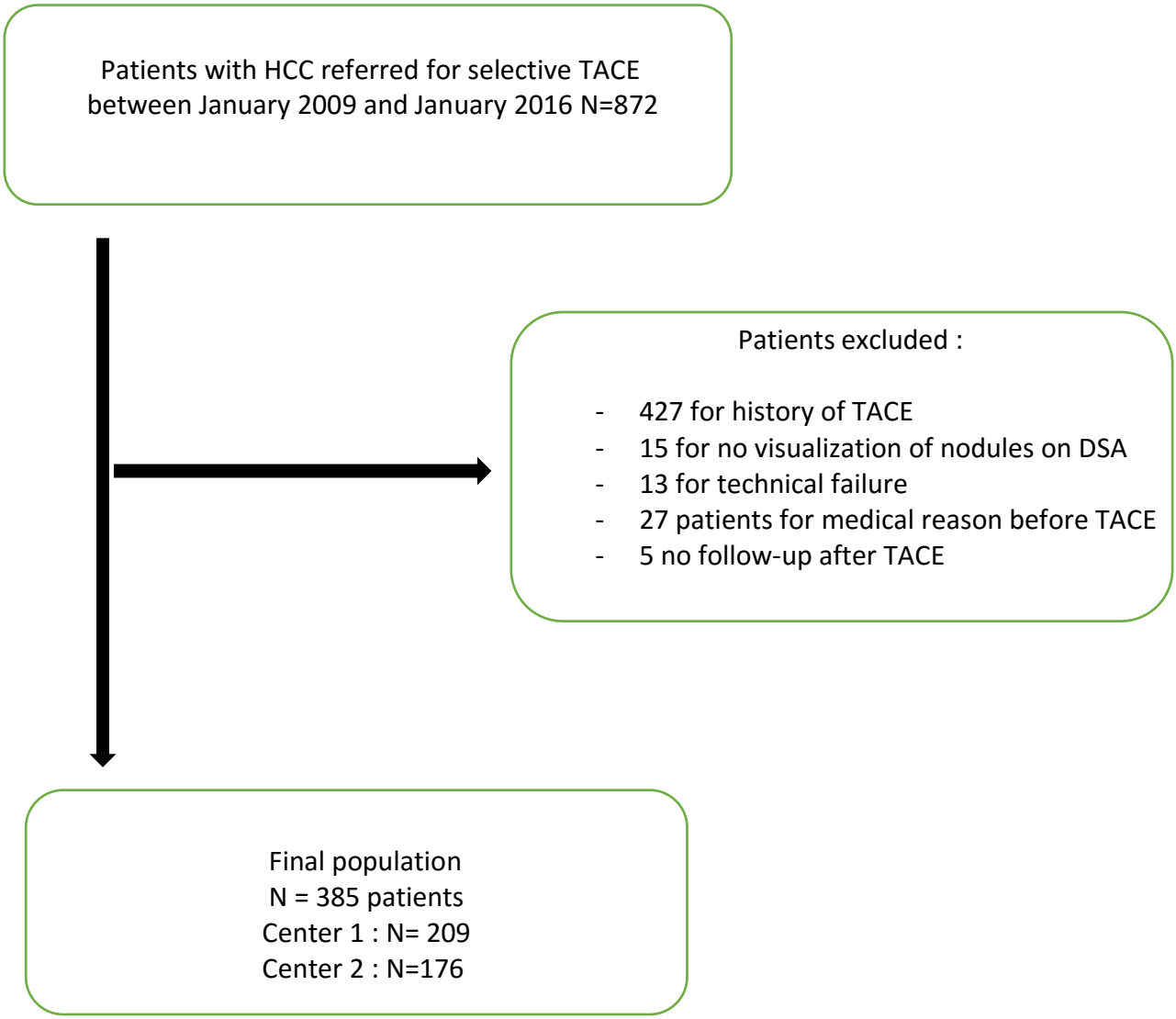


Figure 2: Objective response cTACE vs DEB-TACE and the use of embolic agent.

