

Combined radiofrequency ablation and transarterial chemoembolization in treatment of unresectable primary liver cancer

Abstract

Introduction: HCC is the fifth most common cancer worldwide. Surgical therapy, as a curative option, is indicated only in patients with single HCC without portal hypertension and preserved liver function. Hepatic resection of HCC in patients with cirrhosis is associated with significant peri-operative mortality and morbidity. Cirrhotic patients with non-resectable HCC have a poor prognosis influenced by hepatic reserve function and tumor staging.¹ Surgical resection is the standard of care because it has been shown to provide survival benefits, while systemic chemotherapy and radiotherapy are ineffective. Liver transplantation seems to be the choice for mono-focal HCC less than 5 cm in diameter and in selected cases of multifocal HCC, but may be limited by availability of donor organs and a long waiting time.¹ TACE has been shown to reduce systemic toxicity and increase local effects and thus improve therapeutic results. The core concept includes selective embolization of tumour-feeding arteries with a chemotherapeutic agent in an emulsion with iodized oil and subsequent embolization with a particulate agent. The chemotherapeutic regime varies considerably between centers, as does the choice of embolization agent including non-permanent embolic material such as absorbable gelatine powder or polyvinyl alcohol particles, gelatine-coated tri-acryl embospheres or biocompatible polyvinyl alcohol hydro-gels (bead block). Doxorubicin is the most commonly used agent.² Because blood flow promotes heat loss, and heat loss may reduce the effectiveness of RFA, a possible way to increase the ablation size of RFA thermal lesions would be to reduce or eliminate the heat loss that is mediated by tissue perfusion. Blood flow to hepatocellular carcinoma lesions can be substantially reduced by the arterial embolization effect of TACE treatment. Moreover, TACE has a strong antitumor effect on hepatocellular carcinoma lesions. However, both TACE and RFA have some well-known limitations. In particular, neither results in adequate control of hepatocellular carcinoma tumors larger than 3cm. Consequently, multimodal combined treatment is an appealing alternative, especially for patients with large hepatocellular carcinoma.²

Background: In this study, the outcome of the combination of RFA with TACE was retrospectively evaluated and the effectiveness of this combination treatment on large unresectable primary liver cancer. We carried out a prospective, randomized controlled trial to assess the benefits of combined TACE-RFA for large unresectable hepato-cellular carcinoma.

Method: In the present work, 20 patient with single unresectable HCC from Cairo between 35-50years will be investigated. Patients were randomized into two groups, Group (1), starting by radiofrequency ablation followed by TACE after 4weeks then follow up by TACE, Group (2), starting by chemo-embolization followed by sequential radiofrequency ablation after 2weeks from TACE

Keywords: liver neoplasms, hepatocellular carcinoma, trans-arterial chemo-embolization, radiofrequency ablation

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Abbreviations: HCC, hepatocellular carcinoma; TACE, trans-catheter arterial chemoembolization; RFA, radio-frequency ablation; HbAg, hepatitis B antigens; HBV, hepatitis B virus; HCV, hepatitis C virus; CDNA, complementary double strand deoxyribonucleic acid; CT, computed tomography; MRI, magnetic resonance images; CBC, complete blood count; BCLC, barcelona clinic liver cancer staging system; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombine time; FL, focal lesion; PV, portal vein

Introduction

Hepatocellular Carcinoma (HCC) accounts for most primary cancers of the liver. Worldwide, it is the fifth most common cancer

and the third cause of cancer related mortalities. In Egypt and over the last decade, a remarkable growth, from 4.0% to 7.2%, was observed in the proportion of chronic liver disease patients diagnosed with HCC. Based on a recent worldwide systematic review from 90 studies concerned with viral hepatitis sero-prevalence among HCC cases, a predominance of HBsAg was found in HCCs from most Asian, African and Latin American countries while anti-HCV predominated in Japan, Pakistan, Mongolia and Egypt.³

Apart from hepatitis viruses and liver cirrhosis, there are different risk factors that can increase the hazards ratio of the disease. During the last decade, a significant male predominance was observed in diagnosed HCC cases with a three times higher calculated risk in men than in women. The predominant age group (40-59 years) showed

a slight increase compared with older groups (more than 60years). Environmental pollutants (such as aflatoxin B), chemical carcinogens (such as chlorination byproducts), insecticides and pesticides are all well reported to be classical promoters of HCC development. Having ever worked in farming or as an industrial worker and a lower level of education were all significantly observed in HCC cases compared to different control groups. In addition, a positive correlation between a history of diabetes mellitus and HCC was observed.³

Egypt has the highest prevalence of HCV worldwide and has rising rates of hepatocellular carcinoma (HCC). The number of newly diagnosed patients with HCC increases annually. The prevalence of HCC is high in Nile Delta area, and is more common in males, rural residents and farmers especially in HCV patients. In rural areas there are other risk factors that may be responsible for this high incidence, such as pollution, aflatoxins and use of insecticides, which need more study.⁴

While HCC is more prevalent in certain areas in Africa, like sub-Saharan Africa, nearly half of the data on HCC in Africa came from Egypt, being simultaneously plagued with the highest prevalence of HCV in the world. While 30% of HCV infected individuals may clear the infection naturally, the remaining 70% will develop chronic disease that may result in liver cirrhosis and/or HCC. The two main risk factors for HCC in Egypt (Viral infection with HCV or HBV) took different patterns during the last decades. Two main factors are standing behind this: first, the high rates of HBV infection before the start of the national program for HBV vaccination of newborns in 1992.¹³

Secondly, the wide use of Schistosomal parenteral therapy campaigns for more than 30 years ended in 1980 using non disposable glass syringes.⁵ Over a decade, there was nearly a two fold increase of the proportion of HCC among chronic liver disease patients in Egypt with a significant decline of HBV and slight increase of HCV as risk factors. A-Fetoprotein played a limited role in diagnosis of HCC, compared to imaging techniques. Increased detection of small lesions at presentation reflects increased awareness of the condition.⁶

HCC, as other cancers, is a multi-step process that involves many genetic alterations with an endpoint malignant transformation of hepatocytes. Recently, a study succeeded to provide a complete genetic profile for Egyptian HCC. Genome wide analyses were performed as a first step to identify the predictive signatures. Out of 25,000 studied cDNAs, 958 transcripts were differentially expressed between up and down regulation. Nineteen pathways were up regulated through 27 genes, and 13 pathways were down regulated through 19 genes.

