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Combined percutaneous ethanol injection and mitoxantrone versus radiofrequency ablation in the treatment of hepatocellular carcinoma

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Abstract

New therapeutic choices have been developed for hepatocellular carcinoma, including percutaneous ablation therapy, transarterial chemoembolization, radiation therapy and molecular target therapy. Ablation of liver tumors is currently the main alternative to liver resection. This work aimed at comparing percutaneous combined local injection of ethanol and mitoxantrone versus percutaneous radiofrequency ablation in the treatment of Hepatocellular Carcinoma. This study included 124 patients with hepatocellular carcinoma, they were randomly divided into two groups; group I (64 patients) treated with local injection of ethanol plus mitoxantrone. Group II (60 patients) treated with radiofrequency ablation. Clinical assessment, laboratory evaluation and CT studies were performed to all patients prior to treatment and at 1, 3, 6, and 12 months' post treatment. The percentage of ablation in both groups at 1, 3, 6 and 12 months were 81.3%, 81.3%,76.6 and 71.9% in group I respectively versus 88.3%, 88.3, 85%% and 81.7% in group II respectively with no statistical significant difference between the two groups. Percentage of ablation in small tumors is higher than large tumors in both groups. Side effects and complications are statistically higher in group II than group I. Combination of percutaneous local injection of ethanol and mitoxantrone is comparable to radiofrequency ablation with less frequent complications in the treatment of Hepatocellular Carcinoma when surgical resection or liver transplantation is not amenable or available.

Keywords: Hepatocellular carcinoma, mitoxantrone, radiofrequency

Introduction

Hepatocellular carcinoma (HCC) is a highly malignant cancer and it is the sixth most common cancer worldwide and the third most common cause of cancer related deaths with higher prevalence in Asia and sub-Saharan Africa [1]. Advancement in diagnostic radiology and nuclear medicine contributed to the accurate and early diagnosis of HCC. Ultrasound, CT, Triphasic CT and MRI are used in diagnosis of this tumor [2].

Surgical resection, liver transplantation and cryosurgery are considered the best curative options for HCC. Regional interventional therapies have led to a major breakthrough in the management of unresectable HCC [3]. Furthermore, experiences in interventional radiology, radiation oncology and surgery fields have grown, and new therapeutic choices have been developed including percutaneous ablation therapy, transarterial chemoembolization (TACE), radiation therapy and molecular target therapy [4]. Ablation of the liver tumors is currently the main alternative to formal liver resection. Radiofrequency ablation (RFA) therapy is one of the image-guided thermal ablation methods. RFA is the preferred local ablation therapy for most small HCC [5]. Percutaneous ethanol injection (PEI) is a procedure of easy application, good tolerability and low cost which can be applied in repeated sessions [2].

Mitoxantrone is a cycle specific anthracyclin which induces persistent intracellular DNA damage. It is used as an anticancer agent and has demonstrated clinical activity when administered via multiple routes: intravenous, intraperitoneal, intrapleural, intrapericardial, or intrathecal [6]. Mitoxantrone was selected for palliative local treat ment of malignant liver lesions because of its low tissue toxicity, high intratumoral concentration after intratumoral instillation, since it has a tendency to remain at the application site [7].

Aim of the Work:
The aim of this study was to compare combined PEI and percutaneous intra lesion mitoxantrone (PIM) versus radiofrequency ablation in the treatment of HCC.

Patients and Methods

This prospective interventional study was conducted in Tropical Medicine Department, Faculty of Medicine, Zagazig university, Egypt, during the period from September 2012 to February 2015 and included 124

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patients presented with 124 focal hepatocellular carcinoma lesions, the patients were randomly divided into 2 groups through random assignment of participants to either of the treatment modalities;

Group I: Comprised of 64 focal lesions presented in 64 patients, which were injected intra leiona with ethanol in multiple sessions followed by one session of mitoxantrone.

Group II: Comprised of 60 focal lesions presented in 60 patients, which were treated by radiofrequency ablation.

