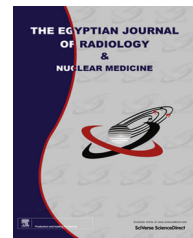




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ORIGINAL ARTICLE

Combined versus single locoregional therapy in the treatment of unresectable hepatocellular carcinoma



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KEYWORDS

Hepatocellular carcinoma;
 Transarterial chemoembolization;
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Abstract *Introduction:* Surgical and locoregional therapies are different options in HCC treatment, several locoregional techniques are used.

Purpose: This study aimed to assess the effectiveness of transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and combined therapy, in HCC management.

Materials and methods: The study was conducted at our University Hospital, from August 2011 to February 2013. It included 60 patients with HCC (40 males and 20 females, age ranged between 45 and 70 years). Patients were classified into 3 groups, group 1 treated with TACE, group 2 with RFA, and group 3 with both techniques. Response was assessed by triphasic CT and alpha fetoprotein. Patients were classified into good and poor responders after one and six months and one year. Patients' survival and incidence of recurrence were recorded.

Results: The percentage of good responders was greater with combined therapy than with TACE and RFA (90%, 70%, and 60% respectively). The overall survival was 75% and the recurrence free survival was 60% in TACE, 90%, and 45% in RFA and 95% and 90% in combined therapy respectively.

Conclusion: Combined therapy is superior regarding good response, overall survival, and free recurrence survival than either TACE or RFA alone.

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1. Introduction

Management of HCC continuously presents many challenges (1). It had been reported that surgical resection considered being the best treatment for early stage HCC. However, only 9–29% of HCC patients are candidates for surgery owing to either underlying chronic liver diseases resulting in poor hepatic reserve or multifocal distribution of the tumor (2). So, the locoregional therapies including radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and others are now the current utilities for management of unresectable HCC (1).

Although TACE or RFA has proved that each of them improves the survival rate definitely (3), however, each of them having its practical constraints and limitations regarding the tumor size, its location and efficacy of the procedure.

It had been reported that combining RFA and TACE can theoretically overcome the limitation of each when used alone (3,4).

Reviewing studies concerning that issue, there were no single three arms study that could be reached, comparing TACE, RFA and combined therapy. Many studies either deal with individual TACE and RFA or two arms study comparing combined therapy with either TACE or RFA alone. In this study, we have investigated the comparison of TACE, RFA and combined therapy, as a three arms study; in treatment of HCC as regards their efficacy and patients' survival.

2. Materials and methods

Sixty patients with HCC on top of liver cirrhosis (40 males and 20 females), their mean age 49 years (range 45–70 years), were included in this 3 arms study. The study was conducted between August 2011 to February 2013 in the South Egypt cancer Institute and Assiut University Hospital. The protocol of the study has been approved by the ethics committee of research of Faculty of Medicine, Assiut University, and informed written consent of the patients has been taken before the study.

Patients were selected on the basis of clinical assessment, liver function tests, abdominal US and triphasic helical CT of the liver with scanning of the whole body to rule out extrahepatic metastasis. The inclusion criteria were:

- 1- Single hepatic focal lesion with size ranging between 5 and 7 cm. (A special 7 cm needle was used to treat these large tumors by RFA).
- 2- Child-Pough class A or B (25 patients class A, and 35 patients class B).
- 3- High serum alpha fetoprotein (AFP) ranging from 200 to 400 ng/ml (mean 230).
- 4- Characteristic CT enhancement criteria of HCC (in arterial, portal venous and delayed phases).
- 5- Platelet count more than 70,000/mm³.

Exclusion criteria

- 1- Evidence of extrahepatic metastasis.
- 2- Presence of portal vein or inferior vena cava thrombosis, or biliary duct invasion.
- 3- Severe liver cirrhosis with Child-Pough class C.

- 4- Severe coagulation disorders (prothrombin concentration less than 60% and platelet count less than 70,000/mm³).
- 5- Presence of uncontrollable ascites.

Patients were classified into 3 matched groups each included 20 patients. Group 1 patients were treated by TACE. In group 2, RFA was done using RITA RF 1500X system USA, and star burst XLI enhanced with tubing set (electrosurgical device). While, in group 3 combined therapy (TACE–RFA) was performed (TACE was carried out first followed by RFA one week later). Chemotherapy used in this study consisted of a mixture of Doxorubicin 50 mg dissolved in 10 cc saline mixed with 8 cc lipidol, 5 cc contrast media (ultravist 300 ml/cc), and gel foam. This dose was fixed for all patients regardless to body surface area due to the superselective injection of the mixture at the tumor feeding artery.

