Common interventional techniques (single versus combined) in management of hepatocellular carcinoma

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OBJECTIVE: To evaluate the role of transarterial chemoembolization "TACE", radiofrequency ablation "RFA" and combination of both techniques in management of hepatocellular carcinoma "HCC".

PATIENTS AND METHODS: This study was carried out at Al-Azhar University Hospital (New Damietta) during the period from May 2013 to June 2015. It included forty patients were included in this study (27 males and 13 females), with age ranged from 43 to 68 year (mean age 51 year). They were divided into three groups after laboratory and radiological assessment: group 1 treated with TACE, group 2 treated with RFA and group 3 treated with combined therapy. The response was evaluated by triphasic MDCT, alpha-fetoprotein as well as clinical follow-up and classified as complete and partial response, and the overall survival was recorded.

RESULTS: There were no major complications detected. At 3 month follow-up, there was complete response “CR” in 32 patients (80%), and partial response “PR” in 8 patients (20%). At 6 months, there was complete response in 34 patients (85%), and partial response in 3 patients (7.5%). At 12 months, there was complete response in 33 patients (82.5%), and partial response in one patient (2.5%). It is proved that complete response with high percentage achieved by combined therapy than either by TACE or by RFA (100%, 88.46% and 75% respectively), with the overall survival was 85%. Conclusion: The study showed that combined therapy achieved better results regarding complete response and overall survival rate than RF or TACE alone.

1. Introduction

Hepatocellular carcinoma (HCC) constitutes the majority of primary liver tumors, which is the 6th most common tumor and the 3rd most common cause of cancer death worldwide. Considering management of HCC is a challenge, it was reported that a great number of HCC patients are suitable for curative therapy due, either to advanced stage of disease or to poor liver functions at time of the diagnosis [1]. In treatment of hepatocellular carcinoma (HCC), less than 40% of patients are candidates for surgery in early stages, and the rate of recurrence after curative surgery is high [2].

So, different strategies are available or being developed for locoregional therapy, but the largest experience is with transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). RFA is a well-studied procedure producing better local tumor control with 2 year recurrence of 2–18% and
5 year survival of 40–70% or better when the treatment groups have been selected [3]. RFA is a minimally invasive, repeatable procedure with few complications. It is performed under radiological guidance [4].

Hepatic arterial chemoembolization (TACE) is one of the most common treatments for unresectable hepatocarcinoma [5]. Each of both techniques has its constrictions and limitations depending on the tumor growth pattern, size and number of tumors, location and number of segments involved, and response to TACE [6]. It had been reported that RFA in combination with TACE is an effective treatment for inoperable hepatic tumors as it can theoretically overcome the limitations of each technique when used alone [7,8].

In this study we evaluated both techniques either separately or as combined therapy in treatment of HCC.

2. Patients and methods

This study was carried out on forty patients (27 males and 13 females), with age ranged from 43 to 68 year and the mean age 51 year. The patients were referred to Radiology Department from General Surgery and Internal Medicine Departments as well as outpatient clinics. Local Ethical Committee approval and patients' consents were obtained.

2.1. Pre-treatment assessment

All patients were subjected to the following:

2.1.1. Complete clinical assessment
2.1.1.1. Laboratory evaluation.
• Liver profile (serum bilirubin, transaminases, alkaline phosphatase and albumin).
• Coagulation profile (prothrombin time, concentration and INR).
• Complete blood picture to detect thrombocytopenia.
• Alpha feto-protein (AFP).
• Viral hepatitis seromarkers: HBV seromarkers and HCV antibodies.

2.1.2. Radiological assessment.
A. Abdominal ultrasonography for detection of HCC with assessment of hepatic echogenicity, hepatic veins, portal vein radicles and focal lesions were commented upon. As regard the focal lesions, their number, location, echogenicity and size measured in two diameters were assessed. Examination of the rest of the abdominal organs and the presence of ascites.

B. Triphasic MDCT scan pre and post procedure, while triphasic MDCT exam. Protocol included the usual triphasic liver protocol in which pre-contrast images were obtained; then, images were acquired 20 s, 55 s, and approximately 1–3 min after the start of injection of 100 mL contrast at a rate of 4–5 mL/s.

