

Comparative study between conventional chemo-embolization and chemo-embolization using drug eluting beads as alternative methods for treatment of hepatocellular carcinoma

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Abstract: Background: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. HCC is associated with a poor prognosis and remains the third most common death-associated cancer due to the paucity of available treatment options. Combination of regional treatment has become a recent area of research and treatment advances. Chemoembolization as an alternative treatment of HCC through achieving high, localized concentration of chemotherapeutic agents within the tumor as well as inducing localized ischemia by embolic material. This mixture of chemotherapeutic and embolic materials helped in reducing the tumor size and vascularity and so causing intratumoral necrosis. **The aim of the work** is to compare the effect of conventional chemo-embolization and chemo-embolization using drug eluting beads as alternative methods for treatment of hepatocellular carcinoma. **Patients & methods:** Our study included 60 patients with HCC and classified into **Group I:** Included 26 patients underwent conventional chemoembolization and **Group II:** Included 34 patients underwent chemoembolization using drug eluting beads. **Results:** In this study the response to treatment in **Group I** was seen in 17 patients (65%) while there were 9 patients (35%) non-responding. In **Group II** there was response to treatment in 33 patients (97%) while there was one patient (3%) non-responding to treatment there was a statistically significant difference $P=0.001$. **Conclusion:** Chemo-embolization using drug eluting beads is a promising method for treatment of HCC.

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1. Introduction:

Hepatocellular carcinoma (HCC) accounts for more than 90% of all primary liver cancers. It is the fifth most common cancer and the third most common cause of cancer-related death worldwide (Sherman, 2010).

The estimated incidence of new cases is about 500,000-1,000,000 cases per year, causing 600,000 deaths globally per year (Yeh *et al.*, 2007). In Egypt, liver cancer formed 11.75% of the malignancies of all digestive organs and 1.68% of total malignancies. Liver tumors were mostly HCC (70.48%), while hepatoblastoma constituted 10.24%, non-hodgkin's lymphoma 4.21% of hepatic malignancies and adenocarcinoma unspecified 9.03% (Anwar *et al.*, 2008).

Epidemiological studies suggest that infections with hepatotropic viruses are linked to the majority of cases of HCC. In fact, it has been estimated that chronic infections with HBV and HCV account for up to 80% of HCCs (El-Serag and Rudolph, 2007).

Khairy *et al.*, 2011 show potential risk factors of HCC among cirrhotic patients were liver cirrhosis was attributed to chronic HCV infection in 69.8%, chronic HBV infection in 9.5%, and to chronic coinfection

with HCV and HBV in 9.5%, while in non-cirrhotic patients, revealed a significant association of HCC with tobacco smoking, manual agricultural job, female gender, metabolic syndrome, underground water use, and fatty liver.

Pesticides had an additive effect on the risk of HCC in rural males, amongst whom the use of carbamate and organophosphate compounds is common place (Ezzat *et al.*, 2005).

Most patients with HCC die within 1 year after diagnosis. Survival is dependent on tumour size and on associated diseases at the time of diagnosis. Patients with cirrhosis have a shorter survival. Surgical cure is possible in less than 5% of patients. The causes of death include bleeding (variceal, intraperitoneal) and cachexia (Daniel *et al.*, 2004).

Hepatocellular carcinoma (HCC) has one of the highest mortality rates for malignancies worldwide, particularly in Asian countries. Although preliminary screening and diagnosis have allowed HCC patients to benefit from radical resection, transplantation, or radiofrequency ablation, tumors in some patients still progress rapidly because of local spreading or metastases, particularly in those with background cirrhosis. Therefore, overall survival (OS) still can not

be acquired the encouraged improvement in most patients (**Jemal et al.,2011**).