Therapeutic efficacy was assessed and classified into good responders, and poor responders. In cases of RFA this depended on the basis of the size of the hypo attenuating non enhancing area, and the lipidol uptake of the tumor in cases of TACE according to Wang et al. (5).

Follow up from the time of treatment for a period of one year could be achieved for all patients. The incidence of recurrence, development of new focal lesion, presence of progressive disease or stable disease, as well as, survival in months was recorded for each patient. Triphasic CT and US (with the same parameters as pretreatment scanning) were performed one month after the procedure, 6 months, and one year later. In addition, serum AFP was estimated before and one month at the same intervals (one month, 6 months and one year) after ablation.

3. Results

3.1. Group 1 (TACE)

This group included 20 patients for whom TACE was done. Twelve patients showed good response (Excellent lipidol uptake with no enhancing residual tumor tissue in triphasic CT). Eight patients showed poor response (residual enhancing tumor tissue) for whom another procedure was done one month later. Two out of the 8 patients showed good response. So, collectively 14/20 patients (70%) showed good response and 6/20 patients (30%) showed poor response (Table 1). AFP in patients who showed good response (14/20) is reduced by 20–35% (the best reduction is by 35% and the least reduction was 20%) in all patients after one month. Moreover, at 6 months and one year follow up periods, AFP was in near normal range. However, it was raised in patients who showed

Table 1 HCC patients' response by triphasic CT after TACE, RFA, and combined therapy.

Group	TACE <i>n</i> = 20	RFA <i>n</i> = 20	Combined therapy <i>n</i> = 20
Good response	14 (70%)	12 (60%)	18 (90%)
Poor response	6 (30%)	8 (40%)	2 (10%)

Table 2 Follow up of HCC patients with good response after 1 year of TACE, RFA, and combined therapy.

	TACE <i>N</i> = 14	RFA <i>N</i> = 12	Combined therapy <i>N</i> = 18
Recurrence disease (RD)	1	1	–
Recurrence with new focal lesions	1	2	–
Progressive disease (PD)	–	–	–
Progressive disease with new focal lesion.	–	–	–
Stable disease (SD)	12	9	18

Table 3 Follow up of HCC patients with poor response after 1 year of TACE, RFA, and combined therapy.

	TACE <i>n</i> = 6	RFA <i>n</i> = 8	Combined therapy <i>n</i> = 2
Recurrence disease (RD)	–	–	–
Recurrence with new focal lesions	–	–	–
Progressive disease (PD)	2	2	1
Progressive disease with new focal lesion	3	4	–
Stable disease (SD)	1	2	1

poor response (6/20). Recurrence at the site of primary lesions was detected in two patients (2/14) who demonstrated good response after the 2nd session of TACE, and one of them developed new focal lesion. One of those patients showed re-raising of the AFP but it did not change in the other patient. While 3/6 patients who demonstrated poor response, developed new focal lesion and had progression of primary tumor size. Regarding the other three patients with poor response, one of them showed stable lesion and the other two showed progression of the tumor only (Tables 2 and 3)(Figs. 1–3).

4. Survival analysis at one, six months, and one year follow up

All patients were alive up to 6 months, while 5/20 patients (25%) died by the end of the 1st year. Those who showed poor response (4 patients), and another patient who showed good response after the 2nd session developed local recurrence with a new focal lesion. Therefore, overall survival was 75% (15/20 patients) but the recurrence free survival was 60% (12 patients) (Table 4).



Fig. 1 (A and B) Triphasic CT scan of the liver showing hepatic mass involving segment 8 in arterial (a) and delayed phases (b). (C) Digital subtraction angiography showing hepatic mass lesion. (D) No subtracted angiography after chemoembolization. (E) Digital subtraction angiography post TACE showing disappearance of tumor vascularity and Lipiodol uptake. (F) CT scan at the same level one month after the last TACE, showing marked response to treatment with dense lipidol uptake.