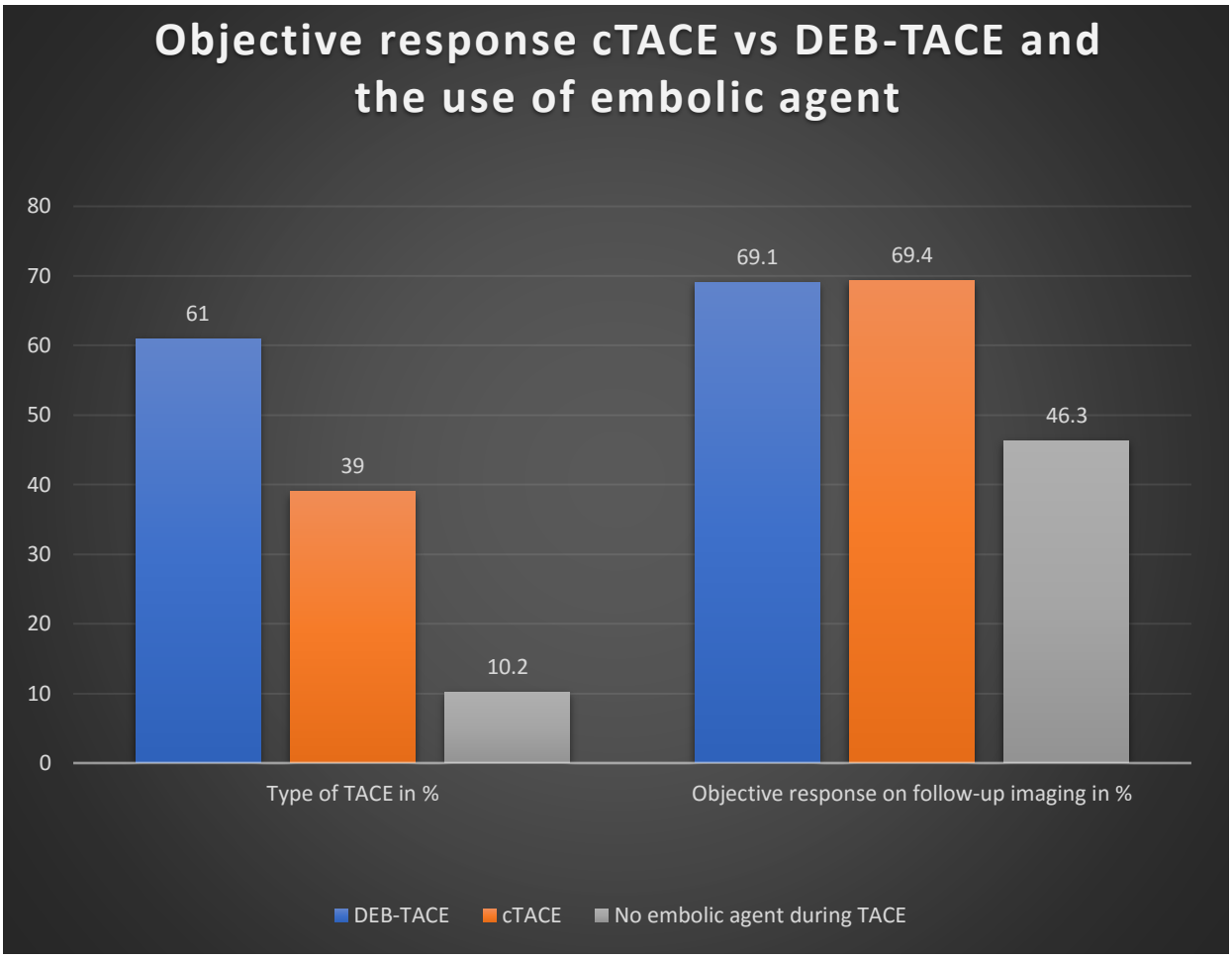


Figure 3: MRI pre DEB-TACE during arterial (a), portal (b) phase and diffusion (c)