Each focal lesion was considered as one subject. The diagnosis of HCC was based on typical characters of focal lesion in triphasic CT: filling of the dye in arterial phase and rapid fade out in venous and delayed phases, CT and/or or by histological confirmation. Inclusion criteria in both groups are: Single lesion < 5 cm [8], Child- Pugh class A and B, Serum creatinine < 2 mg/dl. Performance status 0-2 [9] and Absence of ascites. Pre-treatment assessment of all patients was done by full history taking, thorough clinical examination, laboratory investigations including CBC, liver function, kidney function, α fetoprotein, serological examination for HCV and HBV. Radiological examination including X ray chest, CT study, ultrasound and ultrasound guided biopsy when indicated. Evaluation of the treatment response was done by triphasic CT 3-4 weeks post procedure and at 1, 3, 6 and 12 months. Complete ablation is the absence of arterial uptake by the focal lesion. Partial ablation is patchy or rim of uptake in the arterial phase. No response, the focal lesion shows arterial enhancement, venous and delayed wash-out of contrast. Ultrasonography to assess the size and echogenicity of the focal lesions and other sonographic findings. Follow up of laboratory tests, as CBC, liver and kidney functions and Serum Alpha fetoprotein were done after one month and every 3 months up to one year.

Ethanol injection:

All lesions were injected ultrasound guided by absolute alcohol in multiple sessions once weekly under complete aseptic condition and 10 mg midazolam as a sedative agent. The same operator used spinal needle (20 gauges) to inject ethanol intra lesion and leave the needle for 2 minutes in place, then injection of local anesthetic during withdrawal of the needle to minimize the irritant effect of refluxed ethanol to the capsule. The total amount of ethanol can be calculated according to the following equation: $V=4/3\ \pi(r+0.5)^3$ Where: V=Volume of ethanol, π= 22/7, r = radius of the tumor by cm plus 0.5 cm as safety margin [10]. The average amount per session was 6.8 cc, with average 5 sessions per lesion and average amount of 35 cc per lesion which was calculated according to the above mentioned equation used by Shiina et al. [10]

Mitoxantrone injection:

This was done to patients of group I after completing sessions of ethanol. Ultrasound guided injection of mitoxantrone mixed with lipidol at the time of injection in a single session; the dose of mitoxantrone is 0.5 mg per cubic centimeter of the tumor size. Re-evaluation of the patients was done by laboratory investigations, ultrasound and triphasic CT after treatment and every 3 moths up to one year

Radiofrequency ablation (RITA 1500X RF generator):

All patients were fasting before the procedure. Treatment was performed with the patient under conscious sedationwhich was induced by the administration of midazolam (Dormicum® 10 mg amp; Roche) 0.03-0.1 mg/kg/IV every 30 minutes, propofol (Diprivan® 20 mg amp; Astra) 0.5 mg/kg/IV over 3-5 minutes immediately before treatment. All lesions were ablated by the same operator hands, under complete aseptic condition at Ultrasonography Unit, Tropical medicine department. Multiple curved, retractable electrodes, are kept inside the needle (Starburst XL) until its tip is positioned within a tumor. When properly positioned, a plunger on the hub of the needle is advanced so that the electrodes extend from the needle tip. When fully extended, these electrodes resemble an open umbrella. Multiple electrode tips of an expanding electrode are active. This results in more homogenous heat distribution within the tumor and creates a reproducible sphere of ablation every time**.** Inpatient observation for 6 hours, for blood pressure, pulse, pain and vomiting was done.

This study was carried out in accordance with the World Medical Association code of ethics (Declaration of Helsinki), and informed consent was obtained from all patients and the protocol of the study was approved by the ethical committee of Faculty of Medicine, Zagazig University. Written Informed consents were obtained from all patients.

Statistical analysis

Data were checked, entered and analyzed using SPSS 14 for Windows. Data were expressed as mean ± SD for quantitative variable, number and percentage for qualitative one. Chi-squared or fisher exact, t test and paired t test were used when appropriate. $P < 0.05$ was considered significant.

