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The Advantage of Drug-Eluting Trans-Arterial Chemoembolization Over The Conventional Technique in The Management of Hepatocellular Carcinoma (Bi-Institutional Study)

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ABSTRACT

Background/Aims: To compare the effectiveness of drug-eluting beaded trans-arterial chemoembolization (DEB-TACE) and conventional trans-arterial chemoembolization (C-TACE) in hepatocellular carcinoma patients treated at Assiut University. **Methods:** A bi-institutional prospective controlled clinical trial was conducted at both south Egypt Cancer Institute and Assiut University Hospital interventional radiology units in the period from Aug.2019 to Sep.2021. It included 75 patients, fifty of them performed C-TACE, and the other 25 performed DEB-TACE. The evaluation of the target tumor response was done via mRECIST criteria. Conversion to another therapeutic approach, side effects, post-embolization problems, and altered liver function tests were reported. **Results:** No significant differences between the two therapeutic modalities although the target tumor response showed a slightly significant tendency in favor of DEB-TACE with a significantly lesser complication as it records a lower frequency of post-TACE syndrome (4 (16%) vs. 18 (36%); p= 0.03), and fever (3 (12%) vs. 20 (40%); p= 0.01). The shift to other treatment modalities was not significantly different between the two groups (P <0.001). **Conclusions:** DEB-TACE has a better target tumor response with fewer post-embolization complications when compared to C-TACE in advanced HCC and high-risk patients.

Keywords: Carcinoma**,** Hepatocellular, Chemoembolization; Conventional, Drug-eluting.

INTRODUCTION

The fifth most common malignancy in the world is hepatocellular carcinoma (HCC), and it's the second most common cause of cancer-related mortality worldwide [(1)].

Contrary to the other malignant tumors, it is projected that during the next 20 years, the prevalence and death rates for HCC would considerably increase in some locations around the world, mostly as a result of the expansion of the hepatitis C virus infection [(2)].

Despite the extensive use of surveillance programs for at-risk populations, most people with HCC have a late diagnosis, when it is too late to use curative treatments [(3)].

Curative treatment such as liver transplant, tumor resection, and radiofrequency ablation (RFA) is advised for the early stages of HCC. The alternative for treatment is liver transplantation, particularly for advanced cirrhosis patients, however, there are more recipients than donors. The primary method of treatment for removable HCC is hepatic resection. However, surgery is frequently avoided due to the danger of postoperative hepatic dysfunction. Moreover, there is a high recurrence rate after the therapeutic management trial [(4)].

Trans-arterial chemoembolization (TACE) is the present typical therapy for large or multifocal HCC and reasonably maintained liver function, lack of cancer-related symptoms, and absence of extra-hepatic dissemination or vascular infiltration [(5)]**.**

The reported long-term survival of HCC patients treated with conventional TACE ranges from 8-26% at 5 years. This range is comparable with the other therapeutic modalities (hepatic resection and RFA) provided that the liver functions are balanced among the patients treated with each therapeutic modality [(6)].

Although some individuals needed additional treatments, the majority of the patients who were first treated with C-TACE showed a complete response [(7)]. Particular precautions should be considered to ensure a complete response when using C-TACE as a preliminary treatment, and surveillance for tumor recurrence should be started. In early-stage HCC patients, the overall survival is comparable to hepatic resection [(8, 9)].

Conventional TACE is based on a technique with emulsified combination of chemotherapy such as Doxorubicin and Lipiodol administrated via an arterial feeder. In C-TACE, a combination of Lipiodol and a chemotherapeutic agent live Doxorubicin is injected through an arterial feeding the tumor [(3)].

The main goal of C-TACE treatment is to increase the overall rate of survival and decrease the systemic effect of chemotherapy. However, numerous studies found that there are side effects from C-TACE due to damage to healthy liver cells in addition to killing the malignant cells. These side effects can appear throughout the procedure or within days or weeks after the treatment [(10)]**.** Post-embolization syndrome is the most frequent adverse effect after C-TACE. It includes high body temperature, abdominal pain, nausea, vomiting, and malaise. Subcutaneous bruises or hemorrhage at the site of the

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catheter, increased liver enzymes, respiratory infections, cholecystitis, and tumor-lysis syndrome may also occur [11]. DEB-TACE is a recent technique to deliver the chemotherapeutic agent. Special beads containing the chemotherapeutic agent are injected into the feeding artery, and the drug is slowly sustained-released the drug to damage the malignant cells [10].