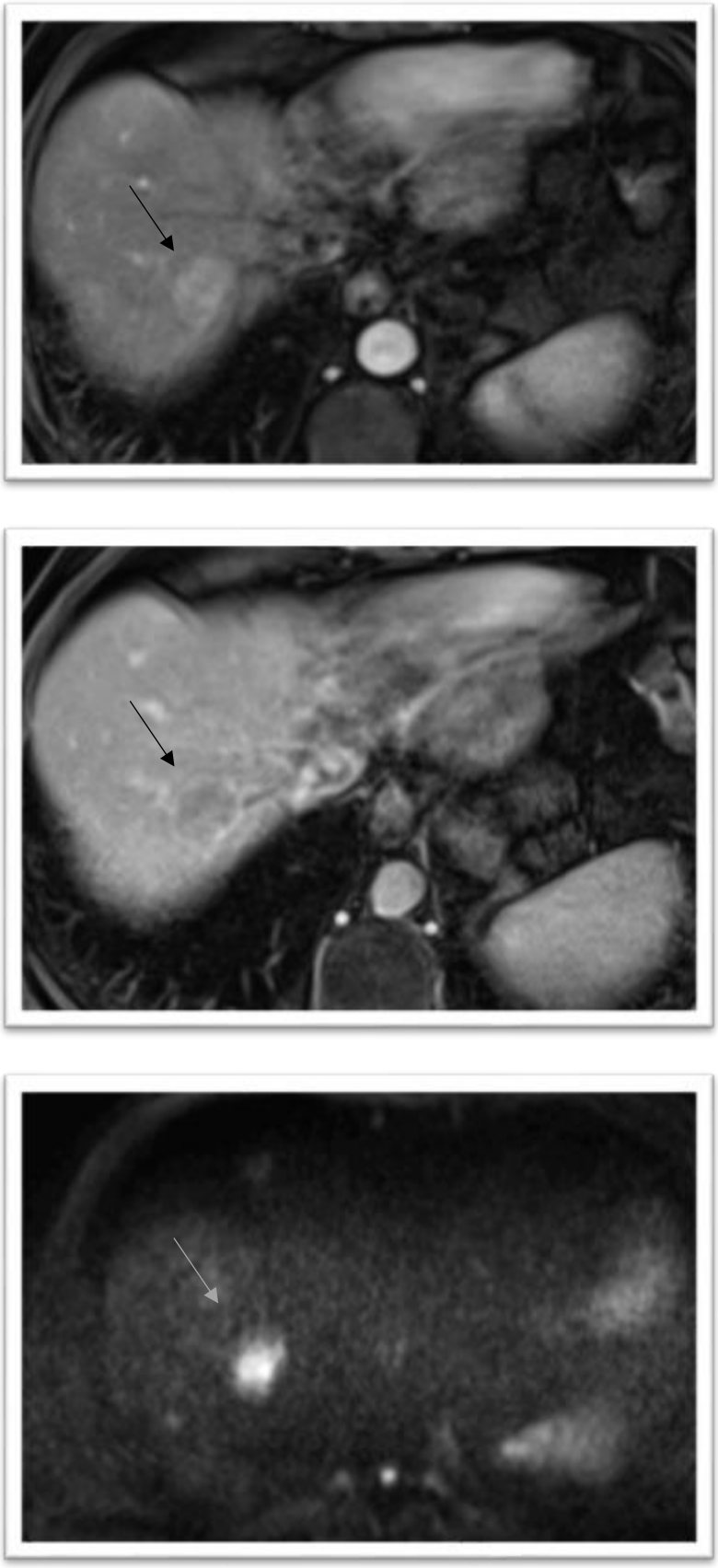
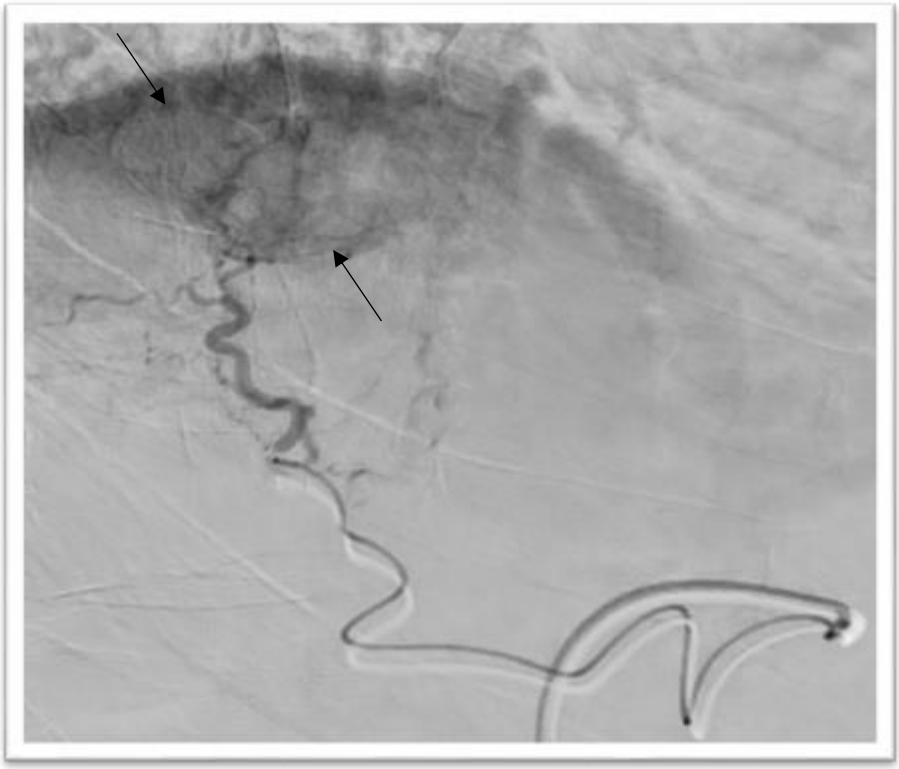