Results

The clinical presentation of the studied patients is shown in table 1. Group I included 48 male patients and 16 females with a mean age of 58 years. Group II included 51 male Patients and 9 females with a mean age of 60 years. There was no statistically significant difference as regard age and sex between the studied groups. Chronic HCV infection was the predominant virus in our study, 108 patients were HCV antibodies positive, where 15 patients were HBs Ag positive and only one patient had co-infection of both viruses. There was no significant difference in the size of tumors between the two groups.

Local ablation therapy for HCC is associated with a variety of complications as shown in table 2. The most frequent complication was intolerable pain (needs analgesics) which was significantly higher in group II (50%) than in group I detected in 14.1% and 50% of patients in group I (14.1%). Other complications; vomiting, peritoneal collection and pleural effusion were comparable in both groups. All these complications were controlled by conservative management. Table 3. compares biochemical parameters among patients of groups I before and 3 months after injection, there was no statistically significant difference as regard all parameters except for ALT which showed statistically significant improvement after treatment. Table 4.

compares biochemical parameters among patients of groups II before and 3 months after injection, there was no statistically significant difference as regard to αFP, AST, serum bilirubin (BIL), serum albumin (ALB) and serum creatinine (CRT), while, ALT showed statistically significant improvement after injection. Table 5, 6, 7 and 8 compare the success of ablation and rate of recurrence at 1, 3, 6 and 12 months with no statistically significant difference between both groups.

Table 1. Clinical presentations of all patients.

	Group I No=64	%	Group II No=60	%
Accidentally	31	48.4%	26	43.4 %
Abdominal pain	18	28.1%	20	33.3 %
Weight loss	9	14.1%	10	16.7 %
Fever	6	9.4%	4	6.7 %

Table 2. Frequency of complications after injection in group I and group II

Complication	group I No=64		II No=60		
	No	%	No	%	p
Intolerable pain	9	14.1%	30	50 %	<0.0001
Vomiting	4	6.3 %	10	16.7 %	
Peritoneal collection	1	1.6 %	0	0%	
Pleural effusion	3	4.7 %	3	5%	
Signs of liver failure	3	4.7 %	2	3.3 %	
No complications	44	68.8 %	15	25%	

Table 3. Biochemical tests in group I before and 3 months after injection.

	Group I before	Group I after	P
α FP	247.9±477	227.2±421	0.178
(normal 10 u/dl)	1.8-2690	2-1950	
AST	69.6±32.3	61.7±19.3	0.520
(normal up to 40 u/dl)	19-150	29-117	
ALT	72.3±20.7	52.9±11	0.00
(normal up to 40 u/dl)	16-115	27-80	
BIL	1.22±0.4	1.32±0.47	0.67
(normal 0.3-1.2 mg/dl)	0.6-2.1	0.8-3.1	
ALB	3.5±0.4	3.4±0.47	0.19
(normal 3.5-5.3 g/dl)	2.9-4.5	2.5-4.4	
ALP	238+40	245+45	0.12
(normal 75-250 u/dl)	115-350	76-590	
PT	14.4±0.9	14.6±1.3	0.75
(normal 11-14 second)	12.2-16	12.05-18.0	
CRT	0.98±0.16	0.99±0.2	0.30
(normal 0.5-1.4 mg/dl)	0.6-1.3	0.6-1.6	

Table 4. Biochemical tests in group II before and 3 months after injection.