The current research aims to evaluate the effectiveness of DEB-TACE in the treatment of HCC and compare it with the effectiveness of C-TACE considering the clinical outcome and safety of both procedures.

MATERIALS AND METHODS

Study design:

We prospectively compared the effectiveness of DEB-TACE and C-TACE for the treatment of HCC from August 2019 to September 2021 with a controlled clinical trial design.

Inclusion criteria: All patients included in this study were histologically diagnosed with HCC. They did not undergo resection or other ablation procedures such as radio frequency, alcohol injection, or microwave ablation.

The two groups did not differ in the patient criteria, concomitant hepatic disease, tumor stage, hepatic function, tumor markers, and tumor size. All patients in this study had Child-Pugh class A or B liver conditions. The baseline demographic data of both groups are shown in **(Table 1).**

Exclusion criteria: Patients with a history of previous therapy such as resection, percutaneous ablation, and systemic chemotherapy (7 patients had been excluded). Patients with impaired coagulation profile (platelets counts < 80000), (prothrombin concentration < 70 %). (4 patients had been excluded after the failure of correction). Patients with ascites impede the maneuver. (2 patients had been excluded) and missed regular follow-up patients in the next year after TACE (11 in numbers), as the study was conducted during the pandemic COVID-19 led to unverified data for these patients.

Ethical considerations:

All patients were not subjected to any kind of risk during this study; their data confidentially were not breached as each patient was coded by a special code created by a computer system and stored in a secure location. Patients were selected randomly from the two different groups of the study by creating a random sample in EXCEL after determining the sample size. Informed consent was signed by all patients and included. The research was conducted only by scientifically qualified and trained personnel. The study was approved by the Ethics Board of Assiut University.

Patients' selection and assessment:

The selection of patients for TACE involves a thorough clinical evaluation with a special focus on concomitant hepatic disease and performance conditions. Also, laboratory evaluations such as liver function tests, kidney function tests, complete blood counts, and coagulation profiles are crucial (summarized in **Table 1**).

Table (1): Demographic characteristics of C-TACE and DEB-TACE groups.

	D-TACE (n=25)	C-TACE (n= 50)	P-value
Age (years)	66.88 ± 8.90	64.09 ± 6.41	0.49
Sex **Male** **Female**	 23 (92%) 2 (8%)	 41 (82%) 9 (18%)	0.21
Diabetes mellitus	9 (36%)	24 (48%)	0.23
Hypertension	20 (80%)	37 (74%)	0.39
Chest diseases	2 (8%)	3 (6%)	0.54
Cardiac disease	1 (4%)	5 (10%)	0.09
liver cirrhosis **HCV** **HBV** **Both**	21 (84%) 1 (4) 3 (12%)	44 (88%) 3 (6%) 3 (6%)	0.45
Bilirubin (mg/dl)	1.25 ± 0.17	1.24 ± 0.24	0.34
Indirect bilirubin (mg/dl)	0.89 ± 0.11	0.84 ± 0.13	0.09
AST (u/l)	48.78 ± 10.3	50.20 ± 12.2	0.35
ALT	75.10 ± 11	47.53 ± 5.3	0.08
Albumin (gm/dl)	3.89 ± 0.41	3.91 ± 0.47	0.13
Prothrombin (%)	87.50 ± 8.77	83.86 ± 7.89	0.22
INR	1.01 ± 0.17	1.02 ± 0.19	0.19
Creatinine (mg/dl)	0.82 ± 0.15	0.86 ± 0.19	0.20
AFP (ng/ml)	456.75 ± 34.87	489.87 ± 55.87	0.14
Child class **Class A** **Class B**	 22 (88%) 3 (12%)	 41 (82%) 9 (18%)	0.45
MELD score	11.78 ± 2.34	12.22 ± 2.09	0.49
BCLC stage **Stage A** **Stage B**	 5 (20%) 20 (80%)	 6 (12%) 44 (88%)	0.09
Partial PVT	6 (24%)	16 (32%)	0.33
Porta hepatis LN	6 (24%)	10 (20%)	0.40

Transarterial Chemoembolization Procedure:

Diagnostic angiography:

The angiographic examination was done in 48 patients using Siemens Artis Zee, Germany. While, it was performed in the other 27 patients using Allura Xper FD 10, Philips, Netherlands.