Figure 4: The same nodule than picture 1 during digital subtraction angiography (DSA) (a)and after using software reconstruction during CBCT (b). We have a better visualization of tumor and tumor feeder's arteries with CBCT than DSA. DEB-TACE was used to treat this tumor.



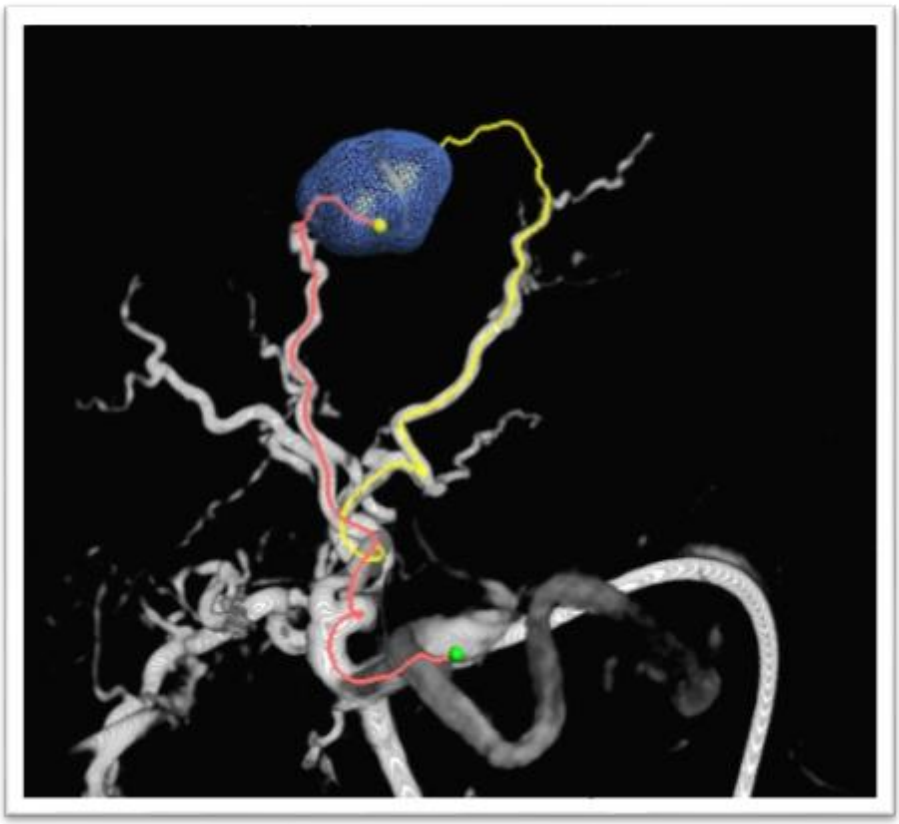


Figure 5: Tumor evaluated by CT scan at one month post DEB-TACE. No contrast (a) and arterial phase (b). We can see a complete response without any tumor enhancement.