Inclusion criteria were as follows:

(a) Patent with non-thrombosed portal vein and liver functions (ALT or AST < 270 IU/L, Albumen > 2.5 g/dl, Bilirubin < 3 mg/dl). (b) No extrahepatic disease. (c) The presence of a single hepatic lesion or multiple lesions (up to 4 lesions ≤3 cm each). (d) Accessible site by US and/or CT (in patients with RF treatment). (e) Coagulation profile (prothrombin time more than 60%, and platelet count more than 70,000/mm³). (f) Patients should be Child’s A class or Child’s B class, and (g) Alpha feto-protein “AFP” ranging less than 20 to more than 500 ng/mL.

Exclusion criteria were as follows:

(a) Distant metastatic. (b) Thrombosed portal vein. (c) Poor liver functions (Bilirubin > 3 mg/dL, ALT or AST > 250 IU/L). (d) Severe debilitation. (e) Active infection, and (f) Poor coagulation profile (prothrombin time less than 60% and platelet count less than 70,000/mm³).

The patients were divided into three groups based on clinical, laboratory “liver functions” and abdominal US as well as triphasic MDCT.

* Group one, included 26 patients treated by transarterial chemoembolization (TACE) using mixture of Doxorubicin 50 mg dissolved in 10 cc saline and mixed with 8 cc lipiodol and 5 cc contrast medium (ultravist 300 mL/cc) for all of them with the same concentration.

* Group two, included 12 patients treated by thermal ablation (RFA) using RITA RF 1500X system USA and star burst Xli enhanced with tubing set (electrosurgical device).

* Group three, included two patients treated by combined therapy of TACE followed by RFA one week later.

2.1.3. Post procedure care. All patients underwent interventional procedures were hospitalized overnight for observation of side effects and administration of medications as needed. The patients were discharged within 24 h if no side effects were noted.

2.1.4. Follow up. Three, Six and 12 months after the procedure, the follow-up included the following:

(A) Clinical: to assess improvement of symptoms such as fever, abdominal pain, anemia, dyspepsia and abdominal distension.

(B) Laboratory: for monitoring of AFP and liver function tests.

(C) Imaging: radiological assessment including US and triphasic CT scan.

Tumor response to treatment was classified into complete and partial response, assessed by imaging and AFP values. At imaging tumor response was measured according to the criteria adopted by the European
Association for the Study of the Liver Disease (EASL) measuring the longest diameter of the viable tumor against the longest total tumor diameter. The percentage of tumor necrosis was also recorded. The necrotic area was identified when a low density/low-echogenicity/fluid signal area that was non-enhancing in any of the time phases was seen. The EASL has officially recommended the use of contrast enhanced CT in the evaluation of response to treatment, and acknowledged as “viable areas” those that “present enhancement” and “necrotic areas” those that “do not present enhancement”. The EASL response criteria were preferred since they take into account the development of necrosis and not only the size of the treated lesion as in Response Evaluation Criteria in Solid Tumor (RECIST) criteria (which depends only on shrinkage in size) since it acknowledged that it is common for liver tumors to liquefy without a significant change in total lesion diameter within short follow-up periods. In EASL criteria, complete response (CR) is recorded when complete disappearance of all known disease and no new lesions are seen; partial response (PR) when a 50% reduction in viable tumoral area of all measurable lesions is present; stable disease (SD) in all other cases and progressive disease (PD) when there is a 25% increase in size of one or more measurable lesions or if new lesions appear [9].

MDCT images were reviewed by two radiologists. In cases the residual viable tumor was at least 1 cm in maximum axial diameter, and further treatment was scheduled.

3. Results

Frequency and percentages of liver cirrhosis and Child–Pugh classification in the whole sample (Table 1).

These AFP levels had been decreased in most patients to be less than 20 ng/mL after interventional procedures except in 5 patients ranging from 50 to 100 ng/mL (see Table 2).

3.1. Group one, included 26 patients treated by TACE

This group showed 24 patients Child’s A class and two patients Child’s B class. 20 patients of them had solitary tumor and 6 patients had multiple tumors. TACE sessions ranged from 1 to 3 sessions. There was complete response in 20 patients after 3 months (76.92%), while partial response was seen in 6 patients (23.07%). Two out of the 6 patients died after 3 months, and two out of the 4 patients showed complete response (CR). So the sum 22 at 6 months and one patient showed partial response (PR) by the end of the year, hence the sum 23 (22 showed CR and one showed PR). Consider addition of the 2 patients treated by combined therapy, so the sum is 25 patients (24 showed complete response “CR” and one showed partial response “PR”).

