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Percutaneous ethanol lipiodol injection therapy versus radiofrequency ablation in treatment of hepatocellular carcinoma

Abstract

Background & aim: Percutaneous ethanol injection (PEI) has become one of the most widely used procedures for treatment of hepatocellular carcinoma (HCC) up to 5 cm. PEI is occasionally ineffective due to in homogenous distribution within tumor while percutaneous ethanol lipiodol injection therapy (PELIT) is useful irrespective of vasculature, as HCC cells are characterized by selective, active uptake of lipiodol. The primary outcome was the higher success rate of PELIT with fewer sessions in comparison to RFA in HCC.

Patients and methods: A prospective study was conducted on 43 patients with HCC, 27 of them under went PELIT & 16 underwent RFA. Both groups had biopsy after one week and lesions with partial necrosis underwent additional PELIT or RFA respectively. Triphasic MRI and CT were performed one month after the end of sessions of PELIT and RFA respectively.

Results: Tru-cut biopsy revealed complete necrosis in 17 (81%) patients of PELIT and 11(68.7%) patients of RFA group. Six patients of PELIT group were not biopsied due to non-visible lesions by ultrasound, ascites or low PC. After additional sessions (in partial necrosis), triphasic MRI for PELIT group showed non-enhancement in 26(92.3%) patients and triphasic CT for RFA group showed non-enhancement in 15 (93.6%) patients and one patient in each group showed peripheral enhancement.

Conclusion: PELIT is safe & effective for treatment of HCC, the number of sessions are equal to the diameter of HCC in cm (fewer sessions than RFA or PEI alone). PELIT can be performed for cases liable or contraindicated to RFA. Triphasic MRI is the standard for follow up of cases of PELIT.

Keywords: hepatocellular carcinoma, radiofrequency ablation, ethanol lipiodol, triphasic MRI

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Abbreviations: PEI, Percutaneous ethanol injection; HCC, hepatocellular carcinoma; PELIT, percutaneous ethanol lipiodol injection therapy

Introduction

The annual incidence of HCC in cirrhotics ranges from 3-5% making it the eighth most common malignancy worldwide. The limitations of surgical resection and the limited efficacy and generalized toxicity of systemic chemotherapy and external beam radiation for hepatic tumors have sparked considerable interest in percutaneous techniques of tumor ablation.[1] One of these methods is percutaneous ethanol injection (PEI) which has become one of the most widely used procedures for treating focal HCC. PEI is generally performed for HCC from 3-5 cm in diameter, although acceptable results have been attained in larger tumors.[2] HCC cells are characterized by lipiodol deposition (an ethyl Ester of fatty acid of poppy seed containing 37-39% iodine by weight) and emulsification on cell surface, active uptake of lipiodol and prolonged intra-cellular retention for their life span.[3] For percutaneous ethanol lipiodol injection therapy the mixture of 99.5% ethanol and lipiodol at a ratio 10:1 was used with better results than ethanol alone.[4]

Study outcomes

The primary outcome of our study was to evaluate the success rate of percutaneous ethanol lipiodol injection therapy (PELIT) in comparison to radiofrequency thermal ablation (expandable & cool-tip needles) in treatment of nodular HCC.

Patients and methods

Study population

This was a prospective study conducted on 43 patients who presented to the Hepato-gastroenterology and Tropical Medicine Department, faculty of Medicine, Cairo University, with HCC (proved by either tru-cut biopsy or the combination of elevated AFP more than 250 ng/dl, and a typically enhancing focal lesion in triphasic CT).

The patients were randomly divided into two groups:

I. PELIT group: consisted of 27 patients (25 males and 2 females) underwent PELIT.

II. RFA group: consisted of 16 patients, 10 patients under went expandable RFA and 6 underwent cool-tip RFA.

Patients' eligibility

We selected patients with lesions less than 5cm, three or less in number for both groups. Patients difficult to be treated by RFA were treated with PELIT. Subcapsular lesions or near PV, IVC, GB were excluded from RFA. These selections we believed did not bias the outcome but decreased the side effects and complications.

We excluded patients with:

I. Child's C cirrhosis

II. PV thrombosis

III. Lesions larger than 5cm, more than three in number

IV. Metastatic HCC

V. Severe uncontrollable bleeding diathesis (INR >1.4 and platelets count <50,000).

This study was approved by the Department Ethics Committee based on the 1975 Declaration of Helsinki. Informed consent was obtained from all participants in the study after explanation of the procedures. The PELIT and RFA procedures were done in our Hepatology department.