Understanding HCC pathogenesis among Egyptian patients with identification and monitoring of gene expression profile changes will provide a chance to identify specific novel targets for disease detection and intervention.⁵ Hepatectomy has been considered the first-line treatment for large HCC, but only 10%-54% of patients with HCC are candidates for hepatectomy because of their poor hepatic reserve resulting from underlying chronic liver disease or a multifocal distribution of tumor nodules. Liver transplantation is another surgical option that can treat both cancer and liver dysfunction. However, the lack of donors and high costs make it difficult for patients to undergo liver transplantation.²

Chemo-embolization has played an important role in the treatment of large HCCs in patients who are not surgical candidates. However, survival after chemoembolization is limited.² Results of recent studies have shown that radiofrequency (RF) ablation is a useful

therapeutic option for the treatment of unresectable small HCCs. However, the limited size of coagulation necrosis usually fails to achieve complete ablation of large HCCs greater than 5cm. Complete coagulation necrosis with no evidence of nodular or irregular contrast enhancement at computed tomography (CT) or magnetic resonance imaging is achieved only in one quarter of large HCCs.²

To increase the area of coagulation necrosis (ablation zone size), arterial occlusion such as balloon occlusion, embolization, and chemoembolization are combined with RF ablation. Blood flow promotes heat loss, and reducing or eliminating blood flow during the RF procedure is known to increase the volume of the ablative zone. The HCCs are supplied almost entirely by hepatic arteries. Therefore, it seems reasonable to perform RF ablation after chemoembolization. Chemoembolization is also effective for the treatment not only of the main HCC but also of satellite tumors adjacent to the main tumor.⁷

A recent randomized controlled trial has shown that combination therapy with RF ablation and chemoembolization is superior to chemoembolization alone or RF ablation alone in improving survival for patients with HCCs larger than 5cm. This combination therapy may also increase the survival of patients with HCCs measuring 5.1-10cm; however, few long-term clinical results have been reported.⁷ Therefore, the purpose and aim of our study is to evaluate, retrospectively, the results of RF ablation combined with chemoembolization in patients with large Unresectable HCCs.

Results

This study was carried out on 20 patients. Radiofrequency was performed before or after chemoembolization as compared to Kim JW et al.,⁸ study that is where comprised of 47 patients with RFA was performed the day after TACE. 15 males and 5 females were included in our study, this male to female ratio is similar to ratio reported by Cheng BQ et al.,² who pronounced male predominance of hepatocellular carcinoma throughout the world. All the patients in our study were Child A or B, none of our patients was Child C, this was a part of the inclusion criteria of the patients involved in the study to achieve high success rate with the least complication this coincides. WHO involved 291 patients in their study with the same inclusion criteria. No significant differences were observed between both groups with respect to the following baseline characteristics, patient age and sex, Child-Pugh class: proportions of patients positive for hepatitis C virus antibody. In our study 52.5% of the HCC lesions were medium-sized (5 cm) and 47.5% are large (5.1 To 7cm), this was not in agreement with Livraghi et al.,⁹ who studied 114 patients with HCC (with 126 focal HCC) and found that 80 tumors were medium and 46 were large. The liver biochemical profile in our study that is at one month after the end of sessions showed slight changes and after six months we found increase in transaminase as well as bilirubin levels above the pre-ablation level in 77% of patients.

The spiral triphasic CT done before the procedure in both groups showed typical HCC criteria in (75%) of patient and atypical criteria in (25%) who were confirmed with histopathology after percutaneous needle biopsy. In our study technique effectiveness (complete ablation) was confirmed by absences of residual active malignant lesions in both arterial phase and porto-venous phase by Triphasic spiral CT, This follow up CT done at one month, 3months, 6months and 12months after finishing the combined approach. Nearly 75% of patients had complete ablation in both groups while 20% had partial ablation after 3months, 4 patients were re-ablated using the same technique and one patient underwent no further therapy due to