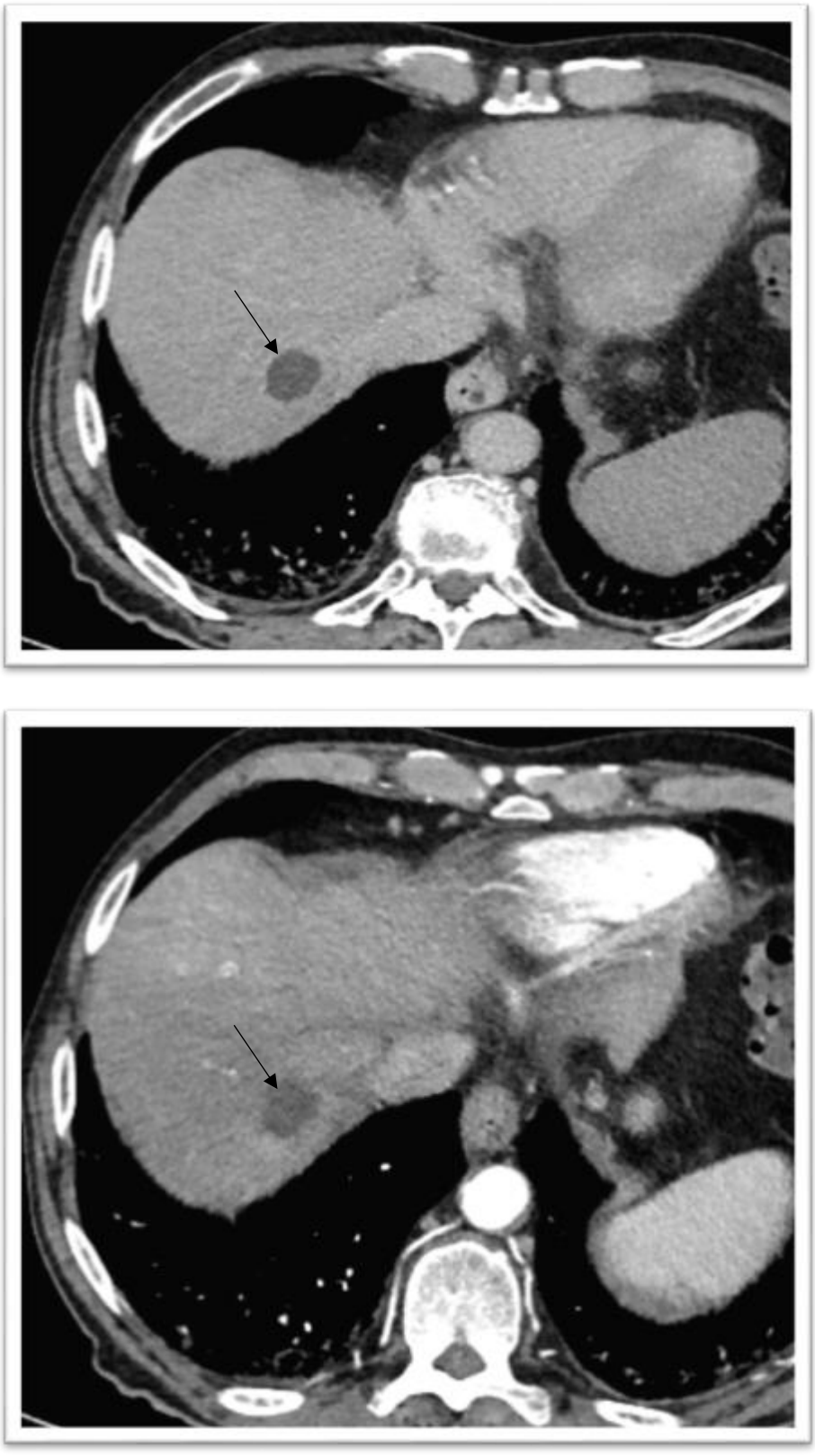


Figure 6 : pre-cTACE CT-scan during arterial phase (a). The same nodule on DSA during c-TACE (b).