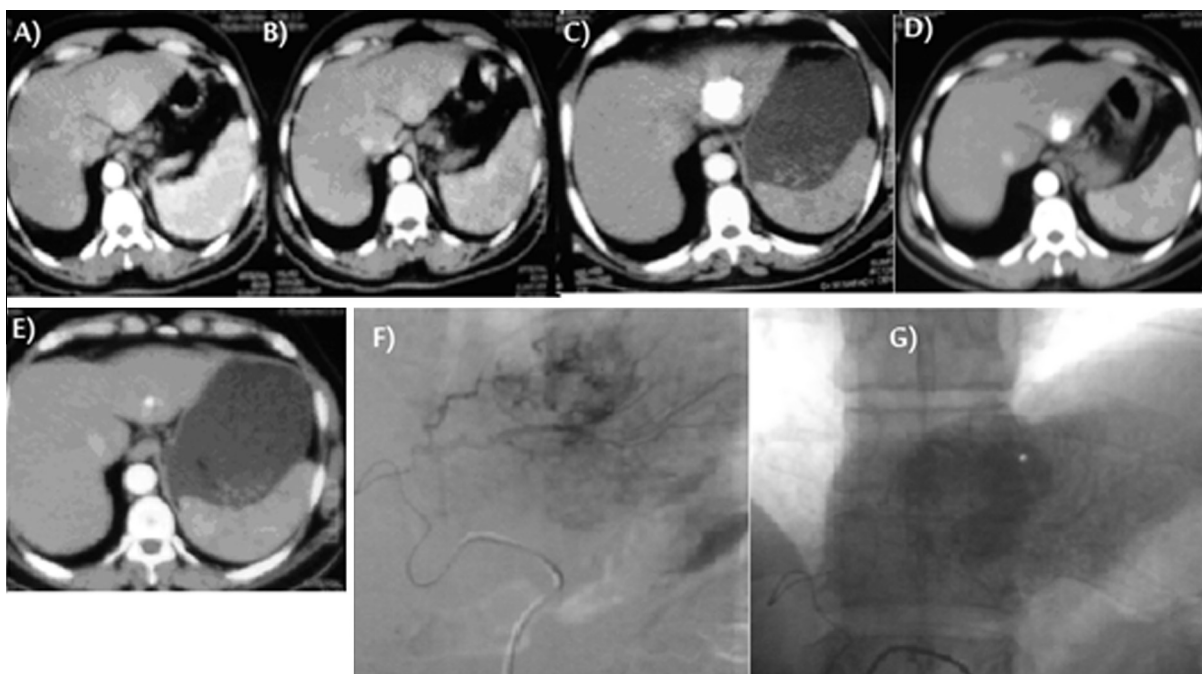


Fig. 2 (A and B) Triphasic CT scan of the liver showing hepatic mass involving Lt hepatic lobe segment 3 in arterial phases (C) CT scan at the same level one month after TACE, showing marked response to treatment. (D) CT scan at the same level six months after TACE, showing reduced size with no residual enhancing tumor tissue. (E) CT scan at the same level one year after TACE, showing vanishing of the focal lesion with no residual enhancing tumor tissue. (F and G) Digital subtraction angiography showing angiographic blush of hepatic mass lesion.

4.1. Group 2 (RFA)

This group included 20 patients for whom RFA was done. Nine patients showed good response (complete ablation with no residual enhancing tumor tissue in triphasic CT). On the other hand, 11 patients demonstrated poor response (residual enhancing tumor tissue), for them another session was done one month later. Three out of 11 patients showed good response after the 2nd session. So, collectively 12/20 patients (60%) showed good response, while 8/20 patients remained with poor response (40%) (Table 1).

AFP decreased initially by about 40% in all patients with good response at the 1st follow up (one month), but was near the normal range 6 months later in those who showed good response (12/20 patients).

Three patients among 12 who showed good response after the 2nd session developed local recurrence with re-rising of the AFP at the near end of the 1st year and two of them developed new focal lesion in addition. While 4 patients out of the 8 patients, who demonstrated poor response, developed new focal lesion in addition to the progression of the primary tumor. Regarding the other 4/8 patients, two of them developed only progression of the tumor while the other two showed stable lesion (Tables 2 and 3).

5. Survival analysis at one, six months, and one year follow up

All patients were alive up to 6 months, while 2 patients with poor response died by the end of the 1st year. So the overall survival was 90% (18/20 patients) but the disease free survival was 45% (9/20 patients) (Table 4).