	Group II before	Group II after	P
α FP	330.6±580.4	185.5±320.4	0.31
(normal 10 u/dl)	4.8-1890	3-1250	
AST	72.5±37.2	66.8±48.3	0.45
(normal up to 40 u/dl)	13-143	32-270	
ALT	53.7±29.1	46.8±15.2	0.014
(normal up to 40 u/dl)	11-147	15-76	
BIL	1.13±0.32	1.4±1.26	0.51
(normal 0.3-1.2 mg/dl)	0.6-1.8	0.8-6.9	
ALB	3.4±0.46	3.27±0.41	0.09
(normal 3.5-5.3 g/dl)	2.8-4.3	2.5-4.5	
ALP	225±41	255±41	0.21
(normal 75-250 u/dl)	107-355	71-650	
PT	14.1±1.3	13.8±0.9	0.007
(normal 11-14 second)	11.7-16.3	12.5-16.5	
CRT	1.01±0.2	1.03±0.2	0.08
(normal 0.5-1.4 mg/dl)	0.6-1.5	0.8-1.4	

Table 5. Follow up of complete ablation in both groups 1 month after treatment.

	Group I No=64		Group II No= 60		P
	No	%	No	%	
Ablation	52	81.3 %	53	88.3 %	0.274
Inappropriate response	12	18.8 %	7	11.7 %	

Table 6. Follow up of complete ablation in both groups 3 months after treatment.

	Group I No=64		Group II No= 60		P
	No	%	No	%	
Stationary ablation	52	81.3 %	53	88.3 %	0.5
Local recurrence	1	1.6 %	0	0 %	97
Death	4	6.3 %	2	3.3 %	
	7	10.9 %	5	8.3%	
Excluded (due to decompensation or new focal lesions)					

Table 7. Follow up of complete ablation in both groups at 6 months after injection.

	Group I No=64		Group II No= 60		P
	No	%	No	%	
Stationary ablation	49	76.6 %	51	85 %	0.423
Local recurrence	1	1.5 %	0	0 %	
New deaths	2	3.1 %	2	3.3 %	
Excluded (due to death, decompensation or new focal lesions)	12	18.7%	7	11.7%	

Table 8. Follow up of patients in both groups one year after treatment.

	Group I No=64		Group II No=60		P
	No	%	No	%	
Stationary ablation	46	71.9 %	49	81.7 %	0.43
Local recurrence	1	1.6 %	1	1.7 %	3
New deaths	2	3.1 %	1	1.7 %	
Excluded (due to death, decompensation or new focal lesions)	15	23.4 %	9	15 %	

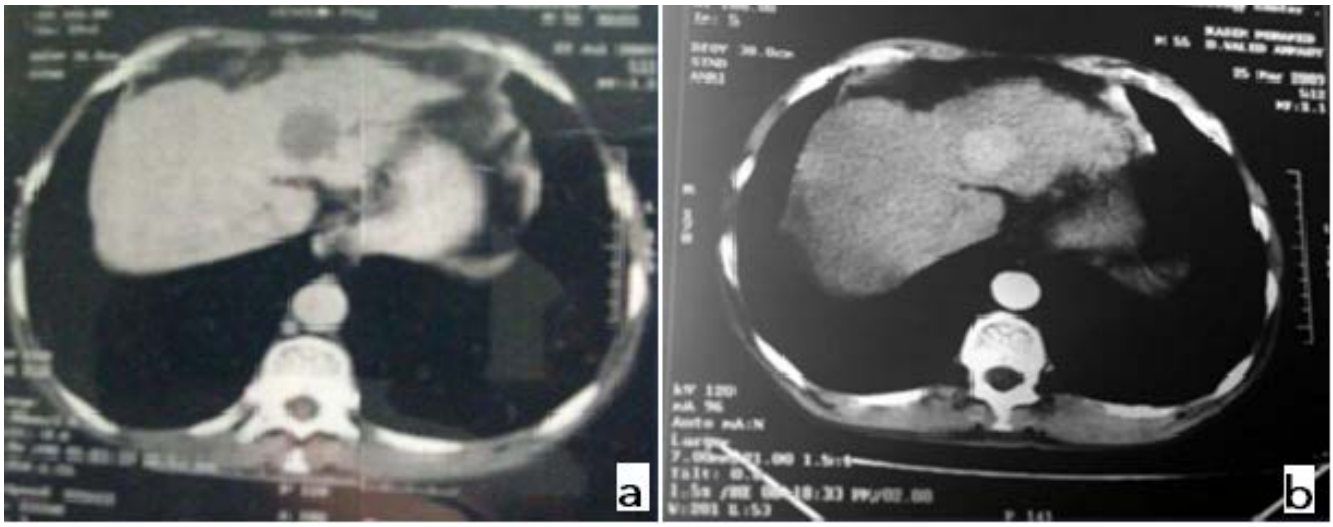

Figure 1. (a) CT study shows HCC with rapid uptake in the arterial phase before treatment. (b) CT study of the same focal lesion shows no uptake (complete ablation) after radiofrequency ablation.