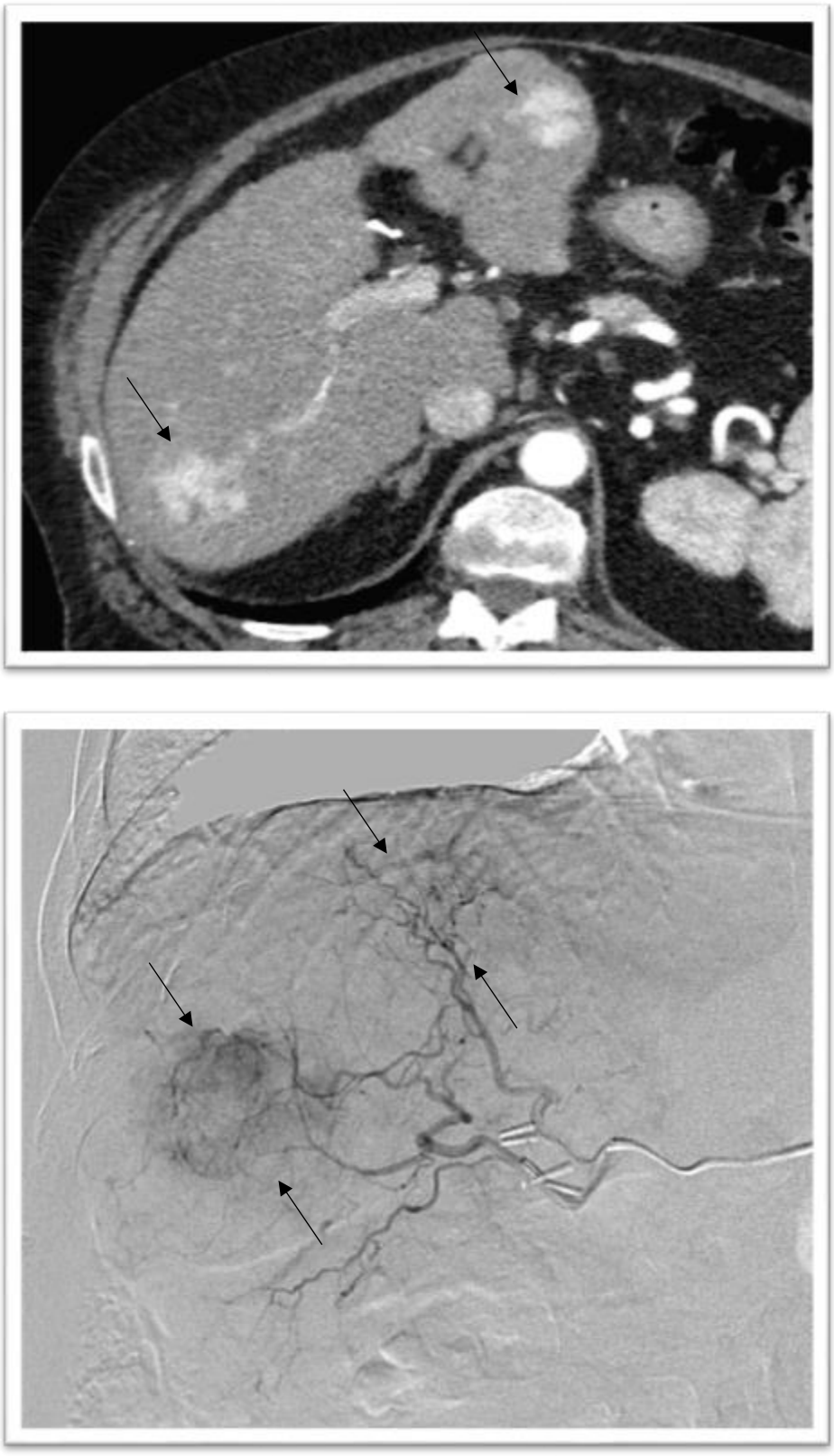