development of extensive PV thrombosis. In our study as regard the diameter of ablated lesions (40%) of near to 5cm HCC lesions and more than (60%) of near to 7cm HCC lesions were partially ablated with residual or recurrent tumoral tissue. This difference results was of better outcome in smaller sized HCC lesions, In comparison to Kim JW et al.,⁸ it was confirmed that Radiofrequency ablation alone achieves complete necrosis in more than 90% of smaller lesions (≤ 3 cm) HCCs. and larger lesions with residual viable tumor cells should treated by combined therapy to avoid local tumor progression during the follow-up period after the procedure. We detected by triphasic CT one patient of the partially ablated lesion shows rapid spread of HCC lesions in both lobes after more than one month (6 weeks) after ablation, Similar cases were reported by Angonese et al.¹⁰ showing rapid unexpected explosive spread of HCC after RFA in nine cases: they explained that by the following poor tumor differentiation, increase intra tumoral pressure with intravascular spread, seeding due to arteriovenous fistula due to the expandable hooks needles, also suggested risk factors have been reported such as: high alpha fetoprotein level, and increased concentrations of growth factors in the liver (transforming growth factor Beta). We found in our study that TACE before RF have combines the effect of targeted chemotherapy with that of ischemic necrosis induced by arterial embolization, more over it reduces or eliminates the heat loss mediated by tissue perfusion by arterial embolization. It is also can be repeatedly administered and can prolong survival in patients with HCC, This is similar to Cheng et al.¹¹ study results. In our study using TACE 1st as in group² also compatible with Kim et al.,⁸ to perform TACE first in order to take full advantage of the synergistic effects of TACE upon RFA, At this later study the efficacy of the chemotherapeutic agents infused during TACE reduced when they were exposed to the hyperthermia of RFA. When the degree and duration of the high temperature generated by a RF system are taken into consideration, the cytotoxic potency of anticancer drugs appears not to be appreciably affected. For lesions larger than 5 cm we use the combined therapy of radiofrequency and TACE to take advantage of therapeutic effect on nodular lesions, but larger non-nodular lesions are still a challenging problem.

This is was compatible with Wang YH et al.,⁷ study confirms that patients treated with TACE+RFA had better overall survival than those treated with TACE alone or RFA alone and this was similar to Cheng et al.,² study but in a smaller size nodular lesions. In our study the results of group (2) using TACE prior to RFA was beneficial than group (1) specially in patients with hepatocellular carcinoma greater than 5cm, This similar to the results of Cheng et al.,¹¹ study. This is explained by, a) the modification in hepatocellular carcinoma tissue conduction that occurs after the sudden occlusion of the hepatocellular carcinoma-feeding artery using gelatin sponge. b) Disruption of intratumoral septa may facilitate heat distribution within the tumor as intratumoral septa and fibrosis influence heat diffusion within the tumor.

The use of TACE in our study as complementary treatment to prolong the survival in patients who has residual lesions after RF ablation, this was compatible with Wang YH et al.⁷ study were TACE used as adjuvant chemotherapy to eradicate the peripheral viable tissue and micro-metastasis. For those cases that could only be partially ablated, so multiple sessions of TACE and multimodality treatments are required. The complications and side effects encountered in our study, in the 1st week (early complication) abdominal pain occurred in 14 patients in both group, it was mild resolved with NSAIDS. Fever occurred in 16patients and resolved with antipyretics, ascites after 3months of follow up developed in six patients and resolved with diuretics. Haematemesis & melen a occurred in three patients caused

by ruptured oesophageal varices revealed by upper endoscopy, after 6months (Late complications), ascites developed in eight patients, hemobilia and pleural effusion (resolved after 2 months) by medical treatment. Several studies evaluating RFA combined with TACE for HCC smaller than 5 cm demonstrated the rates of local tumor progression from 2.9% to 40% as in Kim JW et al.⁸

In our study, local tumor progression was noted in 55 %of patients as it was difficult to directly compare our study result with those of previous studies due to the different basic values, such as the methods of combined therapy, type of electrode used, mean tumor size which is larger than 5cm and follow-up duration. Regarding the survival in our study 12 months survival was recorded in 85% of patients of both groups. Our study was controversial with other studies conducted by Livraghi et al.,⁹ and Cheng et al.² who follow up the survival of the patients for longer periods, this was due to the selection of the patients with medium or large size lesions which seemed to be difficult to follow up for longer period. In our study, no significant differences were observed between both groups with respect to the following baseline characteristics, patient age and sex: Child-Pugh class: proportions of patients positive for hepatitis C virus antibody and positive for hepatitis B surface antigen. Regarding the diameter of the focal HCC, In our study (52.5%) had medium-sized hepatic focal lesion that ranges from 5cm in maximum diameter while (47.5%) had large focal lesion 5.1 to 7cm in diameter. Regarding the triphasic spiral CT criteria before the procedure, the enhancement was homogenous in (87.5%) and heterogeneous (12.5%) who were confirmed with elevated AFP level.

Regarding the Alpha-fetoprotein level (AFP), The AFP level decreased significantly after one month in both groups, and the decrease was more significant after six months. Triphasic spiral CT done one month after the procedure in both group showed that, 75%of patients had complete ablation in both groups while 25%had peripheral enhancement. Regarding CT findings after 6months, (75%) showed maintained ablation while 5 patients showed denovo enhancement adjacent to the original ablated focal lesion. The liver biochemical profile in our study showed slight changes after the procedure (slight increase in bilirubin and ALT and reduction in albumen in both groups). Regarding the complications of both procedures, fever, ascites, Haematemesis & melen a were the most common complications encountered in our study. Regarding success, in our study in both groups after 12 months was (55%) while (45%) showed residual enhancement.

Material and methods

In the present work, 20patients with single unresectable HCC from Cairo between 35-50 years will be investigated. The present work included 20patients having unresectable HCC (medium-sized 5 and large-sized 7 cm in diameter). Patients were randomized into two groups, Group (1), starting by radiofrequency ablation followed by TACE after 4weeks then follow up by TACE, Group (2), starting by chemo-embolization followed by sequential radiofrequency ablation after 2weeks from TACE. The study will approved by informed consent. Patients with early-stage HCC with no previous treatment for HCC, tumor large diameter more than 5cm, Child-Pugh class a liver profile, no vascular invasion, and no extrahepatic metastases. Patients had at least one image examination (Abdominal ultrasound, Helical triphasic contrast-enhanced CT or MRI study) with laboratory investigations (CBC, liver function test, bilirubin level, alkaline phosphatase, albumen and creatinine).