Before TACE, a 5-Fr angiographic catheter (Impress® Angiographic Catheters of Merit Medical Company, U.S.A) was used following the guide wire (SPLASH Wire™ of Merit medical company, Ireland) for diagnostic angiography of the superior mesenteric artery and celiac trunk through the common femoral artery approach to map the hepatic arterial anatomy, recognize tumor feeder, and confirm the portal vein patency.

Segmental arteries were preferentially catheterized in situations of multiple tumor feeders, whereas the subsegmental branch was super-selected in cases of smaller tumors using micro-catheter, 2.8 Fr (Merit Maestro® Microcatheter. of Merit Medical Company, U.S.A) are used.

Embolization material preparation:

C-TACE was achieved in fifty patients with HCC. We used an emulsion of lipiodol and doxorubicin then injected a gelatin sponge to embolize the feeder of the targeted tumor. 50 mg of doxorubicin (Doxorubicin Hexal® 2mg/ml, EBEWE Pharma, Austria) and 10 mL of lipiodol (Lipiodol Ultra Fluid 10 ml, Guerbet, France) were the highest amounts, respectively.

DEB-TACE was performed in twenty-five patients using Hepasphere (HepaSphere™ Microspheres of Merit medical company, France). The dose of doxorubicin was 50 mg per vial. We used 20-40 µm beads in small HCC. For large tumors with high vascularity, we used 30-60 µm beads or a combination of both sizes of DC beads, i.e., small-sized beads were injected distally, and then large beads were injected proximally.

Evaluation of Effectiveness and Safety

The elimination of all target lesions and maintenance of this response for at least 4 weeks after therapy was referred to as a complete response. A partial response was reported if the decrease in the dimensions of the target tumors was more than 30% by applying uni-dimensional measures of the arterially enhanced lesions according to mRECIST criteria. Between a 30% drop and a 20% rise in the total diameter of the target, lesions were considered to be a stationary disease and more than a 20% increase to be a progressive disease [(12)].

We reported all adverse effects within a week after the procedures as per the Society of Interventional Radiology agreement [(13)].

Follow-up:

Unless a residual lesion or a locally recurrent tumor was detected, all patients underwent follow-up by CT or MRI at 1 month, 4 months, and 7 months after the therapy.

Statistical analysis

Data were interpreted by using SPSS (Statistical Package for the Social Science, version 20). Continuous data were expressed in terms of mean ± SD and compared by student t-test while nominal data were shown in terms of frequency (percentage) and compared by Chi² test.

Predictors of complete tumor response were assessed by multivariate regression analysis. The confidence level was kept at 95%; hence, the P-value was considered significant if less than 0.05.

RESULTS

Tumor response among studied groups:

Both groups had insignificant differences regarding tumor response at a different assessment time following injection. Complete response in 1st, 4th, and 7th month following injection occurred in 24 (48%), 22 (44%), and 22 (44%) patients who underwent C-TACE, respectively (**Figure 1**) while occurred in 14 (56%), 14 (46%), and 14 (56%) patients underwent DEB-TACE (**Figures 2 and 3**).

Table (2): Tumor response among the studied patients. Data are shown as a percentage. P-value < 0.05 was considered significant.

	D-TACE (n=25)	C-TACE (n= 50)	**P-value**
At 1st month			
Complete response	13 (52%)	24 (48%)	
Partial response	6 (24%)	10 (20%)	0.35
Stationary disease	4 (16%)	12 (24%)	
Progressive disease	2 (8%)	4 (8%)	
At 4th month			
Complete response	14 (56%)	22 (44%)	
Partial response	7 (28%)	11 (22%)	0.27
Stationary disease	3 (12%)	12 (24%)	
Progressive disease	1 (4%)	5 (10%)	
At 7th month			
Complete response	14 (56%)	22 (44%)	
Partial response	7 (28%)	13 (26%)	0.21
Stationary disease	2 (8%)	10 (20%)	
Progressive disease	2 (8%)	5 (10%)	