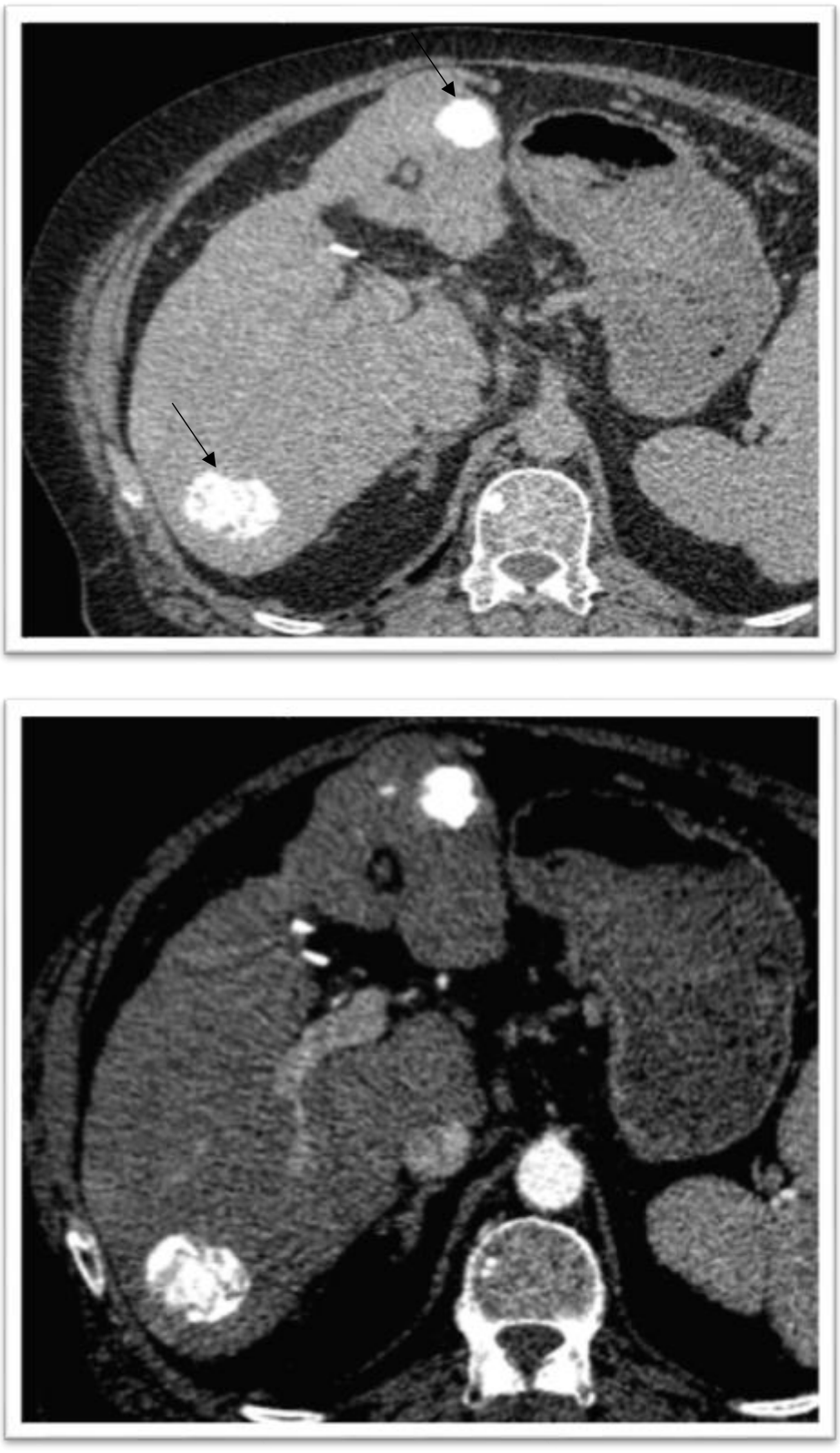