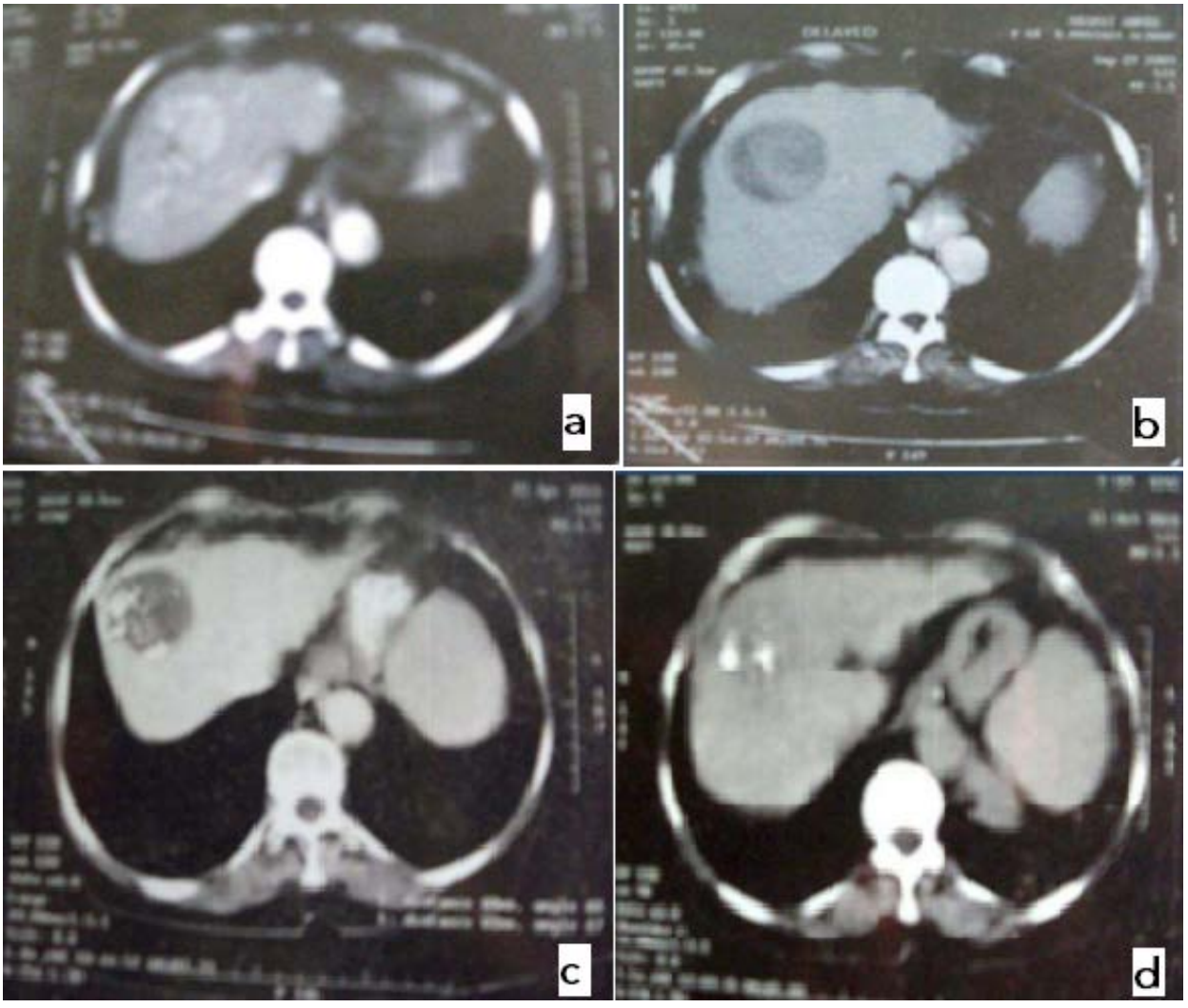

Figure 2. (a, b) CT study showing HCC before treatment. (c) CT study showing complete ablation 3 months after combined ethanol and mitoxantrone (no uptake in the arterial phase) with lipidol inside. (d) CT study showing complete ablation 6 months after combined ethanol and mitoxantrone (no uptake in the arterial phase) with lipidol inside.

Discussion

Percutaneous Ablation is the best treatment option for patients with early stage HCC who are not suitable for surgical resection (SR) or transplantation or when the surgical management is not possible or available or as a bridge to a possible cadaveric liver transplantation in order to keep the patients within the Milan criteria for transplantation [8]. The advantages of PEI are that it is easy to perform and has greater safety and tolerance than (radiofrequency ablation) RFA. However, RFA has the advantage of requiring fewer treatment sessions and yielding a higher rate of complete tumor necrosis with a low rate of local recurrence, it has a risk of a higher rate of major complications [11).

Peng et al. [12] found that radiofrequency ablation (RFA) is considered to be the treatment of first choice for patients with solitary HCC ≤ 5 cm and a well-preserved liver function. Two major limitations for radiofrequency are, first, the risk to provoke heat biliary lesion in case of tumors located proximally to hilar plate, and second, the risk of insufficient ablation due to a cooling effect of large blood vessel [13, 14].

Till the time, this study was planned for at March 2012, many studies had been published to evaluate effect of percutaneous radiofrequency ablation and injection of ethanol in treatment of HCC, but few studies evaluating percutaneous injection of mitoxantron in treatment of HCC were published [15] and only one study- to our knowledge- evaluated the effect of percutaneous injection of combined ethanol and mitoxantron in treatment of HCC [16].

As regard viral hepatitis profile 108 patients (87.1%) had HCV Abs +ve, 15 patients (12.1%) had HBs Ag +ve while only 1 patient (8%) had combined infection, these results are not in agreement with Abdel Wahab and his colleagues [19] who found positive virology in only 82.5% (HCV 61%, HBV 14.5% and combined 7%), this may be attributed to the type of patients selected in the study and locality.