3.2. Group two, included 12 patients treated by thermal ablation (RFA)

This group showed 11 patients Child’s A class and one patient Child’s B class. Eleven patients had solitary tumor and one patient had multiple tumors. RFA sessions were repeated on demand 1–3 sessions. After 3 months, there was complete response in 10 patients (83.33%), and partial response was seen in 2 patients (16.66%), 1/10 patients died after 5 months and further 2/2 patients died after 10 months. Hence the sum is 9 survive patients (75%) at the end of one year (all of them showed complete response “CR”).

3.3. Group three, included two patients treated by combined RFA after TACE

– All patients were Child’s A class with solitary tumor. Complete necrosis was achieved following the first session in the two patients without further sessions (100%) (see Table 3).

3.4. Complications of TACE

A. Immediate post-treatment side effects (PTS): PTS (fever <38 °C, pain, anorexia, nausea and vomiting) occurred in 21 patients (80.7%), all of them recovered

<table>
<thead>
<tr>
<th>Response TACE (n = 26)</th>
<th>RFA (n = 12)</th>
<th>Combined Th. (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>20 (76.92%)</td>
<td>10 (83.33%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (23.07%)</td>
<td>2 (16.66%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>22 (84.6%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (7.7%)</td>
<td>2 (16.66%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (7.7%)</td>
<td>1 (8.33%)</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>22 (84.61%)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (3.84%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (11.53%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

Table 1

<table>
<thead>
<tr>
<th>Etiology of cirrhosis</th>
<th>Frequency</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>HBV</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>HCV</td>
<td>37</td>
<td>92.5</td>
</tr>
<tr>
<td>HCV + HBV</td>
<td>1</td>
<td>2.5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Child – Pugh Classification</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s A</td>
<td>37</td>
<td>92.5</td>
</tr>
<tr>
<td>Child’s B</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>Child’s C</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2

Distribution of the studied cases regarding Alpha Feto-protein level (AFP).

<table>
<thead>
<tr>
<th>Alpha Feto-protein level</th>
<th>No</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 ng/mL</td>
<td>4</td>
<td>cases</td>
</tr>
<tr>
<td>21–500 ng/mL</td>
<td>29</td>
<td>cases</td>
</tr>
<tr>
<td>&gt;500 ng/mL</td>
<td>7</td>
<td>cases</td>
</tr>
</tbody>
</table>

Table 3

 Patients’ response according to EASL criteria at 3, 6, and 12 months.
within 3 days after the procedure with administration of antipyretic and antiemetic.

B. Late post-treatment side effects:

Decompensation occurred in 2 patients in the form of ascites and mild increase in the liver enzymes (treated medically). Liver abscess, cholecystitis, pleural effusion and CNS problems were not recorded in any patient till the end of the study.

3.4.1. Complications of thermal ablation (RFA)

Nearly all the patients experienced post-ablation right hypochondrial pain that was controlled by analgesics, and nausea, which was controlled by anti-emetics. Also all patients experienced post-ablation pyrexia for 2 days, which was controlled by antipyretics. Major post procedural complications were one patient with reactionary effusion, two patients had ascites and liver decompensation and five patients with subcapsular hematoma (see Table 4).

The survival status of all 40 patients was evaluated and reported at 3, 6 and 12 months after treatment. Four patients died from advanced decompensated liver disease, and two patients died from coexisting concomitant illness (chest and cardiac diseases). The overall survival after treatment with combined therapy, TACE and RFA was 100%, 88.46%, and 75% respectively (see Figs. 1–3).

Table 4
Survival percentages of all 40 patients at 3, 6 and 12 months.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group I treated by TACE (26 cases)</th>
<th>Group II treated by thermal ablation (12 cases)</th>
<th>Group III treated by RF after TACE (2 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival Months</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Number of cases</td>
<td>26</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Frequency</td>
<td>100%</td>
<td>92.3%</td>
<td>88.46%</td>
</tr>
</tbody>
</table>