Portal vein invasion is an important survival prognostic factor for HCC. To date, some treatments have been used for portal vein tumor thrombus (PVTT), such as transarterial chemoembolization (TACE), radiation, and systematic chemotherapy, none of which has strong evidence-based support. According to Barcelona Clinic Liver Cancer (BCLC) staging (**Forner et al.,2010**), HCC patients with PVTT, or BCLC stage C, can only receive sorafenib target therapy (**Llovet et al.,2008**). However, for patients with advanced HCC, including vascular invasion or extrahepatic metastases, the median survival time with sorafenib is short – only 6.5 months in Asia (**Cheng et al.,2009**).

In developing countries, such as China, economic conditions restrict the application of sorafenib in some patients. Therefore, consecutive TACE is still used to treat selective patients with PVTT. As the therapeutic approach of choice for unresectable HCC, effects of TACE have been confirmed by some randomized controlled trials (RCTs). A meta-analysis of prospective randomized trials has shown that survival is improved after TACE for unresectable HCC with good liver function preservation(**Llovet et al.,2003**).

Selective arterial treatment of liver tumors with chemotherapeutic and embolic agents (chemoembolization) has been used in Japan for almost 20 years and has produced results superior to those of surgery in some series of patients with resectable HCC, Chemoembolization requires an understanding of the congenital and acquired variations of arterial anatomy that may be seen supplying the liver. Assessment of the patency of the portal vein is also required.(**Gates et al.,1999**).

2. Patients and method:

The present study was conducted on 60 selected patients with HCC, referred from Tropical Medicine department and Surgery department from May 2013 to February 2015.

Inclusion criteria: Patients with HCC diagnosed by imaging either triphasic CT or dynamic MRI, should have adequate contrast enhanced imaging study either CT or MRI to evaluate the size, number, location and extension of the tumor(s), patency of the portal vein and to get an idea about the arterial supply to the tumor(s) as well as the vascular anatomy and should have reasonable performance status (ECOG performance status score) of 2 or less; adequate hematologic function; adequate hepatic function and adequate renal function.

Exclusion criteria include infection, obstructive jaundice, uncontrolled encephalopathy and any

general exclusion criteria of the interventional procedure as bleeding tendency.

The patients were classified into two groups; (group I): Included 26 patients underwent treatment by conventional chemoembolization and **(Group II):** Included 34 patients underwent treatment by chemoembolization using drug eluting beads, the decision of treatment depends on the stage of the disease according to the BCLC (Barcelona Clinic Liver Cancer) staging system. Both groups were performed in patients with BCLC stage B (tumor more than 5 cm or multinodular disease). The study included 40 men (66.6 %) and 20 women (33.4 %) whose ages ranged from 32 to 81 years (mean, 61.4).

All the studied cases were subjected to: Complete history and clinical examination, Complete blood picture & Erythrocyte sedimentation rate (ESR), Liver function tests: Serum bilirubin, ALT, AST, ALP, Serum albumin, prothrombin time (PT) and concentration. Hepatitis markers: For HBV (HBsAg) and for HCV (anti HCV) using ELISA technique according to Abbott laboratories. Alpha fetoprotein: the normal range is under 5 ng /MI (Ball *et al.*, 1992). Abdominal ultrasonography, using Toshiba SSA-340A machine with a 3.5 MHZ curved convex probe. Abdominal spiral CT scan or MRI.

Treatment Technique:Sedation and prophylactic antiemetic were administered in the catheterization. The Patients were placed under non-invasive blood pressure monitoring and continuous Electrocardiographic and oxygen saturation monitoring. Common femoral artery access, selection of the celiac artery and complete hepatic arteriography using DSA was performed at standardized positions with adequate contrast boluses to maximize parenchymal enhancement of malignancies. Contrast enhanced C-arm CT images were obtained with the catheter positioned in the CHA. Multiplanar and maximal intensity projection (MIP) images were reviewed. After determination of anatomy, a coaxial microcatheter was advanced serially into the smallest arterial branches supplying the identified tumor. Multiple superselective catheterizations were frequently required to achieve complete tumor infusion. The chemotherapeutic agent consisted of an emulsion of Ethiodized oil, Cisplatin and Doxorubicin. The emulsion was injected through the microcatheter until tumor uptake was completed or stasis in the feeding vessel was achieved. Hemostasis at the femoral puncture site was achieved by using simple manual compression. All patients underwent TACE were hospitalized overnight for observation and administration of medications as needed. All patients were monitored for mild side effects and symptoms including pain requiring oral analgesics, fever, vomiting or nausea and for severe symptoms

including pain requiring parenteral analgesics, hemorrhage and a decrease in hematocrit by more than 10%. If no unusual or severe side effects were found, patients were discharged within 24 h.