Pre-procedure assessment

All patients were subjected to:

I. Liver assessment tests (Billirubin, AST, ALT, ALP, serum albumin and INR)

II. serum AFP

III. CBC

IV. Conventional abdominal ultrasound (done using a Toshiba SSA. 340 machine with a 3.5 MHz curved sector transducer)

V. Triphasic CT of the abdomen (contiguous 5-mm thick axial CT scans were obtained with High-Speed Siemens (Erlangen-Germany) machine). The non-ionic contrast material Iopamidol (100 – 150 ml Iopamiron; Scherring, Osaka, Japan) was administered at a rate of 3 ml/sec using a power pump and CT images of the entire liver were obtained.

VI. Tru-cut biopsy from focal hepatic lesion was done if the results of triphasic CT and α-fetoprotein were inconclusive.

Percutaneous liver biopsy was performed under conscious sedation with US guidance. A 16-g disposable cutting needle was used. The liver biopsy specimens were fixed in formalin and embedded in paraffin. Then, sections 4 μm thick were stained with hematoxylin and eosin (H&E) and Masson's trichrome and were evaluated by an experienced hepatopathologist.

Technique of radiofrequency ablation

Treatment was performed with the patient under conscious sedation induced by the administration of IV diazepam 10-20 mg (Neuril; Nile) or propofol (Diprivan, 10mg/cc) immediately before treatment. After cleansing the skin with povidone iodine (Betadine) and alcohol, local anesthesia was achieved by using 3 ml of 2% lidocaine (Xylocaine; Astra) to anesthetize the skin and subcutaneous tissue, muscles and liver capsule along the assumed track of entry then a small opening is done into the skin using a scalpel. RF ablation was performed under real-time US guidance (Toshiba SSA 340) using a 3.5 MHz probe by free hand technique. Two types of 20-cm-long, 18-gauge internally cooled RF electrodes (Radionics, Burlington, Moss) were used, depending on the size and location of the tumor. The RF electrodes were attached to a 500-KHz RF generator (series CC-1; Radionics) capable of producing 200 watts of power. During the procedure, a thermocouple embedded within the electrode tip continuously measured local tissue temperature. Tissue impedance was monitored by using circuitry incorporated within the generator. A peristaltic pump (Watson-Marrow, Medford, Mass) was used to infuse distilled water into the lumen of the electrodes at a rate sufficient to maintain a tip temperature of 20°C - 25°C. RF energy was applied for 13 minutes and was repeated for another 13 minutes if the pull back technique was used. After the session, the tumor turns to be completely hyperechoic. The expandable electrode needle has an insulated stainless steel shaft and an exposed active tip with retractable jackhooks (Radiotherapeutics 3000 system), to produce up to a 4-cm-diameter spherical volume necro¬sis, The electrodes are de¬ployed as soon as the needle is placed into the lesion and retracted before it is withdrawn. The power output of the generator is adjusted, either manually or automati¬cally, to keep temperatures between 95°C and 105°C.

Grounding was achieved by attaching two dispersive pads, each with a greater than 400 cm2 surface area, to the patient's thighs. Ablation of the track was done after the end of the RF session in both types of needles (cool-tip or expandable). For lesions located in the right lobe, an intercostal approach with the patient in the left lateral decubitus position was generally performed. For lesions located in the left lobe, a subcostal approach was most often used. In some patients the RFA session was repeated later when the tru-cut biopsy, done one week after the session, revealed viable malignant cells or the triphasic CT, done one month after the session, revealed an area of enhancement within the boundaries of the tumor. Following RFA therapy, patients were put under observation for 6 hours where vital signs were checked every half-hour.

Technique of PELIT

Sedation, anasthesia and sterilization were done with the same technique as RFA session. The mixture of 99.5% ethanol and lipiodol at a ratio of 10: 1 was used as lipiodol and ethanol could be mixed well at this ratio and the mixture is clear not milky. PELIT was performed under real time U/S guidance. A 18 gauge fine needle was inserted into HCC lesion and the mixture of ethanol-lipiodol, was slowly injected into the tumor, this was performed as a multiple session technique. The number of sessions was mostly equal to the diameter of the lesion in centimeters with preference to increase one session, eg. if the diameter was 3.2cm, 4 sessions were given, to produce good curative effect.[5] The sessions were repeated every week, 4 patients developed ascites during the course of injections, so the session was postponed and received diuretics till resolution of ascites and the sessions were completed. Percutaneous ethanol lipiodol injection is not commonly used by physicians as lipiodol is not easily available with hepatologists, also, it interferes with follow-up triphasic CT signals making dynamic MRI more appropriate and MRI is an expensive, not widely available technique.