Patient selection

- I. This study was conducted from May 2009 to December 2012 on 20 Patient with a median age of 47.12 ± 2.98 years having unresectable hepato-cellular carcinoma ≥ 5 cm (proved mainly by combination of elevated alpha-fetoprotein and typically enhancing focal lesions in spiral CT) and having hepatitis C or/ & B viruses.
- II. The study was carried out in National Hepatology Tropical Medicine Research Institute (NHTMRI) through a multidisciplinary team using Triphasic CT, ultra-sonography, liver and kidney profile in assessment and staging of the disease severity for each patient before starting any procedure followed by written informed consent.
- III. The procedure entailed combined treatment of unresectable HCC ≥ 5 cm using transcatheter arterial chemoembolization and radiofrequency ablation.
- IV. Patients were randomized into two groups (10 patients each)
 - A. Group (1), starting by radiofrequency ablation followed by TACE after 4 weeks, then follow up by TACE.
 - B. Group (2), starting by chemo-embolization followed by sequential radiofrequency ablation after 2 weeks from TACE.
- V. Inclusion Criteria
 - A. Patients with unresectable hepatocellular carcinoma with (BCLC) of intermediate stage (child A or B stage)
 - B. Patient having nodular HCC ≥ 5 cm up to 7 cm in diameter.
- VI. Exclusion Criteria

According to (BCLC) stage D Patients with vascular invasion,

 - A. Lesions larger than 7cm
 - B. Patients with Child's score C
 - C. Patients with PV thrombosis
 - D. Patients with moderate to severe ascites
 - E. Patients with extra-hepatic metastatic HCC
 - F. Patients with uncontrollable bleeding diathesis (prothrombin concentration less than 60% and platelet count less than 60,000).
- VII. Patients are subjected to the following
 - A. Full history taken and proper clinical examination and monitor presenting symptoms of uncontrolled liver disease as ascites, hepatic encephalopathy, gastrointestinal bleeding, cancer symptoms and performance Status were evaluated for each patient.
 - B. Laboratory Workup, at least within 2weeks before any procedure. Liver function, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fractional and total bilirubin, Serum protein profile, serum albumin and total protein, Coagulation profile, international normalized ratio (INR), complete blood count, Renal function, blood urea and creatinine, Hepatic viral markers and alpha fetoprotein level.
 - C. Liver Function Status, Child-Pugh class A and B.
 - D. (AST level <100 IU/L),

- E. (Serum albumin >3 gm/dl),
- F. (Bilirubin level <3 mg/dl),
- G. No ascites, hepatic encephalopathy, biliary obstruction, gastrointestinal bleeding or cancer symptoms.
- H. Performance Status stage (0), fully active, normal life and no symptoms or severe co-morbid disease.
- I. Coagulation profile, (Platelet count $>70,000/\text{mm}^3$), (INR <1.4).
- J. Renal function, (Serum creatinine level <1.2 mg/dl).
- K. Radiological Workup, at least within 2weeks before any procedure (Preprocedural), chest radiograph, abdominal ultrasound (size, number, multiplicity, location and echo pattern of the lesion and confirming the patency of portal and hepatic veins). Triphasic Spiral Computed Tomography (CT) studies of the abdomen were performed (pre-contrast scan followed by three phase's scans to arterial, portal/venous and equilibrium phases). (Size of lesion, >5 cm up to 7cm, (Lesion location should have exclusion criteria for RFA) (No extrahepatic spread), multiplicity without evidence of vascular invasion or extra-hepatic metastases or biliary dilatation.
- L. Images guidance biopsies were taken according to BCLC guide line in some patients when pre-procedure imaging and alpha fetoprotein levels were equivocal.
- M. Procedure must be performed on inpatient basis. Most of Patients are admitted the night before the day of procedure.
- N. Some patients are subjected to Intravenous hydration administered 2 hours before treatment to reduce the risk of post procedure dehydration and hypotension.
- O. Informed written consent, explain in it in details the procedures and the possible post operative complications.

Discussion

For better prognosis of Hepatocellular carcinoma patients it is recommended that the staging system takes into account tumor stage, liver function and physical status. So the BCLC staging System is the only staging system that accomplishes these aims in our study (Figure1).¹² Patients who have intermediate-stage hepatocellular carcinoma according to the BCLC staging system are the optimal candidates for Radiofrequency ablation performed before or after transcatheter arterial chemoembolization results in increased volumes of coagulation necrosis, thus enabling successful destruction of large hepatocellular carcinoma lesions and management of residual tumoral tissue.¹³ Our study concluded that RF ablation combined with transcatheter arterial chemoembolization showed superior therapeutic effect than transcatheter arterial chemoembolization alone or RFA alone on the treated unresectable hepatocellular carcinomas and appears to benefit for the patient in terms of improved survival due to the lower local recurrence rate using, TACE procedure and sequential RF ablation therapy, RF ablation before TACE or simultaneously combination of both procedures at the same sitting.¹⁴

The procedure of transcatheter arterial chemoembolization

The angiographic procedure is conducted with a digital angiographic unit to assess the origin and the variants of the hepatic artery. The Seldingers technique is used to access the femoral artery

with A(5 French sheath introducer) under fluoroscopic guidance and local anesthesia, which induced by injecting 10ml of 1% lidocaine hydrochloride. Identification of the hepatic arterial anatomy, vascular supply and arterial flow were performed with use of a {4.0-F Cobra II (Cobra 2) curved catheter} which was advanced by using a hydrophilic coated standard J-curved guide wire (Treumo) into the superior mesenteric and the celiac arteries.