Imaging Analysis: quantifying the size reduction of the tumor as well as the tumor necrosis evaluated by cross-sectional imaging either by CT and/or MRI for all surviving patients 2-3 months after treatment and

approximately every 3 months thereafter, and was categorized according to modified Response Evaluation Criteria in Solid Tumors (RECIST). Responding disease are seen in patient had complete response (CR) or partial response (PR) while patients had either stable disease(SD) or progressive disease (PD) considered non responding disease.

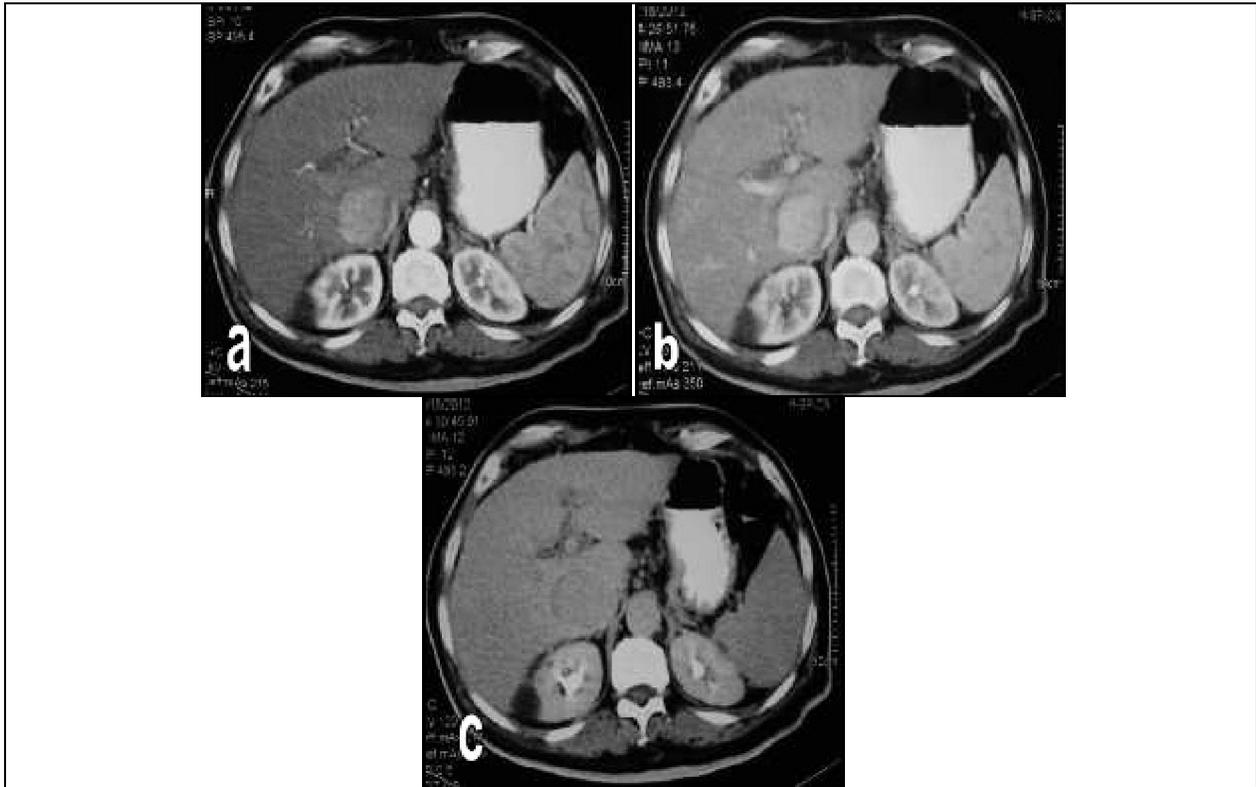
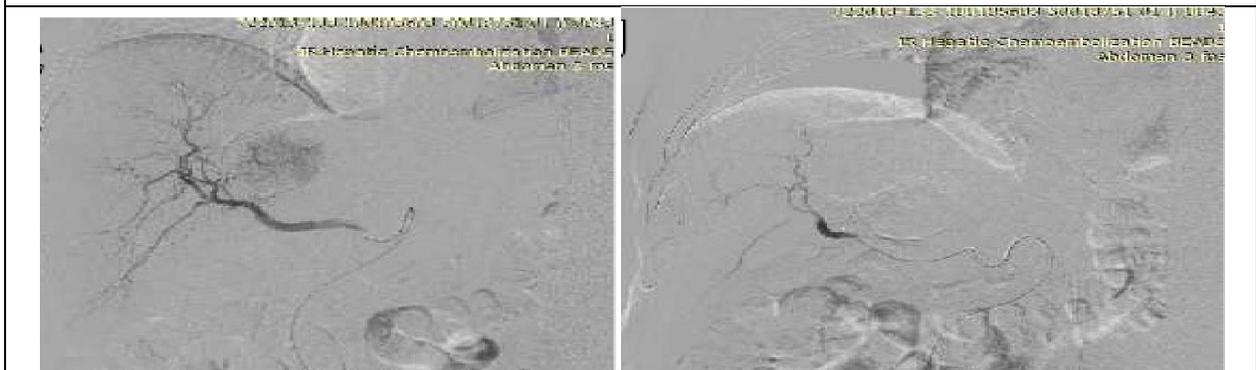
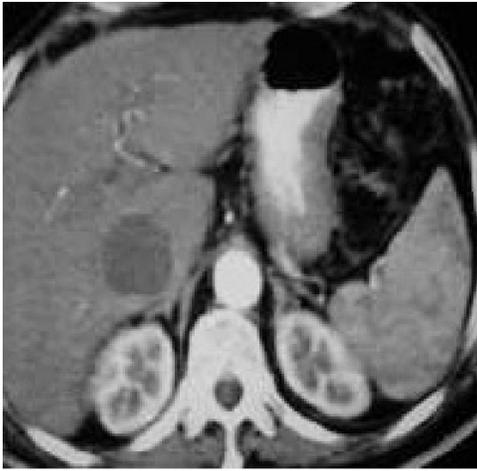