Post -procedure assessment

Included all the investigations that were done before procedure. US, biopsy, AFP were done after one week, triphasic CT was done after one month for RFA group. Triphasic MRI was performed one month from the end of sessions of PELIT group, it is superior to triphasic CT as lipiodol produces strong attenuation that interferes with enhancement in arterial phase during triphasic CT, but does not affect triphasic MRI because signal intensity is not modified.[6] The response to treatment was rated as complete when triphasic CT (for RFA group) or MRI (for PELIT group) after one month showed no contrast enhancement inside the lesion in the arterial phase. The response was rated as partial when triphasic CT or MRI showed areas of enhancement within the boundaries of the original lesion in the arterial phase OR when the pathology showed viable malignant cells. Follow up of patients of

both groups was done for about two years with special emphasis on recurrence of HCC, any remote complication related to RF procedure, development of liver decompansation (ascites, jaundice, encephalopathy, bleeding tendency), haematemesis, or death.

Statistical analyses

The study sample size was relatively small as we were studying different percutaneous ablation therapies for HCC like PELIT, combined RFA with (alcohol, acetic acid, saline[7] hypertonic saline &TACE[8]) and microwave ablation.[9] So, this affected the size of each study. Quantitative variables were expressed as mean and standard deviation while qualitative data were expressed as frequency and percentage. Qualitative variable were analyzed using Chi-square or Fischer's exact test when appropriate. Quantitative variables were analyzed using the student's T-test or Friedman's test when appropriate. p value was expressed as the following: p>0.05=non-significant, p<0.05=significant and p<0.01=highly significant.

Results

Patients' baseline characteristics

The mean age of the RFA group was 53.3+6.4 years and the mean age of PELIT group was 58.4+6.3 years and nearly all the two groups were males (24/92.6% in PELIT group and 14 /75% in RFA group). The liver biochemical profile (before and one week after the end of sessions), in PELIT group, showed significant increase (namely AST, ALT and bilirubin) after treatment (P: 0.00). However, liver tests showed slight changes after the RF procedure. Both groups, after treatment, reported significant decrease in AFP levels (P: 0.00). The ultrasonographic criteria of HCC lesions showed that 19 patients (61.3%) of PELIT group and 10 (62.5%) of RFA group had their lesions in the Rt. Lobe. The diameter of lesions showed that 53.2% were 3cm or less and 76.6% were hypoechoic (Table 1). Triphasic CT results before the procedure in both groups are shown in Table 2. Triphasic CT done one month after the procedure, in RFA group, showed that 15(93.6%) of patients had complete ablation and one (6.4%) had peripheral enhancement (Table 4). The relation of the diameter of HCC lesion to the amount of alcohol-lipiodol injected and the number of sessions are shown in Table 3.

Table 1 U/S findings of HCC of both groups before procedure

Findings	PELIT group (n:27)		RFA group (n:16)	
	No	%	No	%
Diameter*				
≤3cm	14	45.2	11	68.8
>3 -5cm	17	54.8	5	31.2
Echogenicily*				
hypoechoic	24	77.4	12	75
hyperechoic	1	3.2	1	6.3
mixed	3	9.7	2	12.5
Iso echoic	3	9.7	1	6.3
Number*				
One	24	88.9	16	100
Two	2	7.4	-	-
Three	1	3.7	-	-

*There were no significant differences between two groups.

Table 2 Triphasic CT findings of HCC lesions of both groups before treatment

Enhancement	PELIT Group		RFA Group		P value
	No	%	No	%	
Homogenous	13	52	10	76.9	0.14
Heterogeneous	12	48	3	23.1	

Table 3 Relation of HCC diameter to alcohol-lipiodol amount & sessions number

Diameter	≤3cm	>3cm	P value	R value
	M±S D	M±S D		
Alcohol/lipiodol amount	25.7±13.0	55.3±11.5	0.00**	0.95
Sessions Number	2.9±0.96	5.0±1.1	0.000**	0.95

