Combined versus single interventional therapies in treatment of hepatic malignant tumors

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Abstract  Aim of work: To evaluate the effectiveness of transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) in treatment of malignant hepatic focal lesions versus use of either TACE or RFA alone.

Material and methods: The study included 57 patients; 53 with hepatocellular carcinoma (HCC), 3 with hepatic metastases, and one case with cholangiocarcinoma.

They were divided into three groups according to the technique of treatment: the first group (25 patients) was treated by RF alone, the second group (17 patients) was treated by TACE alone and the third group (15 patients) was treated by combined RFA and TACE.

Results: In cases treated with RF only there was good response in 20% of hypervascular tumors and 28% of hypovascular tumors. In cases treated with TACE there was 47.06% good response in hypervascular tumors and 11.76% in hypovascular tumors. While in combined use of TACE and RF there was 60% good response in hypervascular tumors, and 26.66% in hypovascular tumors.

Conclusion: Combined interventional therapies are superior to any single therapy in treatment of either hypervascular or hypovascular hepatic malignant tumors.

1. Introduction

Primary and metastatic hepatic malignancies are leading causes of cancer death. Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, responsible for an estimated one million deaths annually. Liver resection or transplantation is considered as potentially curative treatments. However, the majority of cases are not candidates for these lines of therapy due to many factors such as multicentric tumors, extra hepatic metastases, early vascular invasion and poor hepatocellular reserve due to associated cirrhosis. Recently, over the last two
decades the ability of abdomen imaging to detect HCC has improved dramatically by using cross sectional imaging that can detect even small lesions and replaced more invasive procedures as angiography, exploratory laparotomy and percutaneous biopsy. New hardware and software technology was introduced to improve CT and MRI sensitivity of both modalities (1).

Regional interventional therapies have led to a major breakthrough in the management of HCC, which include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RAF), and laser-induced thermotherapy (LITT). As a result of the technical development of loco-regional approaches for HCC during the recent decades, the range of combined interventional therapies has been continuously extended. Combined RFA and TACE can theoretically overcome the limitations of each when used alone. As the size of the tumor increased, particularly if it exceeds 3.5 cm, the efficacy of RFA is generally reduced, this is likely due to the incomplete ablation and increased blood flow in larger lesions resulting in heat loss (2).

Combined therapies for HCC, radiofrequency ablation (RFA) and hepatic transartery chemoembolization (TACE) prove to have clinical application for local tumor destruction or to control tumor progress and recurrence rate, however different criteria have been put forward for the different techniques such as the type of enhancement of the tumor as depicted by arterial phase of spiral CT which was considered as an important factor in identifying the proper line of therapy, whether one procedure would probably be more successful than the other or if a combined line of therapy should be used (3).

1.1. Aim of the work

The aim of the present study is to evaluate the effectiveness of combined therapy of radiofrequency ablation and transarterial chemoembolization in treatment of hepatic malignancy lesions versus use of either TACE or RFA alone.

2. Patients and methods

This study was carried out in a cancer institute hospital over a period of three years in accordance with the guidelines of the local ethics committee. Written informed consent was obtained from all patients. 57 patients were included in this study; 53 with HCC, 3 with hepatic metastases, and one case with cholangiocarcinoma. 39 cases were males and 18 were females, their ages ranged from 38 to 73 years. Most of the patients were cirrhotic.

The patients were divided into 3 groups:

- The first group: included 25 patients with multiple tumors not more than 3 in numbers, size of the lesions not more than 3 cm and impaired liver functions, to whom only RAF was done (one to two sessions).
- The second group: included 17 patients with large sized tumors, hypervascular tumors, multifocal hepatocellular carcinomas and no portal vein thrombosis is present, to whom only TACE was done (one to two sessions).
- The third group: included 15 patients with small to intermediate sized tumors, multiple foci and tumors with indistinct boundary, to whom transarterial chemo-embolization was done followed by radiofrequency ablation (RF) within 3 days.

All the patients were subjected to:

Laboratory studies: complete blood count, platelet count, prothrombin time and liver tumor marker mainly alpha-fetoprotein (AFP).

(1) Abdominal ultrasound and Doppler study for the liver, to detect the size, echo pattern and number of focal lesions, and to assess the portal vein and its branches to exclude thrombosis.
(2) Multiphasic computed tomography, to examine the liver on arterial phase 22–25 s, portal phase 70–90 s and delayed phase 5–10 min after the start of bolus injection of 100 ml of Ultravist using power injector (rate 3 ml/s). Slice thickness: 7 mm.
(3) Radiofrequency ablation was done under CT guidance for localization of the tumor and accurate insertion of the electrode. We use the cool tips RF systems.

2.1. RF procedure

Number of RF sessions was 1–3 sessions.