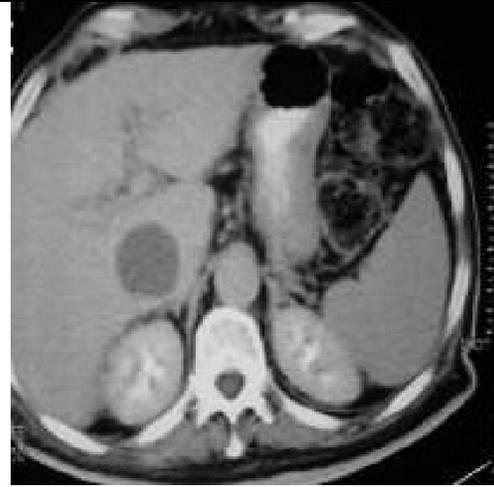
Fig.1: CT showing focal lesion within caudate lobe (segment I) which is enhanced at the arterial phase (a) and washout at subsequent phases (b& c)



(d) Selective celiac arteriography in (d) showing hypervascular stain of the tumor while celiac angiography after embolization in (e) there is complete cessation of the tumor blush after embolization of the feeding arteries



(f)



(g)

Follow up after one month showing complete necrosis of the previously detected caudate lobe vascular mass.



a



b

Fig.2: CT showing focal lesion within segment VI which is enhanced at the arterial phase (a) and washout at subsequent phases (b)

