Percutaneous local injection of combined ethanol and mitoxantron versus radiofrequency ablation in treatment of Hepatocellular Carcinoma.

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Abstract: Background and Objective: Hepatocellular carcinoma (HCC) is a highly malignant cancer and is the fifth common cancer in the World. Regional interventional therapies have led to a major breakthrough in the management of HCC**.** Mitoxantron additive to ethanol may be a highly effective approach in treatment of HCC. A comparison between this approach and radiofrequency ablation RFA will be proposed to compare their relative effectiveness. **Patients and methods:** This study included 40 patients with focal hepatic lesions proved to be HCC. All patients had one single lesion ≤ 5 cm in diameter. The patients were randomly divided into two groups, group A (20 patients) and group B (20 patients), group A patients were treated by percutaneous ethanol injection (PEI) followed by intralesional single injection of Mitoxanterone, while group B patients were treated by Cool-tip RFA. Post treatment response was assessed by alpha-fetoprotein and Triphasic C.T. **Results:** The response rate was slightly higher in PEI, Mitoxanterone treated patients than RFA treated ones after one year follow up as shown by CT 60 Vs. 55% with no statistical significance $P > 0.05$. The patients' survival rate was 100, 95 and 70% for PEI, Mitoxanterone treated patients Vs 100, 90 and 65% for RFA treated patients at 3, 6 and 12 months respectively. For complete ablated lesions the survival was 100, 100 and 82.35% for PEI, Mitoxanterone treated patients Vs 100, 100 and 81.25% for RFA treated patients. **Conclusion:** Combined injection of ethanol followed by Mitoxantrone is a simple, safe, effective & cheap method in the ablation of HCC.

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1. Introduction

Hepatocellular carcinoma (HCC) is a highly malignant cancer and is the fifth most common cancer in the World. The independent risk factors for HCC include; liver cirrhosis, chronic hepatitis B or C infection, age (> 40 years), history of heavy alcohol use, increased liver parenchymal echopattern in ultrasonography, increased level of serum alpha–fetoprotein (> 20 ng/mL) or alanine aminotransferase (> 40 IU/L) **(1).**

For an early diagnosis, abdominal ultrasound and serum alpha–fetoprotein determinations at 6–month intervals are suggested for all patients with liver cirrhosis, since this disease is considered to be the main risk factor for the development of the neoplasia. Recently, advancement in diagnostic radiology and nuclear medicine contributed accurate and early diagnosis of HCC. Ultasound, CT, Triphasic CT and MRI are used in diagnosis of these tumors (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. 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 (3).

Ablation of liver tumors is currently the main alternative to formal liver resection. Percutaneous ethanol injection (PEI) is a procedure of easy execution, good tolerability and low cost, which can be applied during repeated sessions. PEI may provide long-term disease control if the extent of liver tumors is limited (3 or less in number and less than 3 cm in diameter). Quantified ethanol at intervals of 3–5 day could improve the curative effect of hepatocelluler carcinoma. The treatment efficacy is more remarkable for tumors ≤3 cm in diameter (4).

Radiofrequency ablation (RFA) therapy is one of the image-guided thermal ablation methods. It is a localized thermal treatment technique designed to induce tumor destruction by heating the tumor tissue to temperatures that exceed 60°C. The alternating current of radiofrequency waves passing down from an uninsulated electrode tip into the surrounding

tissues generates changes in the direction of ions and creates ionic agitation and frictional heating. This tissue heating then drives extracellular and intracellular water out of the tissue, resulting in tissue destruction by coagulative necrosis. When tumor cells are heated above 45–50°C, intracellular proteins are denatured and cell membranes are destroyed through dissolution and melting of lipid bilayers. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C (5).

Mitoxantrone (Novantrone, Laboratoire Lederle, Rungis, France) 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. It has been injected directly into locoregional recurrences of head and neck carcinomas as a co-adjuvant of radiotherapy and has produced good results (6).