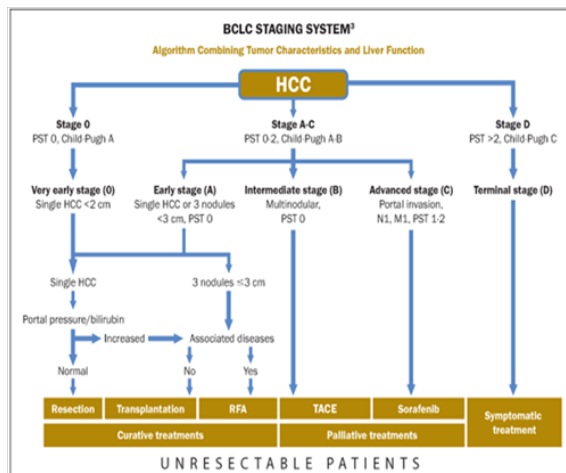


Figure 1 BCLC Staging system.

The angiogram is completed by identifying the tumors blush. Chemoembolization mixture is infused into the artery. This mixture is comprised of the chemotherapeutic agent Doxorubicin hydrochloride dissolved in a non-ionic water-soluble contrast medium and saline, then emulsified in iodized oil (Lipiodol). The Doxorubicin/Lipiodol ratio was calculated according to the tumor size (10mg of Doxorubicin and 2ml Lipiodol per centimeter of tumor diameter). At the end of the procedure, Gelfoam sponge particles were injected as an embolizing agent under fluoroscopic guidance until blood stasis was achieved specially in cases where arterial portal venous shunting was present, the shunt embolized first by using iodized oil. This process should occlude the shunt but preserve the hypervascularity of the tumor. Then, the lesion treated with chemoembolization in the usual fashion. A post-embolization image is acquired to show the distribution of the iodized oil.

Post-procedural workup

After TACE procedure, the patient referred to the ward for overnight observation of vital data, hemostasis of arterial puncture site and signs. Post-embolization syndrome managed by giving the patient proper analgesic and antiemetic with Intravenous hydration continued for at least 24 hours. Post procedural pain management started on need basis and according to patient condition. Prophylactic antibiotics continued by 1gm (Cefobid) every 12 hours for two doses administered intravenously, antifibiotics continued by dose 500mg every 8 hours administrated orally for 7days. Antiemetics continued on need basis. A non-contrast-enhanced CT scan of the liver was obtained immediately before discharge. In most of the cases, patients are discharged the day after the procedure. Evidence of the technical success of the procedure was demonstrated by focal deposition of the mixture of Lipiodol and chemotherapeutic agent in the tumor and relative sparing of the non-tumorous liver parenchyma.

The procedure of radiofrequency ablation (RFA)

Local anesthesia is induced by injecting 10 ml of 1% lidocaine hydrochloride at the entering site and around the liver capsule.

Sedation may be induced in some cases and maintained by expert anaesthesiologist. Radiofrequency System, Generator, We used a common, commercially available RFA technique and system {RITA 1500X RF generator and RITA Star Burst XL, RITA Medical Systems, Mountain View, California}. Grounding was achieved by attaching 2 pads to the patient's thighs. After administration of analgesia (2.5-5.0mg of Midazolam and 0.05-0.1mg of Fentanyl) as well as local anesthesia (5-15 mL of 1% lidocaine). The electrode needles were introduced into the tumor under ultrasonographic or/CT guidance, then a gradual unfolding of the electrodes was obtained, and the generator was activated to achieve RF energy and maintain an average temperature of 100°C. At first, the electrodes were moved by 2cm and then the electrode needles were pushed forward and unfolded gradually to 3cm, 4cm, 5cm, 6cm and 7cm until they reached or crossed the borders of the tumor according to the ablation range. Delivering RF energy for 5minutes for every intermediate step and for 7 to 10 minutes in the final step of the procedure. The ablation area was intended to cover the tumor as well as at least 1 cm of the surrounding tissue. The overlapping mode was used in two separate introductions if the diameter of the lesion was greater than 5cm to maintain safety margin up to 1cm. During ablation, temperature was measured with a thermocouple in the electrode and tissue impedance was monitored by circuitry incorporated within the generator. To prevent bleeding and tumor seeding, track ablation was performed when withdrawing the RFA electrode in all patients. Ultrasound is used for real-time targeting, monitoring and controlling of the entire procedure, including positioning the needle electrode.

The needle path selected to traverse sufficient normal liver parenchyma and to perform cauterization of the needle track after ablation to decrease the risk of intra peritoneal hemorrhage, tumor seeding and skin burn. After skin cleansing using a sterile technique, local anesthetic is injected along the expected needle pathway and a small skin nick is made. The electrode is passed through the neck and advanced through the center of the tumor into the desired portion of the tumor. To avoid tumor seeding, the number of puncture and repeated repositioning of the RF needle electrode should be minimized. Grayscale imaging is used to continuously monitor sonographic changes at the site of ablation: typically, an area of echogenicity developed corresponding to coagulation of the tissues produced by the resulting nitrogen gas microbubbles. After the suggested complete ablation of the tumor is achieved, the arrays are the completely retracted to heat the needle path and prevent seeding of tumoral cells.

Post-procedural workup

After procedure, the patient must be referred to the ward for overnight observation of vital data and signs of post ablation syndrome. The patient rescanned with ultrasound 2hours after treatment to detect any bleeding in the liver or the peritoneal cavity. Post-procedural pain management started on need basis by oral or intravenous drugs. Prophylactic antibiotics continued every 12hours for two doses administered intravenously. Thereafter, antibiotics continued by 500mg every 8hours administrated orally for 5days. For lesions in the dome of the liver, if patient complains of dyspnea or chest pain after ablation, CT chest or fluoroscopy immediately performed to evaluate diaphragmatic injury or thoracic complications. In most of the cases, patients are discharged the day after the procedure.