Fig. 1. 58 years-old male with hepatic focal lesion diagnosed HCC “treated by TACE”. (A) Contrast enhanced CT shows an enhanced lesion at segment IV. (B) TACE showed adequate lipiodol concentration within the lesion. (C) Three months post TACE non-contrast CT study revealed inadequate accumulation of lipiodol within the tumor. Triphasic CT showed small foci of lipiodol with arterial enhancement of the lesion in arterial phase (D) and washout in portal phase (E) and delayed phase (F) denotes inadequate ablation (partial response). AFP = 258 ng/ml before TACE and 200 ng/ml three months after. The patient referred to surgery for tumor resection.
4. Discussion

High incidence rate of HCC has been reported in Egypt. Several studies were done on the association between HCV and HCC [10,11]. Yates et al. [12] found that among Egyptian patients with HCC more than 75% were positive for HCV-Ab. Nearby results (70%) were reported by Darwish et al. [13]. Patients with liver cirrhosis are at greatest risk for developing HCC and should be monitored every 6 months to detect the tumor at an asymptomatic stage [14]. Locoregional therapeutic modalities have been developed and tested clinically over the recent years for treatment of HCC [15]. Several studies have shown that RF ablation (RFA) is a simple, effective, and less expensive technique with a low morbidity compared with surgical treatment [16].

In this study, follow-up of the patients over one-year duration, included reporting the response either complete or partial (CR, PR), recurrent diseases “RD” and progression diseases “PD”.

High percentage of complete response (83.33%) in patients underwent RF ablation “10/12” after one session. One of the two patients showed complete necrosis after a second session and the other one died; this agreed with report by Raut et al. [17].

Teratani et al. [18] reported that RFA for patients with small HCC nodules (less than 5 cm) provides favorable survival with excellent local control. Good response with those underwent RF alone at 3, 6, and 12 months was 100%, 91.66% and 75% respectively. This was in accordance with Chen et al. [19] who reported RFA success rate 93.3%, 84.6% and 66.6% respectively.

All patients exposed to RFA experienced post-ablation right hypochondrial pain and nausea that was controlled by analgesics and anti-emetics. Major post procedural complications were one patient with reactionary effusion,
two patients had ascites and liver decompensation, and this was in accordance with other reports [20,21].

Use of TACE showed complete response in 20/26 (76.92%) after one session, while partial response in 6 patients (23.07%) after second session. Three out of the 6 patients died (11.53%), 2 showed complete response (7.7%) and one (3.8%) showed partial response. This agreed with reports used TACE as an effective palliative treatment for unresectable tumors [22,23].

Regarding post TACE complications in this study, PES (fever <38°C, pain, anorexia, nausea and vomiting) occurred in 21/26 (80.7%) and recovered within 3 days after treatment.
with administration of antipyretic and antiemetic. Yet, the etiology of PES is not fully understood but it is thought to be caused by combination of tissue ischemia and an inflammatory response to chemoembolization [24]. Late post-treatment side effects appear in the form of liver decompensation with ascites and increased liver enzymes. All of them received one session of TACE and treated medically [25]. Patients needed a second sessions of TACE or RFA are those who showed partial response after first session.

Combined therapy showed complete necrosis after one session with no need for further sessions and overall survival rate 100%. However, there were no recurrent lesions detected in combined therapy group.

The overall survival rate was 88.46% in TACE group, 75% in RFA group and 100% in combined therapy group; this agreed with Lo et al. [26] who reported a study of 40 patients assigned to chemoembolization with near survival probability of 82%, and higher than study by Othman et al. [27] who reported survival rates 75% with TACE, 90% with RFA and 95% with combined therapy.

Post therapy follow-up of Alpha feto-protein showed that it was decreased gradually to near normal levels in those patients showed complete response, that agreed with reports stated by Hu et al. [28].

From this study it was noted that combined therapy is superior to either TACE or RFA regarding complete response and survival. TACE has been used to minimize heat loss due to perfusion mediated tissue cooling and to increase the therapeutic effect of RF ablation, thus increasing the range of therapeutic isotherms because of a greater sensitivity of neoplastic cells to hyperthermia [29]. HCC therapy can be divided according to the stage of the disease and degree of liver impairment into curative versus palliative approaches. Curative treatments are reserved for patients without portal vein invasion or distant metastases. Palliative therapy via transarterial chemoembolization (TACE) may be offered for unresectable HCC [30]. The patients should be monitored regularly for exclusion of intrahepatic newly developed/recurrent lesions by follow-up protocol including enhanced MDCT examinations and tumor markers.

Conflicts of Interest

No conflicts of interests.

References