- At the site of needle puncture, local anesthesia was injected to all patients and small skin incision was made.
- Each application of RF energy lasted for 14 min; the entire treatment session was about one hour.
- Grounding was achieved by attaching 2 dispersive pads to patient’s thighs.
- A peristaltic pump was used to infuse normal saline (0 °C) into lumen of the electrodes to maintain a tip temperature to 20–25 °C.

(1) Hepatic arterial embolization:
- Selective hepatic angiography through Transfemoral Seldinger Technique was conducted with a digital angiographic unit.

Patients were injected by a mixture of lipidol and cytotoxic drugs, through the catheter into the tumor vascular bed under screen, until the lipidol was densely accumulated into the tumor, this is followed by occlusion of the tumor vascular bed by gel foam particles before RF ablation.

(1) Most of the patients (53 patients) were referred to subject biopsy to confirm the diagnosis.

2.2. Data analysis

The patients were classified according to the arterial phase of spiral CT which was reviewed before treatment into: type I pattern = predominantly hypervascular lesions (>90% of the lesion enhances more than the adjacent liver parenchyma) and type II pattern = predominantly hypovascular lesions (less than 50% of the lesion enhances more than the adjacent liver parenchyma).

The response was evaluated by multiphasic CT and alpha fetoprotein. Multiphasic CT: the response was considered complete when CT scan showed the total disappearance of enhancement within the neoplastic tissue (the lesion showed
marked hypodense area). This means complete necrosis of the lesion.

3. Results

AFP level in all patients was above 100 ng/ml before treatment, which showed marked decrease in level after treatment.

- In cases treated with RF only, there was significant difference regarding response after RFA treatment in type II patients as compared with response in type I. There was 16 patients of type I enhancement, 5 (20%) of them showed good response and 11 (44%) showed poor response. The other 9 patients were of type II enhancement, 7 (28%) of them showed good response and 2 (8%) showed poor response (Table 1).
- There was significant difference regarding response after RFA treatment in type II patients as compared with response in type I. As regards the level of AFP, there were much decreased levels of AFP in type II compared with type I (pre 300–450 ng/ml and post-treatment 20–30 ng/ml in type II).
- In 17 cases treated with TACE only, there was significant difference regarding response after TACE treatment in type I enhancement as compared with in type II. Hypervascular enhancement type I was in 10 cases; 8 (47%) patients showed good response and 2 (11.8%) patients showed poor response. Hypovascular pattern, type II was in 7 cases; 2 (11.7%) showed good response and 5 (29%) showed poor response (Table 2).
- There were much decreased levels of AFP in type I compared with type II (pre 320–900 ng/ml and post-treatment 20–30 ng/ml in type I).

While in the remaining 15 cases treated with combined therapy TACE + RFA there was hypervascular enhancement (type I) in 10 patients, 9 (60%) cases showed good response and 1 (6.7%) case showed poor response while in the 5 cases with hypovascular pattern there was good response in 4 (26.7%) of them and poor response in 1 (6.7%) case (Table 3).

Combined interventional therapy was superior to any single therapy in treatment of hepatic malignancies of both type I and type II enhancement.

Regarding comparison between levels of AFP pre and post-treatment, there was highly significant difference in AFP level in patients treated by the combined therapy. AFP levels pre and post treatment were 949.26 and 306.72, respectively.

Regarding CT findings, there was a significant tumor necrosis and disappearance of enhancement within the neoplastic tissue in combined therapy.

### Table 1  Response after RF only (group I).

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<th>Type 1</th>
<th>Type 2</th>
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<td>2</td>
<td>13</td>
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<tr>
<td>Total</td>
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<td>9</td>
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### Table 2  Response after TACE only (group II).

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<td>2</td>
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<tr>
<td>Poor response</td>
<td>47.06%</td>
<td>11.76%</td>
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<tr>
<td>Total</td>
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<td>7</td>
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### Table 3  Response after combined therapy TACE + RFA.

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<tbody>
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<td>Total</td>
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<td>5</td>
<td>15</td>
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4. Discussion

There are several interventional techniques aiming to provide local destruction of tumors have been developed and clinically tested over the past few years. Among these procedures are RFA, TACE or combination between each (4).

In our study we categorized the patients into three groups according to the technique done for each group of patients. Group I (25 patients) underwent RFA alone, group II (17 patients) underwent TACE alone and group III (15 patients) underwent combined TACE + RFA therapy. The vascularity of the tumor as depicted by the arterial phase of multiphasic CT was analyzed as an important factor to identify the pattern of tumor enhancement to plane the proper line of therapy.

HCC has a variety of appearances on CT, the typical appearance is lesion that is less dense than the adjacent liver on unenhanced CT and that shows hypervascular enhancement during the hepatic arterial phase, in other, the lesions appeared as hypovascular lesion on contrast CT images (5).