Mitoxantrone was selected for palliative local treatment of malignant liver lesions because of its low tissue toxicity, high intratumoral concentration after intratumoral instillation and long time in the tumor, since it has a tendency to remain at the application site. Maria *et al.*, concluded that, in patient with malignant liver lesions, minimally invasive intratumoral mitoxantrone injection was carried out safely with good tumor delivery of chemotherapy and tumor necrosis was demonstrated at biopsy but they advised further investigations. (7)

Mitoxantron additive to ethanol may be a highly effective approach in treatment of HCC. A comparison between this approach and RFA will be proposed to compare their relative effectiveness.

2. Patients and Methods

This study is a randomized comparative prospective interventional study to evaluate the role of combined ethanol and mitoxantron in the treatment of primary hepatocellular carcinoma when used as percutaneous local injection therapy versus radiofrequency ablation therapy.

The study included 40 patients with focal hepatocellular carcinoma lesions, it was performed during the period from September 2013 to October 2014 at Clinical Oncology and Nuclear Medicine Department, Zagazig University.

40 patients were randomly assigned into 2 equal groups:

Group A (n.20): This group was treated by intralesionally ethanol injection in multiple sessions followed by intralesional single injection with mitoxantron.

Group B (n.20): This group was treated with radiofrequency ablation therapy.

Inclusion criteria:

Single focal lesion ≤ 5 cm or maximum three lesions each ≤ 3 cm. Eastern Cooperative Oncology Group performance status score of 0-2. Liver function of Child-Pugh Class A or B. Adequate kidney functions (Creatinine ≤ 2mg/dl). Adequate hematological values and Patient consent.

Exclusion criteria:

Uncontrollable ascites. History of hepatic encephalopathy. Evidence of extra hepatic disease. Evidence of portal vein thrombosis and history of operation, chemotherapy, and ablative therapy for the lesions.

Pretreatment assessment:

All patients in this study were subjected to the following: Detailed history taking, full clinical examination, routine laboratory tests including complete blood count, liver function tests (Total protein and serum albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, prothrombin time). Renal function tests (plasma creatinine, blood urea). Serum Alpha feto protein. Virological profile of HCV and HBV and liver biopsy when indicated (7 lesions were diagnosed by liver biopsy).

Radiological Evaluation including:

Plain x-ray chest. Abdominal Ultrasonography examination. Abdominal triphasic computed tomography examination and Ultrasonography guided fine needle biopsy when indicated. The diagnosis of HCC was based on histological confirmation or on radiographic findings and a serum alpha-fetoprotein >200 IU/ml.

Maneuver of ethanol injection:

All lesions were injected in Zagazig University Radiodiagnosis Department under complete aseptic condition (using iodine solution and absolute alcohol) and sedation was given using 10 mg Mediathetic IV. Ultrasonography guided injection of ethanol using spinal needle 20f was done and during withdrawal of the needle 2 cc of local anesthetic were injected to minimize the irritant effect of ethanol reflux on the liver capsule. Multiple sessions were done once per week.

The total amount of ethanol was calculated according to the following equation: $V=4/3\pi(r+0.5)^3$. Where: V=Volume of ethanol, r = radius of the tumor by cm plus 0.5 cm as safety margin. Example: if the focal lesion is 3 cm, so r =1.5 cm. Therefor v =4/3 *22/7* (2) ^{3} = 33.5 cm^3. (8).

The dose of mitoxantrone is 0.5 mg/c^3 and not exceeding 20 mg/m^2 of the body surface area mixed with 0.5 cm of contrast medium (lipidol) which has high affinity to hepatocytes (7). This was followed by inpatient observation for 6 hours for blood pressure, pulse, pain and vomiting.

Maneuver of Radiofrequency ablation therapy:

The procedure was performed in Zagazig University Radiodiagnosis Department under ultrasound guidance. A radiofrequency needle is inserted deep into the lesion and multiple electrodes are deployed. The generator is then activated to achieve high temperatures within the tumor.