Most patients in our study were discovered accidentally (47%) during routine follow up of liver cirrhosis or abdominal ultrasound evaluation of non-related symptom. However, abdominal pain (right upper quadrant 30.6%), loss of weight (15.3%) and fever (8.1%) were the most common presenting symptoms, this was in agreement with Kew study [20] who found in a meta-analysis study that abdominal pain (59-95%), weight loss (34-71%), liver cirrhosis (54-98%) were the most frequent clinical features of HCC.

The most frequent complication after treatment was pain 14.1% in group I and 50 % in group II. The second complication was vomiting 6.3% in group I and 16.7% in group II. This was in agreement with Curley et al. [21] who proved that the rate of complications in RF is significantly higher than percutaneous ethanol injection and with Blum [22] who stated that PEI is a simple technique with a low rate of complications and reported that the most common side effect of PEI therapy was leakage of alcohol to the surface of the liver and abdominal cavity, causing pain and fever.

The serious complications were more frequent, in group I; one patient (1.6%) developed peritoneal collection, another three patients (4.7%) developed signs of decompensation and three patients (4.7%) developed pleural effusion. This was in agreement with Di Stasi and his colleagues [23] which included 1066 patients. The mean number of sessions needed to destroy a HCC nodule was 6.7. One death (0.09%) and 34 complications (3.2%) were reported, 8 episodes of bleeding and 7 cases of tumor seeding occurred. However, follow up of these complications showed complete resolutions of ascites and pleural effusion suggesting that they were reactionary. This was in consistent with Brunello et al [24] who also stated that no major complications occurred among a total of 248 PEI sessions with average of 3.65 sessions per tumor. Follow up CT showed intraperitoneal hemorrhage in two patients but these resolved spontaneously.