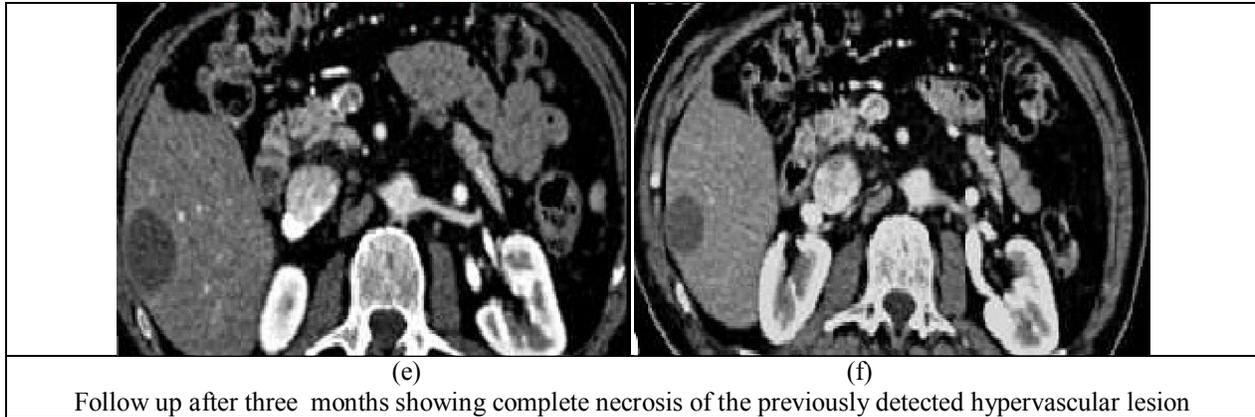


c



d

Selective celiac arteriography in (c) showing hypervascular stain of the tumor while celiac angiography after embolization in (d) there is complete cessation of the tumor blush after embolization of the feeding arteries.



3.Results

The age of the patients ranged from 32 to 81 years and the mean age about 61.1 years. HCC was associated with chronic HCV infection in 54 patients (90%) and Chronic HBV infection in 5 patients (8.3%) and cryptogenic in 1 patient (1.7%) (Table 1). According to performance status (ECOG criteria), 55 patients were graded as grade 0 (91.6%), 3 patients grade 1(5 %), and 2 patients grade 2(3.4%) (Table 2).

Results of liver functions: Compared with baseline for the patient underwent adequate follow up at 1, 3 & 6 months after treatment. **As regard serum bilirubin level** there was increase in the bilirubin level in both groups at 1 month and was greater in Group I with mean about 1.6mg/dl than in Group II with the mean about 1.5 mg/dl. On 3 and 6 months follow up, bilirubin level decreased in Group II greater than in Group I. **As regard ALT &AST** there was decrease in serum level of (ALT & AST) in 1 month follow up with mean about 46 & 56 mg/dl as in respect to baseline laboratory parameters mean 81 & 91.3 mg/dl in Group II, while there was increase in their level in Group I with their mean about 105.4 & 112.2mg/dl in respect to baseline laboratory parameters mean 69 & 83 mg/dl.

Tumor characteristics in the studied groups: As regard Tumor(s) size: The maximum longitudinal tumor dimension in the study was 8cm while the minimum was 1cm with the mean about 3.92 cm while the median about 3.70 cm. In 42 (70%) patients the size of the lesion was ≤ 5 cm, while in 18 (30 %) patients were >5 cm. **As regard Previous intervention:** 47 patients (78.4%) had no previous chemoembolization treatment while 12 patients (20 %) underwent previous chemoembolization sessions and 1 patient (1.6%) underwent previous percutaneous radiofrequency ablation. **As regard location of the lesions:** 5 patients (8.3%) in segment I, 12 patients (20 %) in segment II, 4 patients (6.6 %) in segment III, 4 patients (6.6 %) in segment IV, 6 patients (10.0%) in segment V, 11 patients (18.3 %) in segment VI, 8