CT Technique

All three-phase helical CT evaluations were performed with a CT scanner (HiSpeed; GE Medical Systems, Milwaukee, WI). The scanning parameters included a 120 kVp, 170-200 mAs, 5-mm or 7-mm slice thickness, and a 5-mm or 7-mm/sec table speed (pitch of 1.0) during a one breath-hold helical acquisition of 25-30 sec, and either a 17.5-mm/sec table speed (pitch of 0.875). All the CT images were obtained in the craniocaudal direction spanning the entire liver, and were reconstructed at 5-mm intervals in order to provide contiguous sections.

Each patient received 120 mL of non-ionic contrast material (Ultravist 300 [iopromide]; Shering AG, Berlin, Germany) at a flow rate of 3 mL/sec, using an automatic power injector. Using the bolus-triggered technique, the arterial phase images were acquired 15 sec after the attenuation number of the abdominal aorta increased by 100 HU above the attenuation number of non-contrast CT. This corresponded to a 20-35 sec period beyond the onset of the contrast material intravenous injection. Furthermore, the portal and equilibrium phases were acquired 70 sec and 180 sec after the onset of contrast material injection, respectively.

Image Analysis

All CT images were analyzed retrospectively by radiologist, with consensus, for the presence of a tumor as well as the morphologic and enhancement patterns of the tumors when detected on CT.

Evaluation:

Triphasic CT was done 3-4 weeks post procedure and the criterion of good ablation was the absence of arterial uptake by the focal lesion. Complete ablation was the absence of arterial uptake by the focal lesion and partial ablation was patchy or rime of uptake in the arterial phase. No response was that the focal lesion showed arterial enhancement, venous and delayed wash-out of contrast.

Monthly clinical examination and laboratory testing including hematological profile, liver and kidney functions and alpha feto protein.

Follow up triphasic CT was performed every 3 months to detect disease recurrence and progression as well as Ultrasonography to assess the size and echogenicity of the focal lesions and other sonographic findings.

3. Results

The present work included 40 patients with focal hepatic lesions proved to be HCC. The patients were randomly divided into two groups: Group A included 20 patients, this group was treated by percutaneous ethanol injection followed by intralesional single injection of Mitoxanterone and Group B included 20 patients, this group was treated by radiofrequency ablation. All lesions were ≤ 3 in number and ≤ 5cm in maximum diameter.

Patients and tumor characteristics:

There was no significant difference in the age and sex distribution between the two groups. HCC was commonly presented in males more than females (29 Vs 11) with age ranging from 36- 69 years with a mean of 49.18 + 9.586.

There were no statistically significant difference between the two groups as regard the focal lesion site, diameter and echogenicity. Most of the studied lesions were present in the right lobe (77.5%) and most of the lesions were Hypo-Echoic (72.5%). After treatment, all lesions showed changes in their Echo-pattern, usually from Hypo-Echogenicity to Iso- or Hyper-Echogenicity and from Iso- or Hyper- Echogenicity to marbled appearance; however, U/S wasn't sufficiently reliable for recognizing areas that had remained viable. (Table 1).

Table (1): The ultrasound characteristics of the focal hepatic lesions.

Findings		Group A (n.20)		Group B (n.20)		Total (n.40)		*P* Value
		No.	%	No.	%	No.	%	
Site	Rt. Lobe	15	75%	16	80%	31	77.5%	0.705
	Lt. Lobe	5	25%	4	20%	9	22.5%	
Diameter	≤3cm	8	40%	9	45%	17	42.5%	0.749
	3-5cm	12	60%	11	55%	23	57.5%	
Echogenicity	Hyper-Echoic	0	0%	1	5%	1	2.5%	0.674
	Hypo-Echoic	14	70%	15	75%	29	72.5%	
	Heterogonous	5	25%	3	15%	8	20%	
	Iso-Echoic	1	5%	1	5%	2	5%	

Complications:

There were different complications after injection in group A and group B patients. Pain, fever, peritoneal collection and vomiting were comparable in both groups where as hemopneumothorax was present only in group B, while subcapsular hematoma and portal vein thrombosis were only present in group A. (Table 2).

Table (2): Complications after injection in group A and group B.