**The correlations are significant at 0.01 level (2.tailed).

Evaluation of efficacy of both procedures

The tru-cut needle biopsy, after the procedure, showed no viable cells in 17(81%) patients in PELIT group and in 9(60%) patients in RFA group. Four patients of PELIT group (19%) and six patients of RFA group (40%) showed residual viable cells. In the 27 patients of the PELIT group, triphasic MRI after the procedure showed that 25(92.6%) patients had non enhancing lesion, but 2 (7.4%) patients showed enhancing lesion either peripheral or heterogeneous. So, the success rate in the PELIT group was 92.6%. The remaining two (7.4%) patients received additional sessions of PELIT and lesions were ablated (Table 4). The success rate in the RFA group was 60% after the first session by tru-cut needle biopsy and increased to reach 93.6% after the second session of RFA by triphasic CT. The remaining one (6.4%) patient received additional RFA session and was ablated (Table 4).

Table 4 Criteria of response after treatment in both groups (PELIT & RFA)

Criteria of response	PELIT group (n:27)		RFAG (n:16)		P value
	No	%	No	%	
Needle biopsy					
Complete necrosis	17	81	11	68.7	0.3
Partial necrosis	4	19	5	32.3	
Triphasic CT (RFA group)					
Non enhancing	-	-	15	93.6	
Enhancing	-	-	1	6.4	1
Triphasic MRI (PELIT group)					
Non enhancing	25	92.6	-	-	
Enhancing	2	7.4	-	-	-

Relation of response to size of the lesion could not be assessed in PELIT group as two patients only had treatment failure. There was no significant difference in the response to treatment between Child A and Child B patients in both groups (P: 1.0). In PELIT group, Child A reported 90.9% success and Child B 100% success. In RF group, Child A reported 92.9% success and Child B 100% success. In the immediate period of follow up after the procedure, fever occurred in six (22.2%) patients in PELIT group and in four (25%) in RFA group, it resolved with antipyretics. Ascites developed in three (11.1%)

patients in PELIT group during the course of sessions & resolved with diuretics.

Haematemesis & melena occurred in one (3.7%) patient in PELIT group, upper endoscopy revealed bleeding duodenal ulcer. Abscess occurred in one (6.3%) of RFA group & resolved with repeated aspiration. Later follow up (after 6 months) showed non-significant difference between both groups (Table 5). In PELIT group, none had primary recurrence, PV thrombosis, increase in jaundice or encephalopathy. The procedure success (event free patients) was 62.9% and the cancer free success (cancer free patients) was 77.7%. In RFA group, one patient (6.2%) had recurrence at the site of ablated tumor after one year of follow-up and one had PV thrombosis after 7 months. None had increase in jaundice, encephalopathy or liver abscess. The procedure success was 50% and the cancer free success was 56.2%. De novo lesions in the liver, in both groups, were diagnosed mostly within the first year of follow up.

Table 5 Comparison of late follow-up results between the two groups

Finding	PELIT (n=27)		RFA (n=16)		P value
Primary recurrence	0	0%	1	6.20%	0.99 (NS)
De novo lesions	6	22.20%	5	31.20%	0.25 (NS)
PV thrombosis	0	0	1	6.20%	0.31 (NS)
Ascites	4	14.80%	1	6.20%	0.99 (NS)
Procedure success	17	62.90%	8	50%	0.69 (NS)
Cancer free success	21	77.70%	9	56.20%	0.69 (NS)

Discussion

HCC is the eighth most common malignancy worldwide. Cirrhosis is the most important risk factor and underlies 60-80% of cases. Annual incidence of HCC in cirrhotics ranges from 3-5%.[1] For PELIT, the mixture of 99.5% ethanol and lipiodol at a ratio of 10:1 was used as lipid-base lipiodol and ethanol could be mixed well at this ratio.[4]

Lipiodol was used because:

I. Percutaneous ethanol alone is occasionally ineffective modality because inhomogeneous distribution within the tumor.[10]

II. Percutaneous administration of lipiodol is thought to be useful for treatment of tumor irrespective of vasculature.[4]

III. Hepatoma cells are characterized by selective active uptake of lipiodol and prolonged intracellular retention for their life-span.[3]