Laboratory workup: Liver function status, (ALT, AST, bilirubin), Serum protein profile, (serum albumin and total protein), Coagulation profile, (prothrombin time, and international normalized ratio), Complete blood count, Renal function, Hepatic tumor markers, alpha fetoprotein.

Radiological workup: Triphasic CT scan of the abdomen, the presence of a well-defined area of non-enhancing tissue including the treated tumor on images obtained in both the arterial and portal phases of enhanced CT images was considered to indicate complete necrosis. Evaluation repeated at 3, 6, 8 months and yearly thereafter for evidence of disease recurrence on triphasic CT scan and status of underlying liver function. The size of the lesion treated, and recurrence pattern (either intra-hepatic or extra-hepatic).

Statistical analysis

Data were analyzed using mean and SD, median, minimum and maximum values. Qualitative data were summarized using frequencies and percentage. Chi-square, Fisher exact tests were used for detection of association whenever appropriate. Comparison of lab data before and after intervention was done using Wilcoxon Signed Ranks test.

Binary logistic regression analysis was done to exclude the effect of significant variables between groups on the significant final outcome difference. Differences were considered significant when p value was ≤ 0.05 and highly significant when p value ≤ 0.01 . Comparison of survival curves was done by log rank test. The difference between general features of both groups was statistically not significant regarding sex, virology and Child classification. Most of our patients were males and HCV positive (Table 1). The difference between the ages was statistically not significant (Table 2). No significant change in the laboratory profile in both groups before the procedures with gradual increase after 6 and 8 months of follow up (Table 3). After 12 months of follow up 10 patients developed elevation of bilirubin level above 3 mg/dl and also elevation in liver enzymes that is controlled by medical treatment and liver support.

Table 1 General features of the two studied groups

Sex	Group (1) (n = 10)		Group (2) (n = 10)		Total (n = 20)		P value
	No	%	No	%	No	%	
Male	7	70	8	80	15	75	0.606
Female	3	30	2	20	5	25	
Virology							
HCV	6	60	9	90	15	75	0.231
HBV	4	20	1	10	5	25	

Table 2 Age distribution of both groups

Group	Mean \pm SD	P value
Group (1)	47.12 \pm 2.98	0.3
Group (2)	48.30 \pm 1.70	

Table 3 Comparison of laboratory results in both groups after 6 months

		Group (1)	Group (2)
Albumin (N: 3.5-5.5 mg/dl)	Before	3.34 \pm 0.34	3.22 \pm 0.23
	Aft. 6 months	3.20 \pm 0.30	3.12 \pm 0.24
	P value	0.029	< 0.001
Bilirubin (N:<1 mg/dl)	Before	1.44 \pm 0.55	1.24 \pm 0.39
	After 6 month	1.47 \pm 0.47	1.53 \pm 0.34
	P value	0.743	< 0.001
AST (N: 0 - 40 IU/l)	Before	57.40 \pm 32.27	52.75 \pm 23.64
	After 6 months	57.20 \pm 25.68	54.85 \pm 22.85
	P value	0.945	0.412
ALT (N: 0 - 45 IU/l)	Before	52.20 \pm 40.86	47.45 \pm 25.30
	After 6 month	50.30 \pm 29.62	53.75 \pm 25.41
	P value	0.710	< 0.001
PT (80 -100%)	Before	72.60 \pm 8.18	66.85 \pm 5.72
	6 months later	68.95 \pm 6.25	69.60 \pm 5.94
	P value	0.125	0.174

There was no significant difference in criteria of HCC lesions in both groups and most lesions showed typical arterial enhancement and rapid wash out in porto-venous and delayed phases (Table 4). There was no statistically significant difference between both groups regarding post procedure complications. Abdominal pain and fever were the most recorded complications occurred to 14 to 16 patients. Haematemesis occurred in 3 patients. Ascites developed due to the effect of the chemotherapy on the hepatic synthetic function (Tables 5 & 6). The difference after 6 months was statistically not significant. The majority of the patients showed complete ablation in each group

while 5 patients showed partial ablation retreated by the sequential method of ablation, De novo lesions was recorded in 5 patients that is retreated again. The difference between the two groups started to be significance after the 8th month as we noticed that 6 patients having de novo lesions with residual reactivity and 7 patients was having portal vein thrombosis (Table 7). The difference was statistically insignificant after 12 months at both groups we had 9 patients with residual tumoral reactivity, 7 patients showed portal vein thrombosis and denovo lesions (Table 8).

Table 4 Triphasic spiral CT criteria of lesions in both groups before procedure

	Group (1) (n = 10)		Group (2) (n = 10)		Total (n = 20)		P value
	No	%	No	%	No	%	
Typical Enhancement	8	80	7	70	15	75	0.606
Atypical Enhancement	2	20	3	30	5	25	

Table 5 General post-procedure related complications in both group

	Item	Group (1)		Group (2)		Total		P value
		No	%	No	%	No	%	
General Complications	Abdominal pain	8	80	6	60	14	70	0.329
	Fever	7	70	9	90	16	75	0.264
	Haematemesis	1	10	2	20	3	15	0.531
	Ascites	2	20	4	40	6	30	0.329

Table 6 Success rate of both procedures after 3 months of follow up

Item		Group(1)	Group(2)	Total	P value
According to Spiral Computed Tomography	Successful Ablation	-80%	-70%	-75%	1
	Partial Ablation	-15%	-25%	-20%	
	Absent Tumoral Reactivity	-80%	-70%	-75%	1
	Failure with Re-Ablation	-5%	-5%	-5%	

Table 7 Triphasic spiral CT findings of both groups after combined procedure for one year of follow up