In group II, two patient (3.3%) developed signs of liver failure and three patients (5%) pleural effusion with no patients developed ascites. this study was less than the 13.1%(10) of 76 patients in the study of Curley et al. [21] using the same LeVeen electrode and RF generator but slightly higher than the 2.4% (56) of 2320 patients (p.0.1), including six deaths, in a multicenter analysis using a cool tip electrode [25].

In group I there was no statistical significant difference as regard αFP, AST, BIL, ALB, ALP and creatinine, while ALT showed statistical significant improvement after treatment in comparison to that before treatment and this may be due to loss of tumor burden on the liver and more adherence to treatment. This is in agreement Maria and his colleagues [15] who stated that the doses of 10-20 mg intra tumor mitoxantrone produce no side effects and no hematological toxicity.

In group II there was no statistical significant difference as regard αFP, AST, BIL, ALB, ALP and creatinine, while ALT showed statistical significant improvement after treatment in comparison to that before treatment. This was in consistent with other studies [26]. No statistical difference in both groups for αFP, this could be explained by that the most of patients had a normal αFP before procedure and the high grade HCC probably has satellite nodules that are further away from the main nodule, possibly implying that local recurrence in the same segment can be caused by satellite nodules that may be obscured under sonography, Moreover, a larger tumor is more often manifest with higher differentiation, thus

having satellite nodules along or above the margin of the tumor which might be obscured during sonography.

Follow up CT after one month revealed complete ablation (response) in 52 patients (81.3%) in patients of group I, whereas in group II 53 patients (88.3%) showed complete ablation. These results showed no statistical significant difference between the two groups (p=0.38). Our results are comparable to Giogio and his colleagues [27] who compared 112 patients treated by percutaneous alcohol injection or radiofrequency ablation showed that 47 of 52 (90.3%) treated by RF had complete tumor necrosis with a median of 1.2 treatment sessions versus 45 of 60 (75%) having complete ablation by alcohol injection with 4.8 sessions required, those authors suggested that RF was more effective but had a higher complication rate. This difference in the injection group could be attributed to the effect of mitoxantrone on HCC, which was clarified by Ohishi and his colleagues [28] who stated that Intratumoral instillation of mitoxantron results in a 1000fold higher concentration in the tumor compared with intravenous administration, moreover; lipidol have high affinity to malignant hepatocyts so it vvincreases the duration and efficacy of mitoxantron. Also, we suggest that ethanol injection leads to tissue necrosis and thrombosis of the blood vessels draining the tumor, leading to low systemic effect of mitoxantron and more anti-tumor efficacy.

Ethanol diffuses into the cell and causes nonselective protein denaturation and cellular dehydration, leading to coagulation necrosis, subsequent fibrosis and small vessel thrombosis which contribute to cellular death [29]. Compared with PEI, RFA required fewer treatment sessions and achieved a slightly better rate of complete tumor ablation for HCC lesions; however, a significantly higher rate of complication was noted in the clinical trials [30]. Follow up CT of the completely ablated lesions of both groups after 3 months revealed: In group I, 52 lesions (81.3%) were still completely ablated (stationary course) where 1 lesion (1.5%) showed local recurrence. In group II 53 lesions (88.3%) were still ablated (stationary course) where no lesions (0%) showed local recurrence, While, follow up CT of the completely ablated lesions of both groups after 6 months revealed: In group I, 49 lesions (76.6%) were still completely ablated (stationary course) where 1 lesion (1.5%) showed local recurrence. In group II 51 lesions (85%) were still ablated (stationary course) where no lesions (0%) showed local recurrence.