IV. The uptake of lipiodol into liver cells is by pinocytosis as intracellular vesicles.[11]

To or knowledge, this is the first study applying PELIT to treat HCC in Egypt. Kurokotichi et al.[4] recommended PELIT for HCC lesions difficult to treat with RFA, local recurrence after RFA, hypovascular HCC or HCC not visible by US or CT & with severe liver dysfunction. But in our study, we performed PELIT for cases both liable to be treated or difficult to be treated with RFA. The mean age of the RFA group was 53.3+6.4 and the mean age of PELIT group was 58.4+6.3. All the Egyptian studies had close mean ages, as the study done by Salama et al.[12] that included 158 patients with ages ranged from 35 to 69 years, Nabeel [13] had 58 patients with HCC with a mean age of 50.5+6.9 years, El-Kady et al.[7] their mean age was 51 to 57 +9 years and El-Kady et al.[8] their mean age was 50.60±3 to 53.80±7.37 years. Also Omata et al.[14] study had a mean age of 56.3 years. However, Livraghi et al.[15] had 42 patients with mean age of 68.9 years and the Japanese and Italian patients in the study done by Omata et al.[14] had a mean age of 62.5 and 64.8 respectively. The earlier age in Egyptians could be explained by the early age of acquisition of viral hepatitis due to the high incidence of HCV and HBV in some areas, so although the patients in Egypt are relatively young they may still have had 30-40 years of continuous inflammation and necrosis which might be sufficient to develop cirrhosis and eventual HCC at early ages.

The liver biochemical profile in our study (before and one week after the end of sessions) showed slight changes after the RFA procedure. Salama et al.[12] who used the multiple array (LeVeen) RFA needles, found transient increase in transaminases above the pre-ablation level in 77% of patients. In PELIT group, there was significant increase in liver profile after treatment, similarly Kurokohchi et al.[4] who treated 19 patients with HCC, observed reversible liver dysfunction with slight elevation of serum levels of transaminases in 2 patients. The PELIT procedure, in our study, was successful in 24 (92.6%) patients. The PELIT procedure needed fewer sessions than RFA to ablate HCC lesions. Also, in Kamimura et al.[16] study, they treated HCC with PELIT and had success rate comparable to hepatectomy. In our study, we performed a multisession PELIT technique and the number of sessions was always equal to the diameter of the lesion with preference to increase one session if the diameter had a millimeter fraction, but Kurikohchi et al.[4] performed PELIT mostly as one session technique and the volume of injected ethanol-lipiodol was always kept below the double volume of estimated tumor volume. Ko et al.[17] performed alternative injection of lipiodol and pure ethanol in their treatment of HCC. In Tateishi H et al.[18] study, a 10% volume of lipiodol was mixed with ethanol so the location of injected ethanol could be easily confirmed. The effectiveness of PELIT was thus confirmed by CT, performed on the following day. Defective lipiodol accumulation in the tumor and/ or neighboring tissues was able to be corrected by additional ethanol injections.

The RF procedure, in our study, was successful in 9 (60%) patients after the first session by tru-cut needle biopsy and increased to reach 93.6% after the second session of RFA by triphasic CT. Also, Soliman et al.[19] obtained complete ablation in 71.4% of patients and all his patients had two sessions of RFA. Kurikohchi et al.[4] recommended different options for follow up after PELIT:

I. Biopsy from the lesion and ablation is considered when the specimen showed disappearance of nuclei of all cells & complete necrosis of HCC cells, although the accumulation of lipoidol was not microscopically observed in specimens

II. Triphasic CT and response is considered when there is non enhancing area outside the lipiodol retaining lesion

III. Plain CT and response is considered by comparing the size of the lesion before and after PELIT.

But in our study, we performed dynamic MRI (after 1 month) as lipiodol produces strong attenuation that interferes with the enhancement in the arterial phase during triphasic CT but lipiodol does not affect dynamic MRI.[6]

The complications encountered, in PELIT group in our study, were more than Kurikohchi et al.[4] study, as they recorded only reversible liver dysfunction after their PELIT sessions. But the complications encountered, in RFA group in our study, were comparable to the results of Salama et al.[12] as in their study, 57% experienced fever (short term, 38°C), that resolved 1-3 days with the administration of paracetamol three times daily. Our complications were much less than

those of Livraghi et al.[14] study who recorded one major complication (2%), hemothorax due to damage of an intercostal vessel along the needle track which required surgical drainage, and four (8%) minor complications: one intra-peritoneal bleeding (reduction of Hb level by 4g/dL), hemobilia (indicated by the appearance of sludge in the GB during procedure, pleural effusion (resolved after 2 months) and mild cholecystitis. All five complications occurred during 24 hours after the RFA procedure and all procedures were performed using cool-tip system. With lesser number of sessions in PELIT compared to PEI, the less cost compared to RFA, with a simple procedure and cheaper materials, application in HCC patients who can't be treated by RFA with subsequent decrease of complications like liver or other organs failure and death, PELIT offers better cost-effectiveness benefit. For routine clinical practice, hepatologists should combine lipiodol with ethanol (instead of ethanol alone) as it will decrease the number of sessions and enhance the outcome.