Complication		Group A (n.20)		Group B (n.20)		*P* Value
		No	%	No	%	
Pain	Tolerable	13	65%	12	60%	0.726
	Intolerable	4	20%	6	30%	
Fever		2	10%	3	15%	0.633
Vomiting		3	15%	5	25%	0.429
Peritoneal collection		1	5%	1	5%	1.00
Hemopneumothorax		0	0%	1	5%	0.311
Subcapsular hematoma		1	5%	0	0%	0.311
Portal vein thrombus		1	5%	0	0%	0.311

Treatment response:

There was no statistical significant difference between the two groups regarding complete ablation rates 3 months after the treatment (table 3). 6 months after treatment, there was also no statistically significant difference between both groups, one patient of those fully ablated in each group showed local disease progression while only additional one patient in group A showed multifocal progression (table 4). Comparing the follow up response to injection among patients of groups A and group B 1 year after treatment, still there was no statistically significant difference between both groups with 12 (60%) in group A & 11 (55%) in group B maintaining complete ablation at one year. (Tables 5, 6; Figure 1).

Table (3): Comparison of percentage of ablation between both groups 3 months after injection.

Ablation	Group A (n.20)		Group B (n.20)		*P* Value
	No	%	No	%	
Complete	17	85%	16	80%	0.677
Partial	3	15%	4	20%	

Table (4): Follow up of patients with complete ablation in both Groups 6 months after injection.

	Group A Complete ablation (n.17)		Group B Complete ablation (n.16)		Total (n.33)		*P* Value
	No.	%	No.	%	No.	%	
Stationary	15	88.2%	15	93.8%	30	90.9%	0.616
Local recurrence	1	5.9%	1	6.3%	2	6.1%	
Multifocal	1	5.9%	0	0%	1	3%	
Died	0	0%	0	0%	0	0%	

Table (5): Follow up of patients with complete ablation in both Groups 1 year after injection.

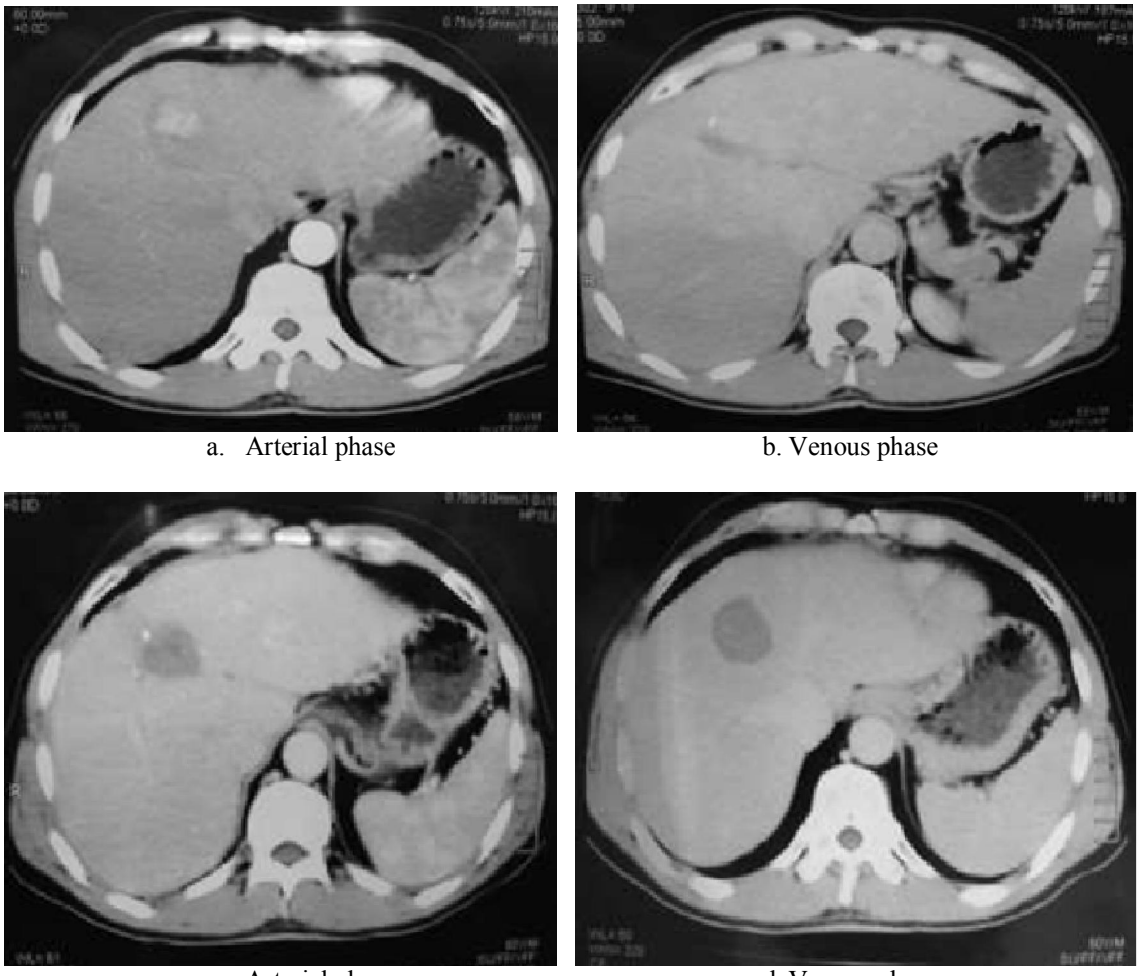
	Group A Complete ablation (n.17)		Group B Complete ablation (n.16)		Total (n.33)		*P* Value
	No.	%	No.	%	No.	%	
Stationary	12	70.6%	11	68.8%	23	69.7%	1.00
Local recurrence	1	5.9%	1	6.3%	2	6.1%	
Multifocal	1	5.9%	1	6.3%	2	6.1%	
Died	3	17.6%	3	18.8%	6	18.2%	