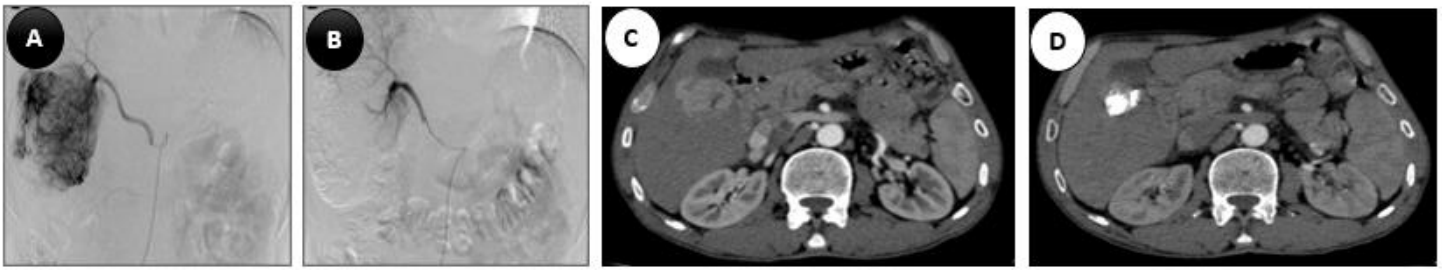

Figure (1): Selective celiac catheterization and angiogram revealed a right lobe hepatic focal lesion with tumoral blush (A). Super selection of the feeding artery was done by micro-catheter followed by injection of 15 ml of Lipiodol/ chemotherapy mixture. Then an injection of 10 ml of lipiodol ensures feeder occlusion. Near total disappearance of the hepatic focal lesion tumoral blush (B). Pre embolization and after 7 months of follow-up triphasic MSCT ensures total devascularization of the hepatic focal lesion as revealed in (C) and (D).

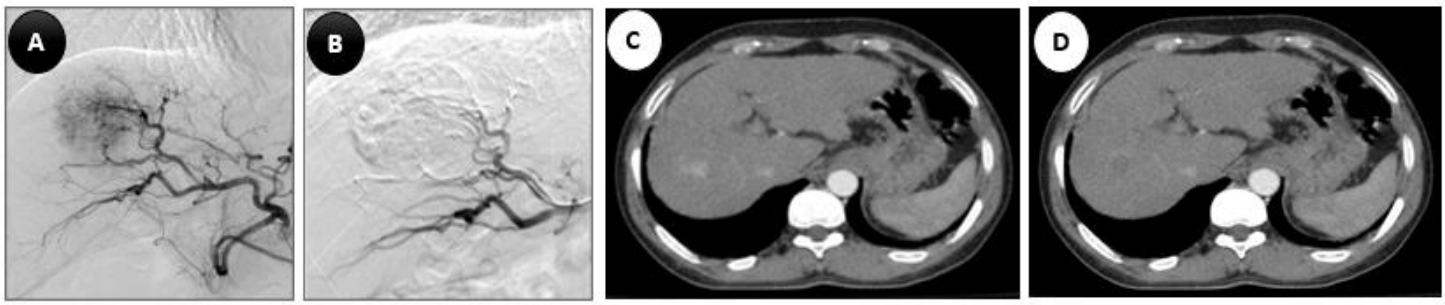

Figure (2): Selective celiac catheterization and angiogram revealed a right lobe hepatic focal lesion with tumoral blush (A). Super selection of the feeding artery was done by micro-catheter followed by injection of 20 ml of calibrated micro-spheres. Near total disappearance of the hepatic focal lesion tumoral blush was seen (B). Pre embolization and after 7 months of follow-up triphasic MSCT ensures total devascularization of the hepatic focal lesion as revealed in (C) and (D).

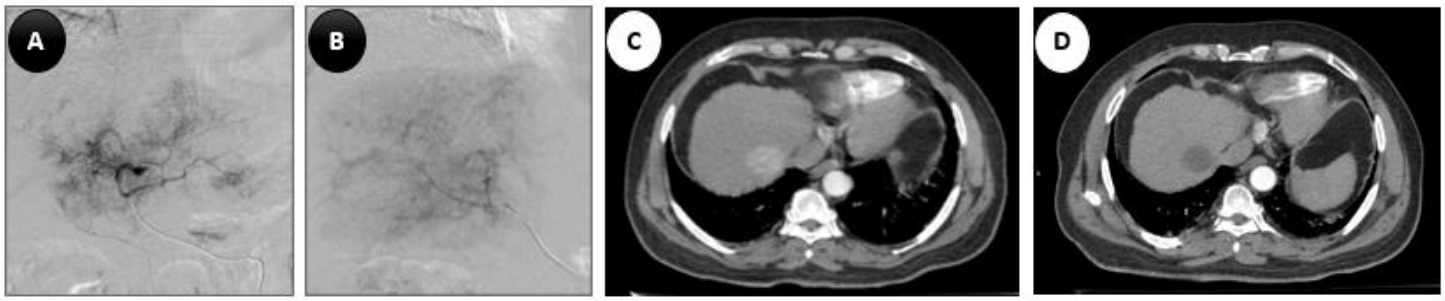

Figure (3): Selective SMA catheterization and angiogram revealed a right lobe hepatic focal lesion with tumoral blush (A). Super selection of the feeding artery was done by micro-catheter followed by injection of 25 ml of calibrated micro-spheres. Near total disappearance of the hepatic focal lesion tumoral blush (B). Pre embolization and after 7 months of follow-up triphasic MSCT ensures total devascularization of the hepatic focal lesion as revealed in (C) and (D).