patients (13.3%) in segment VII, 10 patients (16.6%) in segment VIII. **As regard radiological character of the lesion:** Well defined lesions were seen in 58 patients (96.7%) while 2 patients (3.3%) had ill-defined lesion surrounded by few satellites in different segment. **As regard the state of the portal vein:** All the patients had patent portal vein except 1 patient (1.8%) had anterior sectorial right portal vein thrombosis. Portal hypertension was present in 46 patients (76.6%). (6) Regarding the number of sessions, the patients underwent from 1 up to 4 sessions with the mean 1.24 while the median 1.00. 52 patients (86.6%) underwent 1 sessions, 6 patients (11.6%) showing 2 sessions, 1 patient (1.6%) underwent three sessions, 1 patient (1.6%) underwent 4 sessions.

Imaging Response and follow up Adequate follow-up imaging was available for all patients in the study. During the follow up period, 49 patients were followed by CT(81%) and 9 patients were followed by MRI(15%), 2 patients was followed by both CT and MRI(4%). Regarding mRECIST response rate; (complete response (CR) was seen in 36 patient (60%), partial response (PR) was seen in 14 patients (23.4%), stable disease (SD) was seen in 4 patient (6.6%) and 6 patient had progressive disease (10%). According to mRECIST response rate, it was found that responding disease was seen in 40 patients with lesion size ≤ 5 cm and 10 patients with lesion size >5 cm. while non responding disease was seen in 2 patients with lesion size ≤ 5 cm and 8 patients with lesion size >5 cm, the difference was statistically significant ($P = 0.0001$). According to mRECIST criteria responding disease was seen in 33 patients underwent DCB chemo-embolization and 17 patients underwent conventional chemo-embolization. While non responding disease was found in 1 patient underwent DCB chemo-embolization and 9 patients underwent conventional chemo-embolization. The difference is statistically significant $P=0.001$.

Table (1): Hepatitis percentages in the studied cases

%	Frequency	
90.0	54	HCV
8.3	5	HBV
1.7	1	Cryptogenic

Table (2) : Performance score (ECOG classification) in the studied cases

%	Frequency	ECOG
91.6	55	0
5.0	3	1
3.4	2	2

Table (3): Modified RCIST response to Size of lesion

p-value	Non –responding (n=10)	Responding (n=50)	mRCIST response
			Size of lesion
0.0001*	2 (5%)	40 (95%)	≤5cm (n=42)
	8 (44.5%)	10 (55.5%)	>5cm (n=18)

Table (4): m RECIST response rate regarding procedure used

p-value	Non –responding (n=10)	Responding (n=50)	mRCIST Response
			Technique
0.001*	1(3.0%)	33 (97.0%)	DCB (n=34)
	9(34.6%)	17 (65.3%)	Conventional chemoembolization (n=26)

4. Discussion:

Transarterial chemoembolization (TACE) is the most widely used treatment for hepatocellular carcinoma in non-surgical patients not suitable for radiofrequency ablation. To best assess the prognosis of hepatocellular carcinoma patients it is recommended that the staging system takes into account tumor stage, liver function and physical status (Maluccio *et al.*, 2008).

The strategic advantage of embolization is to allow greater concentrations of chemotherapeutic agents within a tumour. It has been reported that the concentration of chemotherapy within tumour tissue can be 10–100 times higher after chemoembolization than after systemic chemotherapy. Because embolization reduces arterial inflow to tumours, the chemotherapeutic agents will remain in contact with tumour cells for prolonged periods of time. This is due to ischemia induced failure of trans-membrane pumps in tumour cells, resulting in greater absorption of chemotherapeutic agents by the tumour cells, and prevention of the washout of the agents from the cancer cells (Ramsey *et al.*, 2002).

In Conventional TACE therapy, tumor selectivity is achieved when chemotherapeutic agents are mixed with lipidol, to induce ischemia in tumors. In addition, there are side effects of Lipidol as it penetrates the

portal venules and hepatic sinusoids and affects the hepatic microcirculation; also doxorubicin is lost from lipidol in a very short period of time (Malagari. *et al.*, 2008).