Table (6): Follow up of complete ablation in all patients of both Groups at 3, 6 and 12 months after injection.

Complete ablation	Group A (n.20)		Group B (n.20)		Total (n.40)		*P* Value
	No.	%	No.	%	No.	%	
3 months	17	85%	16	80%	33	82.5%	0.783
6 months	15	75%	15	75%	30	75%	
1 year	12	60%	11	55%	23	57.5%	

Direct overall survival:

There was no statistically significant difference in the survival rate at one year between group A (70%) and group B (65%). 2 patients in group A died due to disease progression, one due to cardiac cause and the remaining 3 were lost follow-up. While in group B 3 patients died due to disease progression, 2 due to hepatorenal syndrome after spontaneous bacterial peritonitis and the remaining 2 were lost in follow-up (Figure 2).



a. Arterial phase b. Venous phase

c. Arterial phase d. Venous phase

Figure (1): Pre and post treatment CT for a completely ablated Group A patient 1 year after treatment.

a and b shows focal mass with enhancement in arterial phase and rabid wash out in venous phase, while c and d shows completely ablated lesion with no enhancement throughout the study.

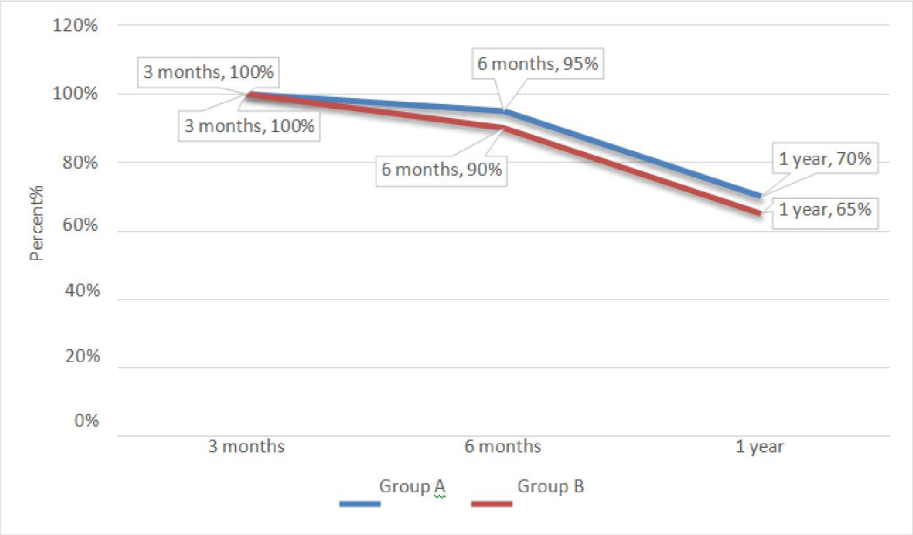


Figure 2: Overall survival at 3, 6 and 12 months

4. Discussion

Hepatocellular carcinoma is one of the most common solid cancers in the world, with an annual incidence estimated to be at least one million new patients especially in Eastern Asia and South Africa **(9).**

Although, there is no doubt that early diagnosis and treatment improve survival**,** the criteria by which a specific treatment is selected as the first line option remain to be established. Surgery offers the chance of potential cure, either by curative hepatic resection or transplantation. However, resection is applied only to patients with good hepatic reserve and localized tumors. Alternatively, local ablation therapy has gained a clinical position in treating small HCC **(10).**

Both PEI and RFA are the most commonly used methods worldwide**.** PEI is aimed at producing tumor necrosis as a result of protein denaturation, cellular dehydration and occlusion of small vessels. Absolute alcohol is injected through a thin needle and the procedure is repeated once or twice per week for up to four to six sessions depending on the tumor size **(11).** Many studies had been published to evaluate effect of percutanous injection of ethanol in treatment of HCC, but few studies evaluating percutanous injection of mitoxantron in treatment of HCC were published **(9).**