Radiofrequency ablation is a widely accepted minimally invasive treatment option for selective patients because of its efficacy, safety, easiness and can be performed in an outpatient basis (6).

The postablation imaging is a critical component of the procedure not only for the interventionalist who perform the procedure but also for the diagnostician who interprets the postablation imaging to differentate normal from abnormal post-ablation imaging findings to prevent overcalling benign changes as abnormal and can thus avoid needless treatment (7).

In our study, group I included (25 patients) to whom only radiofrequency ablation was done. These patients are sub grouped according to arterial phase multiphasic CT images before the procedure into, patients with type I enhancement ‘‘hypervascular lesions’’ and patients with type II enhancement ‘‘hypovascular lesions.’’ It was noted that hypovascular tumors (type II) showed a significantly success rate with RFA than hypervascular tumors (type I), denoting that increased vascularity is an important factor in hindering the process of ablation. Our results showed 28% good response in type II and 20% in type I, and 2% poor response in type II in comparison to 44% poor response in type I (Fig. 1).
Alternatively to surgical resection of liver tumor, radiofrequency ablation induces in situ thermal coagulation necrosis through the delivery of high frequency alternating current to the tissue. Multiphasic CT is used to determine whether the ablation has been completed and to screen for early recurrences that may benefit from reablation. Complete ablation creates an area of necrosis that, at CT, is of low attenuation compared with the surrounding liver tissue (8).

In a contrast enhancement CT, when the ablation zone is well demarcated with no enhancement seen this suggests a lack of viable tumor and so indicates that the treatment was adequate (9).

In our study we use multiphasic CT to discriminate ablated from residual viable tumor in the hepatic arterial phase imaging, which showed a region of hypoattenuation devoid of characteristic tumor or tissues enhancement where enhanced tissue within the hypoattenuated ablated area indicates residual tumor. It was also noted that images during arterial phase may also show a thin rim of contrast material corresponding to an early inflammatory reaction to the thermal damage. These inflammatory changes can be seen immediately after ablation and often regress during the first month after treatment and should not be misinterpreted as residual tumor.

Treatment by RF of low vascular tumors as shown by the low contrast enhancement in CT scans, shows a higher success rate whereas highly vascular lesions are difficult to treat with rapid progression and post treatment regrowth (10).

In our study, tumor of pattern II enhancement showed a significantly higher success rate to RFA than those of type I enhancement, denoting that increased vascularity is an important factor in hindering the process of ablation.

Indication of RFA should be candidates based on impaired liver function or can be used as bridge therapy for patients awaiting transplantation or with multiple tumors (not more than three in number and <3 cm in size). He also stated that, potential candidates for RFA include patients with inoperable tumors that cannot be chemoembolized due to severe liver dysfunction or hypovascularity and patients with tumors that failed chemoembolization. The main advantage of RFA is the ability to create coagulation necrosis by heat regardless of the presence of fibrous tissue or septa (11).

Many complications for RFA include recurrent or residual tumors, tumor seedling along tracks of ablation electrodes. Biliary or vascular complications although rare could occur. Mild to moderate pain during the procedure and for one to two days after the procedure, hyperpyrexia for several days following treatment as a result of necrotic phenomena, skin burn at the site of needle introduction and rarely abscess formation could occur (10).

In our study, no major complications were recorded. But the majority of patients had mild to moderate pain which needed only sedation.

4.1. Group II

Included (17 patients) to whom transarterial chemoembolization was done, and these patients were sub grouped according to multiphasic CT results before the procedure into, patients with type I enhancement “hypervascular lesions” and patients with type II enhancement “hypovascular lesions” (Fig. 2).

Transarterial chemoembolization is an effective treatment not only for multifocal HCCs, but also for large monofocal and infiltrative HCCs, where the liver is a particularly favorable organ for arterial supply of portal vein alone, where portal vein supplies 70% of the blood reaching the liver (12).

TACE takes the advantages of the fact that most HCC is very vascular tumor, gets its blood supply exclusively from branches of the hepatic artery, in contrast to systemic chemotherapy, this procedure has additional steps of blocking (embolizing) the small vessels by gel foam, causing exposure of the tumor to high concentration of chemotherapy and confining the agents locally since they are not carried away by blood stream. In addition, this technique deprives the tumor from its needed blood vessels and so tumor shrinks up to 70%, the new trend in TACE is blockage of blood vessels by microscopic drug-eluting beads which is more effective (13).