Adverse events among studied patients:

As regards adverse events in the current study, it was found that patients who underwent DEB-TACE had a significantly lower frequency of post-TACE syndrome than C-TACE (4 (16%) vs. 18 (36%); p= 0.03), and fever (3 (12%) vs. 20 (40%); p= 0.01). Abdominal pain was reported but insignificantly higher among patients who underwent C-TACE (22 (44%) vs. 10 (40%); p= 0.23) in DEB-TACE. Other adverse events following injection are summarized in (**Table 3**):

Table (3): Reported side effects and complications among the studied patients:

	D-TACE (n=25)	C-TACE (n= 50)	P-value
Abdominal pain	10 (40%)	22 (44%)	0.23
Post-TACE syndrome	4 (16%)	18 (36%)	**0.03 ***
Fever	3 (12%)	20 (40%)	**0.01 ***
Diarrhea	3 (12%)	5 (10%)	0.09
Vomiting	1 (4%)	3 (6%)	0.07
Liver cell failure	2 (8%)	3 (6%)	0.45
Renal insufficiency	0	1 (4%)	0.98

Conversion to another modality of treatment:

During the period of follow-up; 2 (8%) patients underwent DEB-TACE required conversion to another modality (one patient underwent radiofrequency ablation, and the other patient had alcohol injection) while in the case of C-TACE; one patient underwent surgical resection and three patients required radiofrequency ablation. This conversion was mainly due to no significant response of lesion to TACE or after using it as a downstaging technique before surgical resection.

Table (4): Conversion to another modality of treatment

	D-TACE (n=25)	C-TACE (n= 50)	P-value
Conversion to another modality	2 (8%)	4 (8%)	
Radiofrequency	1 (4%)	3 (6%)	0.11
Resection	0	1 (2%)	
Alcohol injection	1 (4%)	0	

Data expressed as frequency (percentage). P-value was significant if < 0.05.

DISCUSSION

HCC lesions are hypervascular due to the occurrence of neoangiogenesis. On CT and MRI, these tumors show intense contrast enhancement in the arterial phase with washout of the contrast in the venous phase [(14)].

Trans arterial chemoembolization (TACE) is currently performed as a treatment of large and multifocal HCC when the patients have maintained liver function, absent vascular infiltration, or extrahepatic dissemination [(15, 16)].

Standard patients' selection and detailed assessment of liver laboratory and clinical status, patient preparation, and pre-, intra-, and post-procedure imaging follow-up should be performed.

The most common chemotherapeutic agent used in TACE is doxorubicin in a dose of 50–100 mg/m^2 surface area [(15)]. The second drug that can be used alone or with doxorubicin is cisplatin in a dose of 50–100 mg/m^2 [(16, 17)]. An emulsion is made from the mixture of the chemotherapeutic drug(s) and Lipiodol. Water-in-oil

emulsions are injected to be more tightly kept within the lesions than the substitute oil-in-water emulsions [18]. In water-in-oil emulsions, the amount of the chemotherapeutic agent solution should be less than the amount of Lipiodol [19]. To prepare doxorubicin aqueous solution, a contrast medium may be utilized; using a non-ionic contrast medium will raise the density of the chemotherapeutic agent solution and, by reducing the process of sedimentation brought on by gravity, will enhance the stability of the drug/Lipiodol emulsion [20].

In this study, a mixture of doxorubicin vial 50 mg/25 ml and Lipiodol 10 ml, to make a water-in-oil emulsion. All recommended technical steps and endpoints are performed as available leading to near similar effectiveness results with the same or less reported side effects compared to other similar recent studies.