Radiofrequency ablation was introduced by an Italian team in 1993 **(12)** for treatment of hepatic tumors not amenable to resection. It employs a high frequency current to cause thermal coagulation and protein denaturation. The procedure is carried out using a needle electrode connected to radiofrequency generator. As ions attempt to follow the change in direction of the alternating current, there is frictional heating within the tissue. This results in coagulative necrosis of the target tissue **(13).**

In our study, 20 HCC nodules were treated by PEI followed by Mitoxanterone, complete response was achieved in 17 lesions (85%) with mean number of sessions of (5.9 ± 2.7). Results for PEI only were reported by Ikeda *et al.,* **(14)** who studied 96 HCCs $\leq$ 3 cm in diameter, complete ablation was achieved in 90 HCCs (94%) with mean number of sessions of 4. Livraghi *et al.,* **(15)** also treated 60 HCCs < 3 cm in diameter with PEI, complete response was achieved in 48 HCCS (80%) with mean number of sessions of 4.8 sessions per tumor. In our study only 40% of lesions were $\leq$ 3 cm in diameter which makes higher difference than mentioned. This difference could be attributed to the effect of mitoxantrone on HCC, which was clarified by Ohishi and his colleagues **(16)** who stated that Intratumoral instillation of mitoxantron results in a 1000-fold higher concentration in the tumor compared with intravenous administration, moreover; lipidol have high affinity to malignant hepatocyts so it increase the duration and efficacy of mitoxantron. Also 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 tumoral efficacy and consequently low local recurrence.

In our study, 20 HCC nodules were treated by RFA, complete response was achieved in 16 (80%) with mean number of sessions of 2 and mean duration of session of 26 min. In our study only 45% of lesions were $\leq$ 3 cm in diameter. Similar results were also shown by the Barcelona Clinic Liver Cancer (BCLC) group, they studied 25 HCCs $\leq$ 3 cm

in diameter, complete response was achieved in 19 (76%) with mean number of sessions of 1.25 and mean duration of session of 22.1 min **(17).** In contrast, higher results for RFA were reported by Livraghi et al **(15)**, who treated 52 HCCs ≤ 3 cm in diameter with RFA, complete response was achieved in 47 (90%) with mean number of sessions of 1.2 and mean duration of session of 12 min.