TACE is the combination of TAE and regional chemotherapy, this combination has synergistic anti-tumor effect with high objective response rate and with a lower systemic drug level, therefore has less toxicity. There are different embolic agents, and it is important to choose the most appropriate agent according to tumor size and tumor vascularity. The potential therapeutic effects are considered to be a function of micro infarction and prolonged drug release. The desirable feature of such a modality is the lessened systemic toxicity of the chemotherapy and simultaneous necrotic effect on the
tumor, the technique will increase the local drug concentration and increase the contact time of the chemotherapeutic agent with the neoplasm and increase the tissue permeability because of the anoxia (14).

TACE technique is rarely a cure for malignant liver cancer, their studies had shown that 20–70% cancer shrinks in size compared with untreated cases, it may relieve pain and other signs and symptoms, make patients more comfortable, but it has some limitations: it cannot be done to all patients as it necessitates good general condition, reasonable liver condition, absence of portal vein thrombosis, albumin > 3.5 gm/dl, and has its own complications which are: liver abscess, septicemia, deteriorated liver function and Gall bladder or splenic infarction. 60–70% patients treated by TACE die due to tumor progression during follow up or due to eventual regrowth of the residual tumor cells after regaining a vascular supply or due to disease complications (15).

No major complications occurred in our work except post embolization syndrome: fever, nausea, vomiting and abdominal pain, which resolved spontaneously.

The response of our study was evaluated by multiphasic CT, significant response to TACE was more in type I enhancement tumors, 47% showed good response in type I with only 11% with type II this, finding was also confirmed by (10).

4.2. Group III

Included (15 patients) to whom combined transcatheter hepatic arterial chemoembolization was done followed by radio frequency ablation. RFA combined with chemoembolization has a therapeutic effect on small and intermediate size HCCs regardless of tumor morphology and is a promising treatment option for large nodular lesions (16). CT criterion is disappearance of enhancement within the neoplastic tissue due to tumor necrosis.

The combination of radiofrequency ablation and transcatheter arterial chemoembolization markedly increased the extent of induced coagulation compared with radiofrequency alone. He found that local response of RFA alone and in combination with TACE was 17.3% and 70%, respectively, recurrence rate in RFA alone and in combination with TACE was 20% and 6.7%, respectively (17).

In our study combination therapy was done for (15 patients) and the therapeutic response was evaluated by multiphasic CT (arterial phase) and alpha-feto-protein level, patients showed good response in hypervascular type 1 enhancement (60%) and 26% in the hypovascular type 11 enhancement and patients who were treated with combined therapy showed a significantly higher success rate as compared

Fig. 2 59-year-old male patient with a large well defined hepatic focal lesion in the posterior segment of right lobe (proved by biopsy to be HCC), with type 1 enhancement at multiphasic CT (a). The patient was treated by TACE. Follow up after five weeks, revealed good response with dense lipidol concentration in the lesion (b).

Fig. 3 66-year-old patient had liver cirrhosis with focal of HCC in the right lobe of liver, in arterial phase of multiphasic CT, the lesion was of type 1 enhancement (a). Selective hepatic angiogram revealed vascularity of the mass (b). The patient was treated by combined therapy (tumor embolization followed by one RF session). Followed up after three weeks, CT revealed complete ablation with embolization of the feeding artery (c–d).
with patients who treated by RFA only or TACE only (Fig. 3). These results were completely in agreement with what was concluded by many authors (5,9).

Zhu and Salem (2), reported that for those hepatocellular carcinoma over 3 cm in size, located in the porta hepatis, or with indistinct boundary or the presence of multiple foci, TACE can be performed first and then followed by RFA in suitable time this might reduce or eliminate the heat loss that is mediated by tissue perfusion to enlarge the necrosis range and increase the rate of complete necrosis of tumors, thereby decrease the recurrence and improve the disease free survival and total survival of patients.

Gary et al. (1) stated that new hardware and software technology was introduced to improve CT and MRI sensitivity of both modalities in ability to detect HCC and can now replace more invasive procedure in diagnosis as angiography, exploratory laparotomy and percutaneous biopsy. He also added that, combined therapy of TACE and RFA has further advantages it provided a way to highlight and treat lesions not recognizable through other imaging techniques, increased the accumulation of lipid contrast in the tissue surrounding the lesion and in the vessels not occluded by thermal ablation in the lesion and enables further treatment of tumor residue possibly left untouched by thermal ablation in large tumors.

Our results showed also that there was highly significant difference in AFP level in group III than in group I or II. Upon comparison regarding survival after one year, there was a significant difference after combination treatment in group III than that of group I or II.

5. Conclusion

- Combined interventional therapies are superior to any single therapy for improving the prognosis and survival of patients with HCC.
- With the advent of new interventional techniques aiming at providing local destruction of HCC, the proper selection of appropriate therapy has become mandatory, and we found that patients who responded to RFA and TACE had correlated closely with tumor vascularity as shown on hepatic arterial phase multiphasic CT.

Conflict of interest

The authors have no conflict of interest to declare.

References

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