DC bead microspheres are a new embolic material for TACE, in which the embolization particles are made from a unique drug –eluting bead (DEB) technology based on polyvinyl alcohol (PVA) hydrogel that has been modified with sulphate groups. They can be loaded with a chemotherapeutic agent widely accepted for treatment of HCC (Malagari *et al.*, 2008).

In our study, 60 patients were included. 34 patients (56.7%) underwent chemoembolization with drug eluting beads while 26 patients (43.3%) underwent conventional chemoembolization. The DEB groups showing significant higher rates of objective response and disease control compared to c-TACE group (93 vs. 72% and 96 vs. 80% respectively). In Poon *et al.*, 2007, 35 patients with un-resectable HCC were included into trial of chemoembolization using DEB. Two courses of TACE using DEB were given at an interval of 2 months. In Nawawi *et al.*, 2010 19 patients (84.2% male; 15.8% female; mean age 59.2 years ± 11.0; range, 32-80 years) with documented HCC of size 1.8-10cm (mean, 4.0cm ± 1.8 undergoing DEB-TACE was reviewed.

In our study According to performance status (ECOG criteria), 55 patients were grade(0) (91.6%), 3 patients were grade 1(5 %), and 2 patients grade 2 (3.4%). The maximum longitudinal tumor dimension in the study was 8cm while the minimum was 1cm with the mean about 3.92 cm while the median about 3.70 cm. In 42 (70%) patients the size of the lesion was ≤ 5 cm, while in 18 (30 %) patients were > 5 cm. All the patients had patent portal vein except 2 patients (3.3%) had anterior sectorial right portal vein thrombosis.

In **Reyes et al.,2009**, ECOG performance status was 0 or 1 in 19 of the 20 patients liver cirrhosis. The mean tumor size was 6.9 cm (range, 1.9–16.2). A portal vein thrombosis was present in 4 patients.

In our study there was decrease in serum level of (ALT & AST) in 1 month follow up in Group II, while there was increase in their level in Group I.

Sacco et al.,2011 concluded that a significant variation in ALT levels was observed after treatment in the overall population. The ALT increase was more pronounced after conventional chemoembolization compared with DEB chemoembolization; nonetheless, ALT levels rapidly decreased in both groups.

In our study according to mRECIST criteria; responding disease was seen in 30 patients (93.3%) underwent DEB chemoembolization and 20 patients (72%) with conventional chemoembolization. While non-responding disease was found in 2 patients (6.6%) underwent DCB chemoembolization and 4 patients (28%) underwent conventional chemoembolization.

In **Malagari et al.,2008**, complete response was observed in 4.8% after the first procedure and 3.6 and 8.3% after the second and third procedures, respectively. At 9 months, complete response was seen in 12.2% according to RECIST tumor response criteria.

In another study done by **Sacco et al.,2011**, Regarding RECIST tumor response at 1 month, complete response and partial response rates were 70.6% (24 of 34) and 29.4% (10 of 34), respectively, after conventional chemoembolization and 51.5% (17 of 33) and 48.5% (16 of 33), respectively, after DEB chemoembolization, the difference was not significant ($P = .100$). No cases of stable or progressive disease were observed.

While in **Reyes et al.,2009**, based on mRECIST criteria, partial response was achieved in 2 patients, and the remaining 18 patients had a stable disease measured by magnetic resonance imaging 1 month after initial DEB-TACE. At 6 months, the disease control rate (objective response plus stable disease) was 95%. In 6 patients, a complete loss of arterial tumor enhancement was documented, and in 6 additional patients a decrease of 30% was reported.

In conclusion:

Finally we concluded that Chemo-embolization using drug eluting Beads is a promising method for treatment of HCC as shown In our study, The DEB groups showing significant higher rates of objective response and disease control compared to c-TACE group. In addition there is decrease in the level of the liver enzymes one month after injection in the DEB group which considered a good indicator of functional preservation of liver tissue compared to the c-TACE group which show elevation of the liver enzymes.

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