In our study, after complete ablation by PEI, Mitoxanterone local recurrence was detected in 1 out of 17 HCCs (5.9%) during a follow up period of 1 year. Higher recurrence was shown in livraghi series i.e. 176 out of 1,038 ablated HCCs (17%) during a follow up period of 5 years **(18).**

In our study, after complete ablation by RFA, local recurrence was detected in 1 out of 16 HCCs (6.3%) during a follow up period of 1 year. Chi-Jiang *et al.,* **(19)** reported higher recurrence (19%) in 21 HCC patients during a mean follow up period of 10 months. while Curley *et al.,* **(20)** reported lower recurrence (1.8%) in 110 HCC patients during a mean follow up period of 19 months.

In our study, out of 17 completely ablated lesions treated with PEI, Mitoxanterone new lesions developed in 1 (5.9%). In Livraghi series, new lesions developed in 348 out of 717 patients (48.5%) during a follow up period of 5 years **(18).**

In our study, out of 16 completely ablated lesions treated with RFA, new lesions developed in 1 (6.3%). Horiike *et al.,* **(21)** treated 47 patients with 80 HCCs less than 3 cm in diameter with RFA, new lesions developed in 38% at 1 year and 60% at 2 years. Also, Curley *et al.,* **(22)** treated 110 patients with 149 HCCs less than 5 cm with RFA, new lesions developed in 50 patients (45%) during a mean follow up period of 19 months.

In our study, the survival of patients with HCCs < 5cm for all patients was 100, 95 and 70% for PEI, Mitoxanterone treated patients Vs 100, 90 and 65% for RFA treated patients at 3, 6 and 12 months respectively. For complete ablated lesions the survival was 100, 100 and 82.35% for PEI, Mitoxanterone treated patients Vs 100, 100 and 81.25% for RFA treated patients.

Shiina *et al.,* **(23)** treated 50 HCCs < 5cm in diameter with PEI, the survival was 87, 62, 43% at 1, 3, 5 years respectively. Liovet *et al.,* **(24)** treated 32 patients with HCCs < 5 cm in diameter with RFA, after median follow up of 10 months, 4 patients died, the causes of death were tumor progression (1 case), liver failure (2 cases) and acute myeloid leukemia (1 case), the actuarial 1 year survival was 85%. In another study conducted by Francicia and Marone, **(25)**, who treated 15 HCCs <5 cm in diameter, 3 patients died during the follow up time (median 15 months), the 1 year survival was 80%.

In the present study which we tried the addition of Mitoxanterone to PEI as a local ablative measure for HCC < 5 cm in diameter, complete response rate after 1 year follow up (assessed by Triphasic CT) was slightly higher in PEI, Mitoxanterone treated patients than RFA treated ones i.e. 60 Vs 55% with no statistical significance P > 0.05. Such results were obtained with average of 2 sessions for RFA and 5.9 sessions for PEI. The complications rate was slightly higher with RFA than PEI, Mitoxanterone (17.5% Vs 15.6%) with no statistical significance P > 0.05. There was no significant difference in the local recurrence rate between the two groups i.e. 5.9% for PEI, Mitoxanterone Vs 6.3% for RFA. PEI is cheap and easy to perform. All that is needed is experience with interventional US; hence, many, even outlying hospitals can perform PEI without need for referral. Patients are treated in the outpatient clinic, and many of them continue in their normal life. Use of an ordinary US scanner is sufficient. The material (needle, syringe, alcohol) costs little and is readily available. The addition of local injection of Mitoxanterone to PEI was safe and well tolerated and seems to add to the local ablative effect of ethanol, and with no much cost.

Conclusion

1. Combined injection of ethanol followed by Mitoxantrone is a simple, safe, effective & cheap method in the ablation of HCC.
2. The addition of local Mitoxantrone to PEI may add to the ablative effect of ethanol without increasing side effects or cost.
3. Combined injection of ethanol followed by Mitoxantrone was as effective as RFA as an ablative procedure for localized primary HCC ≤ 5 Cm. in diameter regarding the response rate and local tumor control. Both treatment arms were equally well tolerated.

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