	Group (1) (n = 10)		Group (2) (n = 10)		Total (n = 20)		P value
	No	%	No	%	No	%	
(After 3 Months)							
Non-Enhanced (No Activity)	8	80	7	70	15	75	0.606
Residual or De Novo F.L	2	20	3	30	5	25	
(After 6 Months)							
Non-Enhanced (No Activity)	8	80	7	70	15	75	0.606
Residual Or De Novo F.L	2	20	3	30	5	25	
(After 8 Months)							
Non-Enhanced (No Activity)	8	80	6	60	14	70	0.329
Residual Or De Novo F.L.	2	20	4	40	6	30	
Progression (P.V Thrombosis)	5	50	2	20	7	15	
(After 12 Months)							
Non-Enhanced (No Activity)	5	50	5	50	10	50	0.653
Residual Or De Novo F.L.	4	40	5	50	9	45	

Table 8 Triphasic spiral CT findings after 12 months of follow up

	Group (1) (n = 10)		Group (2) (n = 10)		Total (n = 20)		P value
	No	%	No	%	No	%	
Ablated Focal Lesion	5	50	5	50	10	50	0.653
Non-Enhanced Residual/Recurrent (Enhanced)	4	40	5	50	9	45	
De Novo Focal Lesion	4	40	5	50	9	45	0.653
P.V Thrombosis	5	50	2	20	7	35	0.16
Ascites	5	50	3	30	8	40	0.36

Demonstrative cases

Case number (1): A 55years old female patient known to have hepatitis C virus with right hepatic lobe malignant lesion proved by imaging and elevated AFP. Her CT findings was right hepatic lobe (segment VI) well defined focal lesion of about 5cm showing early enhancement in arterial phase and rapid wash out in porto-venous and delayed phases, mild splenomegaly, no ascites. Her labs before doing any procedure was as follow (AFP 850, ALT 110, AST 90, Direct Bilirubin 1.1, Albumen 3 U/L and Creatinine 0.9). This patient was not candidate for surgery because she is cardiac patient with ejection fraction 38% and she were having poor bleeding profile with INR 1.5, that is medically controlled before starting the procedure.

CT images before doing any procedure: We decided to do RF as a starting treatment. She was complaining of mild post RF syndrome that controlled by medical treatment and after three weeks from RF ablation her AFP drop to 500 (Figure 2).



Figure 2 CT images before doing any procedure.

CT images after three weeks from RF ablation: Her CT showing partial about 50% ablation of the lesion with residual tumoral reactivity and no newly developed lesions. Then we decided to do TACE after 4weeks from RF ablation. She developed mild abdominal distension and minimal pelvic ascites that is controlled with drop of the AFP level to 46.6IU/DL. Follow up by Triphasic CT after 3months of combined therapy showing, Good uptake of lipiodol droplet by the residual tumoral tissue with no newly developed lesions. Follow up after three months of combined therapy was showing reduction of the size of the lesion into a hypo-dense non enhanced 3cm area with no residual tumoral reactivity and AFP reached 40 IU/DL (Figure 3).



Figure 3 CT Images after three weeks from RF ablation.

Follow up by triphasic CT after 3 months of combined therapy showing: Good uptake of lipiodol droplet by the residual tumoral tissue with no newly developed lesions. Follow up after three months of combined therapy was showing reduction of the size of the lesion into a hypo-dense non enhanced 3cm area with no residual tumoral reactivity and AFP reached 40IU/DL. After 6months patient developed mild ascites with mild elevation in AFP reaching 90IU/dl with deterioration of the liver function and CT showing no reactivity. After 8months of follow up she developed mild increased in AFP level reaching 110IU/DL then returning to 90IU/DL and a triphasic CT was done revealed no newly developed lesions or reactivity (Figure 4).

The last triphasic CT was done shows no residual tumoral reactivity and drop in the AFP level: After 12months the patient

developed significance elevation in AFP level reaching 565.6mg/ml and triphasic CT showing recurrence of tumoral reactivity that is will treated again by TACE (Figure 5) and Figure 6 shows Triphasic CT after 12months showing recurrence of the tumoral.



Figure 4 Follow up by Triphasic CT after 3 months of combined therapy.

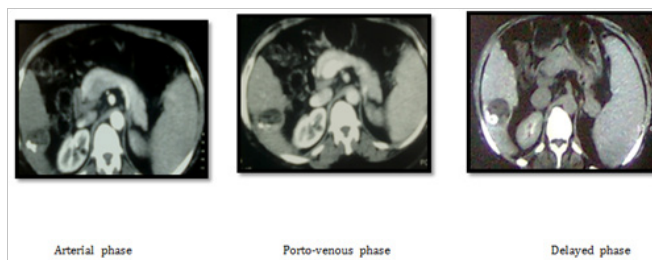


Figure 5 The last Triphasic CT was done shows no residual tumoral reactivity and drop in the AFP level.



Figure 6 Triphasic CT after 12 months showing recurrence of the tumoral.

Case number (2): A 50years old male patient known to have hepatitis C virus with right hepatic lobe HCC of about 5.5 cm by triphasic CT scan. His laboratory tests was as follow AFP 6.3 IU/ML, ALT 94, AST 72, Direct Bilirubin 2, Albumen 3.2g/dl, Creatinine 0.9) with normal CBC , PC 65%, INR 1.3).

CT images before doing any procedure: His CT showing right hepatic lobe segment VIII well defined focal lesion of about 5.5cm very close to the right portal vein branch with early nodular enhancement in arterial phase and rapid wash out in delayed phases, mild splenomegaly and no ascites. We decided to start by RF ablation (Figure 7).