Figure 7: Tumors evaluated by CT scan at one month post c-TACE, no contrast (a) and arterial phase(b). We can see on DSA a complete response without any tumor enhancement and high Lipiodol retention in the tumors.



SERMENT

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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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RESUME

Introduction : L'objectif de cette étude est d'identifier les différents facteurs, notamment techniques, associés à une réponse objective (OR) selon les critères mRECIST, lors de la première cure de chimiothérapie transarterielle (TACE) sélective, dans le cadre du traitement du carcinome hépatocellulaire (HCC).

Méthodes : Nous avons réalisé entre janvier 2009 à janvier 2016 une étude bi-centrique, rétrospective, incluant 385 patients dont 325 hommes (84.4%), pour un total de 702 tumeurs examinées. La taille moyenne des tumeurs était de 40 ± 27mm. Les patients ont reçu une première cure de TACE sélective dans le cadre du traitement de leur HCC. Les critères démographiques, biologiques et les facteurs techniques associés à une OR, selon les critères mRECIST, ont été évalués lors de l'imagerie de contrôle réalisée à 1 mois. Les facteurs techniques analysés étaient : l'utilisation du cone beam computed tomography (CBCT) comme aide technique au traitement et le type de TACE (soit conventionnelle avec du Lipiodol ou des billes chargées). La réponse objective était définie comme une réponse complète ou partielle selon les critères mRECIST.

Résultats **:** Après une première cure de TACE, nous avons observé une réponse objective chez 66.9% des patients. En analyse univariée, les facteurs associés à une OR étaient : l'utilisation d'un agent embolisant durant la TACE (69.4% vs 46.3% p = 0.010), l'absence de thrombose veineuse portale (68.2% vs 45.8% p = 0.041), un nombre de tumeurs < 3 (69% vs 55% p = 0.041), et l'absence de localisation des tumeurs dans les segment I et IV (45% vs 74% dans les autres localisations, p < 0.001). Les facteurs techniques non associées à une OR étaient le type de TACE (p = 0.824) et l'utilisation du CBCT (p = 0.451).

Conclusion : Cette étude réaffirme le haut taux de réponse objective après une première cure de TACE sélective. La réponse individuelle semble être liée aux nombres de tumeurs par patient ainsi qu'à leurs localisations. Au contraire, les facteurs techniques tel que l'utilisation du CBCT ou le type de TACE ne semblent pas avoir d'effet sur la réponse thérapeutique par patient.