Follow up after one year in group I, there were 46 lesions (71.9%) still showing stationary course, and 1 patient (1.6%) developed local recurrence. In group II there were 49 lesions (81.7%) still showing stationary course, where 1 patient (1.7%) showed local recurrence. These good results in injection group were explained by Fox and Smith [31] who selected mitoxantrone for local treatment of malignant liver lesions because of its low tissue toxicity, high intra tumor concentration after intra tumor instillation, and long time in the tumor, since it has a tendency to remain at the application site.

These results, although they were better in group II, it showed no statistical significant difference between group I and group II as regard stationary complete ablation (disease free period), which was76.8%, 85%, and 71.9% 81.7%, % at 6 months and one year respectively. This could be due to the additive DNA damaging effect of mitoxantron on HCC lesions, which was evaluated by Ohishi and his colleagues [28]. The histological effects of locoregional mitoxantrone treatment are evaluated by Hoffmann [32] and characterized by complete tumor necrosis in which dead tumor cells are surrounded by an inflammatory infiltrate and a fibrotic organization of liver tissue around the tumor. Also we can't neglect the effect of ethanol on the tumor tissue and vascular thrombosis, leading to more localization and hence more effect of mitoxantrone on malignant tissue.

The local recurrence rate was higher in patients with HCCs larger than 2.5 cm. This finding was similar to those in other reports. The independent factors related to local recurrence were large tumor size (> 2.5 cm) and high Edmondson's grade of tumor. This result was consistent with that of Komorizono and colleagues [26]. A larger tumor usually has a higher rate of local recurrence because it frequently requires multiple overlapping ablations, and targeting of its viable foci is difficult because of lack of clarity of the image obtained between the ablated and non-ablated tumor after repeated ablation is performed under sonography [33]. Moreover, a high grade HCC probably has satellite nodules that are away from the main nodule, possibly implying that local recurrence in the same segment can be caused by satellite nodules that may be obscured under sonography. Despite the wider range (1 cm safety margin) of injections of ethanol or acetic acid herein, the distribution of ethanol or acetic acid might be unpredictable both within the tumor and outside due to interference of the fibrous septum [11] and the presence of satellite nodules around the target tumor, respectively [34], Therefore, a 1 cm safety margin can be achieved in patients treated with RFTA but not in patients treated with PEI or PAI. This limitation of the homogenous distribution of ethanol or acetic acid around the safety margin of the target tumor may explain the benefit of lower local recurrence favoring RF than PEI or PAI in treating HCCs larger than 2 cm in the present study or in other investigations. The rates of new HCC recurrence were also similar between the two groups, perhaps because of the similar baseline parameters [35].

Our results also showed that overall survival showed no significant difference in the RF group (91.7%) and in the PEI group (87.5%). This finding is similar to that of Giorgio et al [27]. The cause of death was HCC progression in most cases.

The disease free period at one year showed no statistical significant difference between group I and group II,(71.8%) and (81.7%) respectively (p=0.5), The one year survival rate showed no statistical significant difference between all patients of group I and group II,(87.5%) and (91.7%) respectively, this was in agreement with Bouza and his colleagues [36] who found the overall survival rates at one year was 92% and the corresponding cancer free survival rate was 56% respectively .

As regard to all patients, the percentage of ablation in both groups at 3, 6, 12 months were 81.3%, 76.6% and 71.9% in group I respectively versus 88.3%, 85% and 81.7% in group II respectively with no significant difference between the two groups. Song and his colleagues [37] agreed that the present ultimate goal of treatment of HCC is to prolong the quality of life by eradicating the malignancy while preserving hepatic function but they said "no strong evidence could be found that any chemotherapy, hormonal therapy, or immunotherapy regimen trialed to that date benefits survival in HCC.

Conclusion

PEI followed by PIM seems to be comparable to radiofrequency ablation in the treatment of the HCC when surgical resection or liver transplantation is not possible or available and this is reflected by similar rates of complete ablation of focal hepatic lesions at 3, 6 and 12 months.

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