Conclusion

Percutaneous combined ethanol-lipiodol injection therapy for HCC is safe, effective, needs fewer sessions than RFA and ethanol alone. It could be used for lesions up to 5cm and lesions difficult to be treated with RFA.

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References

1. Aguayo A, Patt YZ. Non surgical treatment of HCC. *Seminar Oncology*. 2001;28(5):503–513.
2. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radiofrequency ablation of medium and large lesions. *Radiology*. 2000;214(3):761–768.
3. Chou FI, Fang KC, Chung C, et al. Lipiodol uptake and retention by human hepatoma cells. *Nucl Med Biol*. 1995;22(3):379–386.
4. Kurokohchi K, Masaki T, Miyauchi Y, et al. Percutanous ethanol and lipiodol injection therapy for HCC. *Int J Oncol*. 2004;24(2):381–387.
5. Nakao N, Uchida JH, Kamino K, et al. Determination of optimal dose level of lipiodol in transcatheter arterial embolization of primary HCC based on retrospective multivariate analysis. *Cardiovasc Intervent Radiol*. 1994;17(2):76–80.
6. Kubota K, Hisa N, Nishikawa T, et al. Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of lipiodol CT, power doppler Sonography, and triphasic MRI. *Abdom Imaging*. 2001;26(2):184–190.
7. El Kady N, Hasan E, Esmat G, et al. Study of the enhancing effect of sodium chloride injection on radiofrequency ablation of hepatocellular carcinoma. *Arab Journal of Gastroenterology*. 2009;10(2):63–67.
8. El-Kady NM, Esmat G, Mahmoud EH, et al. Hypertonic saline-enhanced radiofrequency versus chemoembolization sequential radiofrequency in the treatment of large hepatocellular carcinoma. *Eur J Gastroenterol Hepatol*. 2013;25(5):628–633.
9. Medhat E, Abdel Aziz A, Nabeel M, et al. Value of microwave ablation in treatment of large lesions of hepatocellular carcinoma. *J Dig Dis*. 2015;16(8):456–463.
10. Yamasaki T, Kurokawa F, Shirahashi H, et al. Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow. Comparison with standard percutaneous radiofrequency ablation therapy. *Cancer*. 2002;95(11):2353–2560.
11. Towu E, Al-Mufti R, Winslet M. Uptake of lipiodol cytotoxic conjugutes by hepatocellular carcinoma cells. *J Pediatric Surg*. 2004;39(2):203–206.
12. Salama HM, Hassan NHA, Hassan EM. Percutaneous radiofrequency ablation of hepatocellular carcinoma using a multiple array needle electrode. *HPB*. 2003;5(1):11–18.
13. Nabeel MM. *Comparison between Radiofrequency ablation and percutaneous ethanol injection in treatment of patients with hepatocellular carcinoma*. M.Sc. thesis, Tropical Medicine, Cairo University, Egypt. 2003.
14. Omata M, Dan Y, Daniele B, et al. Clinical features, etiology, and survival of hepatocellular carcinoma among different countries. *J Gastroenterol Hepatol*. 2002;17 (Suppl.):S40–S49.
15. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology*. 1999;210(3):655–661.
16. Kamimura S, Hirano M, Iwata K. Experience of Percutaneous Ethanol with Lipiodol Injection Therapy for Hepatocellular Carcinoma; a Comparison with Hepatectomy. *Medical Bulletin of Fukuoka University*. 1999;26(3):97–103.
17. Ko HK, Jong Tae L, Won JY. *Percutaneous ethanol lipiodol injection therapy of recurred hepatocellular carcinoma after transarterial chemoembolization in high-risk locations*. Poster No.: C-540 Congress: ECR 2009. 2009.
18. Tateishi H, Oi H, Masuda N, et al. Appraisal of combination treatment for hepatocellular carcinoma: long-term follow-up and lipiodol-percutaneous ethanol injection therapy. *Semin Oncol*. 1997;24(2 Suppl 6):S6-81-S6-90.
19. Soliman AF. *Predictive factors of response in the treatment of hepatocellular carcinoma by radiofrequency versus acetic acid injection*. MD Thesis, Tropical Medicine, Cairo University, Egypt. 2003.