5.1. Group 3 (combined TACE and RFA)

Twenty patients were included in this group for whom combined therapy (TACE and RFA) was performed. Seventeen patients showed good response, while 3 patients showed poor response for whom another session of TACE and RFA has been performed one month later. One patient among the three showed good response. So, 18/20 patients (90%) demonstrated good response in that group, while 2/20 patients showed poor response (10%) (Table 1).

AFP decreased by 45% in all patients with good response at the one month follow up and nearly normal by the end of one year in patients who demonstrated good response (18/20 patients). Neither local recurrence nor new focal lesion had been demonstrated in the 18 patients who developed good response. On the other hand, one of the two patients who demonstrated poor response showed stable disease, while the other had progressive disease and died (Tables 2 and 3).

6. Survival analysis at one, six months, and one year follow up

All patients were alive at the end of the 1st year except for one patient who died (who demonstrated poor response). So, the overall survival was 95% (19/20 patients) while the recurrence free survival is 90% (18/20 patients) (Table 4). The single patient who survived out of the two who demonstrated poor response showed stable lesion.

Complications were minor in the three groups and included pain, nausea, and mild hyperthermia and these could be managed conservatively. However there was one patient in the group of RFA who developed minimal pneumothorax which

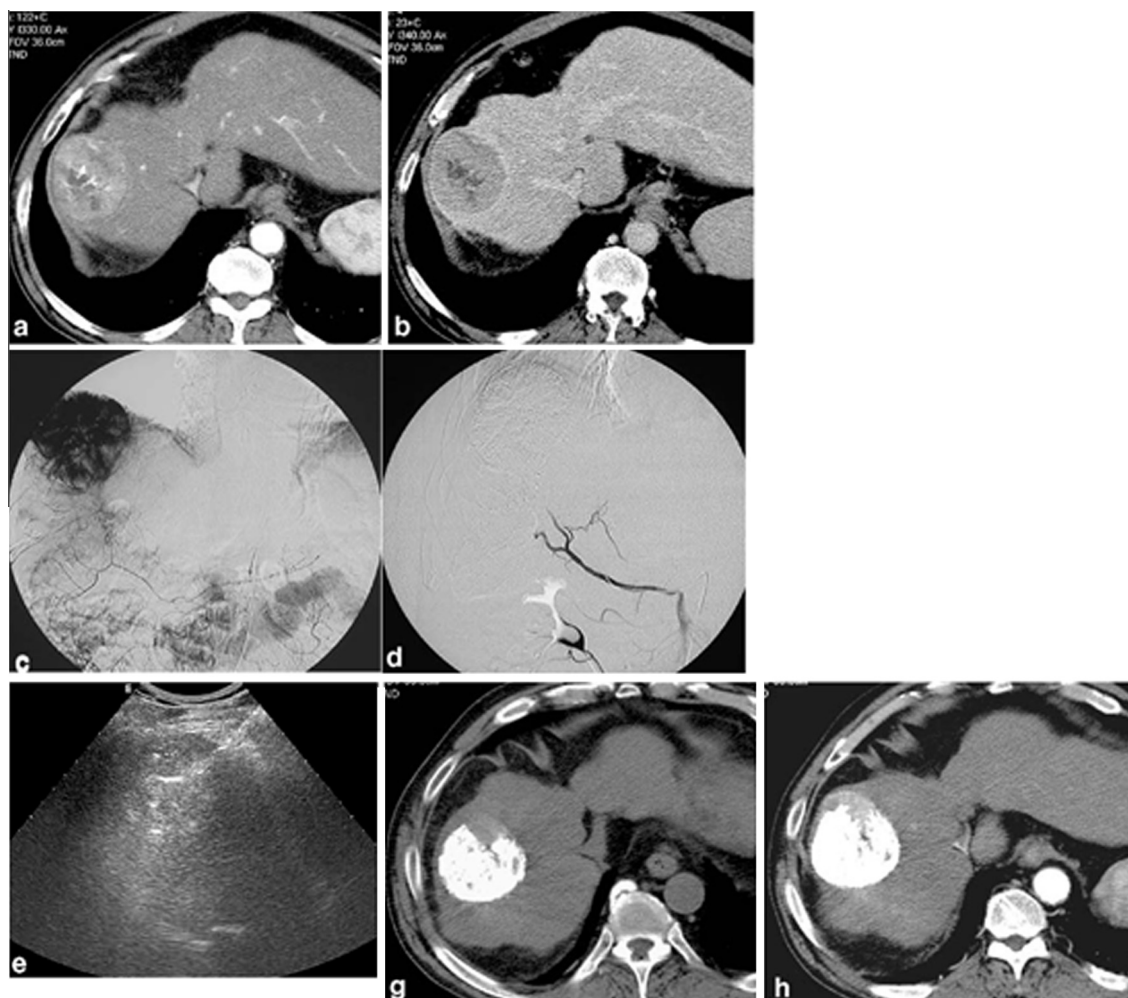


Fig. 3 Right hepatic lobe HCC, pretreatment triphasic CT in arterial (a) and late phase (b). (c) Angiography before TACE. (d) Angiography after TACE complete devascularization of the lesion. (e) US-guided electrode-needle insertion in the lesion and RF good lipidol uptake with small peripheral lack of lipidol. (g) Corresponding to some hypervascular tissue in the arterial phase (h), consisting of very small residual tumor.

Table 4 Survival of HCC patients.

	TACE (%)	RFA (%)	Combined therapy (%)
Overall survival	75	90	95
Recurrence free survival	60	45	90

disappeared spontaneously later on. Another patient in combined therapy group with Child-Pough II, developed minimal ascites but controlled with diuretics and salt free albumin.

7. Discussion

HCC is the third most important cause of cancer related mortality worldwide. Locoregional treatment options such as TACE and RFA are minimally invasive treatment options that may individually or in combination address the pertinent issue of successful tumor targeting and preservation of liver function (6).

The current study is three arms one planned to compare TACE, RFA and combined therapy with matched patients groups.

One year follow up of all patients could be achieved hardly and with great effort reporting the response; the recurrence (RD), the development of new focal lesion, the progression (PD) and stable disease (SD), in addition the overall survival and the recurrence free percentage in the three groups.