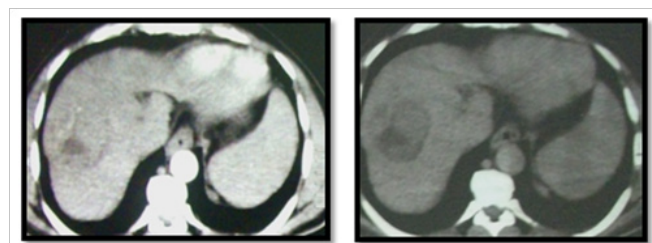


Figure 7 CT Images before doing any procedure.

CT images after three weeks from RF ablation: Post RF CT showing partial about 50% ablation of the lesion with residual tumoral reactivity and newly developed intra-lesional portal shunts. Then we

decided to complete treatment by TACE after one month from RF ablation. 1st we did angiography that revealed right hepatic artery superior branch small aneurysmal dilatation (pseudo-aneurysm), that is appears after RF ablation. It was affecting the flow as seen in next images (Figure 8). So we decided to embolize the aneurysm and correct the flow into the tumoral tissue as seen in the following images (Figure 9). Lastly we injected the chemo-lipiodol mixture into the right lobe lesion (Figure 10).

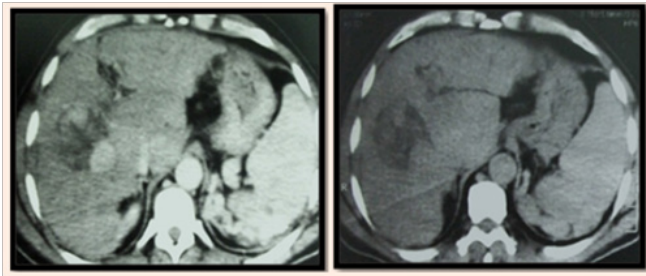


Figure 8 CT Images after three weeks from RF ablation.

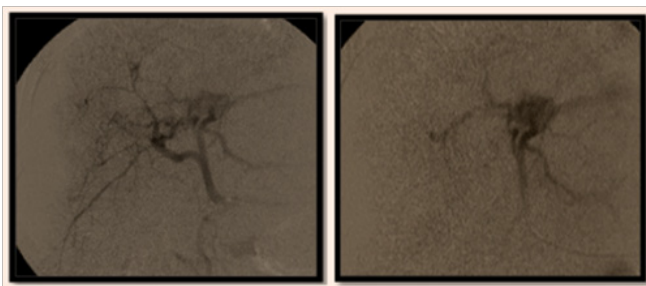


Figure 9 Flow into the tumoral tissue.

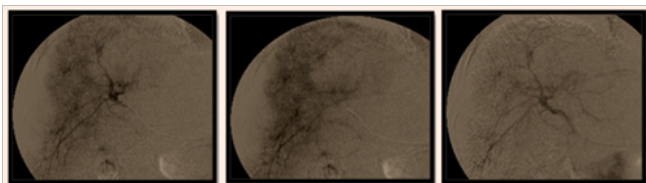


Figure 10 Chemo-lipiodol mixture into the right lobe lesion.

Follow up by triphasic CT after 3 months of combined therapy showing: Good uptake of lipiodol droplet by all residual tumoral tissues with small segment VIII residual active lesion that were noticed and treated by another session of TACE after one month (Figure 11). After 8 month patient developed two new left hepatic focal lesions and small satellites around the 1st ablated one with mild elevation of AFP reaching 50IU/DL that is further retreated by TACE. After 12month patient follow up showing no newly developed lesions with AFP reaching 25 IU/DL (Figure 12).

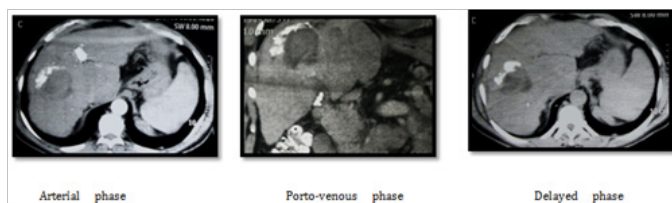


Figure 11 Follow up by Triphasic CT after 3 months of combined therapy after 1 month.



Figure 12 Follow up by Triphasic CT after 3 months of combined therapy after 8 months.

Conclusion

Combined technique of treatment gives the best results for medium and large unresectable primary hepatic neoplasm up to 7cm in comparison to each individual technique. Combined therapy between radio-frequency and trans-arterial chemo-embolization techniques considered safe and effective in treatment of medium and large-sized unresectable primary liver neoplasm. AFP is an important tool in the follow up of HCC cases especially in cases with higher values before the procedure. Regular follow up of HCC cases is mandatory for early detection of recurrence or de novo lesions. From the previous study, HCV constitute the main risk factor in Egypt triggering an alarm that eventually of high percentage of chronically infected patients with HCV will develop HCC if left untreated and unscreened. This supports the need for an effective preventive therapy and effective therapy for HCV related chronic liver disease.

There was no statistical difference in our study between the two groups, so TACE prior to RFA is beneficial in patients with large hepatocellular carcinoma more than 5cm, because TACE reduces or eliminates the heat loss mediated by tissue perfusion through embolization, also TACE help in disruption of intra-tumoral septa that may facilitate heat distribution within the tumor. Also TACE can be performed after RFA for patients with unresectable HCC especially for medium and large size tumour, to eradicate the peripheral viable tissue and micro-metastasis or partially ablated tumors by using multi-time TACE or other multimodality treatments. More studies are needed for better management of large (more than 7cm) unresectable HCC.

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Conflicts of interest

Authors declare there are no conflicts of interest.

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