DEB-TACE is an emerging technique in which microspheres are injected to make a resorbable embolization. This maintains the feeding artery of the tumor patent and is valid for future endovascular treatment. This is the reason that mixing drug/Lipiodol emulsion with an embolic substance is not advised. If microspheres are employed, their size should be between 100 and 300 microns to guarantee distal blockage while protecting feeding segmental arteries. The likelihood of adverse outcomes because of shunting through hypervascular tumors and bile duct damage rises with smaller diameters without superselection [21].

In the current study. we used calibrated microspheres 30-60 microns in DEB-TACE with super-selection for the tumor performed ensuring distal feeder occlusion with no residual tumoral blush. One patient recorded a small peripheral lesion which needed a smaller size of microsphere 20-40 microns.

When the disease has spread throughout the entire lobe, lobar therapy is appropriate. Treatment must focus on a smaller area of the liver and multiple procedures must be arranged in cases with significant tumor burden and low liver reserve. Due to the higher chance of complications, treating the entire liver in one session is not recommended [22].

When we compare C-TACE and DEB-TACE we should consider the post-procedure side effects and the clinical outcome. Some recent studies reported that there was an insignificant difference in the tumor response between C-TACE and DEB-TACE, while DEB-TACE has fewer adverse effects. This suggests that both techniques have similar effects [23-26]. Although, further research revealed that in patients with more severe diseases, the DEB-TACE group's overall survival and disease control were much higher than the C-TACE group's [27, 28].

Another point has to be considered; the technique of drug-eluting beads allows long-term exposure of the tumor for chemotherapy which had been loaded on the microspheres. That may lower the frequency of embolization sessions in comparison with conventional TACE.

The results of the current research showed that the two treatments were similarly effective, with a marginally high tendency to favor DEB-TACE as it recorded lesser side effects than C-TACE.

Regarding the side effects of both procedures such as bradycardia and marked abdominal pain during the procedure, PES, and impaired hepatic function, DEB-TACE is lower than C-TACE. This difference between the two techniques' adverse effects is due to the fundamentally different properties of the chemo-vehicles and embolic substances used in C-TACE and DEB-TACE. In C-TACE, the emulsion of the chemotherapeutic drug and lipiodol produces irritation to the peri-biliary plexus and liver capsule, leading to significant ischemia, and abdominal discomfort throughout the process. While in DEB-TACE, the pain and discomfort are often uncommon and if it occurs, they will be acceptable. Moreover, the patient's vital signs remain steady during the technique [29, 30].

C-TACE and DEB-TACE are two embolic techniques that impair liver functions and cause post-embolization syndrome. Yet, the majority of papers and meta-analyses have revealed that post-embolization syndrome incidence and liver function profile fluctuations are much higher with C-TACE compared to DEB-TACE. Even though doxorubicin was administered at a very high dose to patients receiving DEB-TACE. This outcome is consistent with pharmacokinetics profiles from preclinical research [31, 32].

One of the most feared complications during DEB-TACE is non-target organ embolization like the stomach, gallbladder, or pancreas due to possible showering of the embolizing microspheres. One patient reported abdominal pain in the right upper quadrant immediately after the procedure, possible reflux of microspheres into the cystic artery causing acute cholecystitis is highly considered. This patient was treated symptomatically and no surgical intervention was needed, most of the included cases developed abdominal pain and revealed resolution of pain in the first 24 hours.

In this research, we detected a significantly higher frequency of bradycardia and intense abdominal pain, alterations in liver enzymes, and PES in the patients treated with C-TACE compared to those treated with DEB-TACE.

The high frequency of complications in C-TACE is probably due to the spread of the chemo-lipoidal emulsion into the adjacent peri-tumoral portal veins. The most dangerous side effect of C-TACE is a severe tumor and

hepatic infarction that causes biliary tree necrosis and the creation of abscesses [31, 32].

Study limitations:

1- We only evaluated the progression-free survival rather than the total survival due to the little follow-up period. Some patients were excluded from this study due to the loss of follow-up considering the effect of the pandemic COVID-19.

2- The comparison of DEB-TACE with C-TACE in patients with HCC may be prone to selection bias. Additionally, the medication dose was less in the C-TACE group than it was in the DEB-TACE group. To establish the effectiveness and safety of these two procedures, additional prospective trials with dose adjustment should be carried out.

3- The majority of cases were referred to another therapy upon recurrence, including surgery, RFA, and systemic chemotherapy leading to improper follow-up data.

CONCLUSION

DEB-TACE has a relatively better target tumor response with less post-embolization complication in comparison to C-TACE in advanced HCC and high-risk patients.

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