The percentage of good response was 70% in the TACE group which is in accordance to the data of many other reports (7–11), however it was higher than other reports (12). Meanwhile, it was 60% in the RFA group that was in the agreement with other study (12). On the other hand, it was 90% in the combined therapy group, and this goes with data of other authors (13–15). Local recurrence (RD) and new focal lesion were observed in 2 patients of the TACE group and 3 patients of the RFA group, while neither recurrence nor new focal lesions was detected in the combined therapy group.

It was noticed that recurrence developed in patients who needed 2nd session either of the TACE or RFA group.

Regarding patients who demonstrated poor response in the three therapeutic modalities, 5 patients developed progression of the disease (PD) and 1 patient showed stable disease (SD) in the TACE group. Meanwhile, 6 patients developed PD and 2 patients showed SD in the RFA group. In the combined

therapy group, one of the two patients who demonstrated poor response showed stable disease, while the other died.

In the TACE group the overall survival was 75%, while the recurrence free survival was 60% and this goes with other published data (16). On the other hand, the overall survival in RFA group was 90%, while the free recurrence survival was 45% and this goes with the data of other reports (17–19). Alternatively, in the combined therapy group the overall survival was 95%, while the free recurrence survival was 90%, and this is in accordance with the data of other authors (14,20). The results in other reports show decrease in the percentage of overall and free recurrence survivals (21,22).

From the previous data we can conclude that combined therapy is superior regarding the good response, overall survival, and the free recurrence survival to either TACE or RFA alone. This has been explained by Peng et al. (15) that occlusion of hepatic arterial flow by means of TACE before RF ablation reduces the cooling effect of hepatic blood flow on thermal coagulation. Furthermore, lipidol and gelatin sponge particles used in TACE reduce the portal flow around the tumor by filling the peripheral portal veins around the tumor with lipidol via multiple arterio portal communications, thus the necrotic area induced by RFA may be increased, in addition to, the positive thermal impact on the anticancer effect of the retained chemotherapeutic agent. While TACE therapy is relatively superior to RFA, one considering the percentage of good response and the recurrence free survival that is in accordance with other studies (23–26) which reported that RFA is 100% effective in lesions not more than 3 cm, while TACE is more suitable for larger lesions.

Regarding the alpha-fetoprotein, it was decreased gradually near to the normal levels in all patients who developed good response in the three groups, and this goes with data reported by other authors (11,23).

In fact, the current study has three limitations. The first is small sample size relative to other studies. The second is short period of follow up, which is one year only, and of course we cannot predict the result data of each group on a longer follow up. Thirdly the study was not blindly randomized to avoid selection bias during evaluation of patients.

Conflict of interest

There is no conflict of interest in this study.

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