Radiofrequency ablation plus drug-eluting beads transcatheter arterial chemoembolization (DEB-TACE) for the treatment of single large hepatocellular carcinoma

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Aims and objectives

The main purpose of research in HCC disease should be to increase the number of patients with single HCC larger than 3 cm suitable for non surgical curative treatment and a reasonable approach could be to combine therapies with possible synergistic effects. Recent studies show that combined therapy with RFA and TACE could be more effective than TACE or RFA alone in local disease control and survival improvement, but it is not clear how the lesion size affects the follow-up response. The primary aim of this study was to evaluate the effectiveness of the single step combined therapy with RFA and DEB-TACE in single HCC # 3 cm. The secondary aim was to compare the results with those obtained in a matched population treated with DEB-TACE alone.
Methods and materials

Study design/Study population

A prospective single-center pilot study was carried out to test a new single-step combined therapy of HCC with RFA of the lesion followed by selective DEB-TACE. Requirements for inclusion were: (a) single HCC larger than 3 cm (b) liver cirrhosis classified as Child-Pugh score A5-6 or B7, (c) no vascular invasion or extrahepatic metastases, (d) no previous treatment of HCC. The exclusion criteria were: (a) Child-Pugh score B #8 or class C, (b) platelet count < 40,000/µL and/or international normalized ratio >1.5, (c) serum creatinine levels > 2.0 mg/dL, d) diuretic resistant ascites. All patients had been excluded from surgical resection due to one or more of the following reasons: severe portal hypertension (defined as presence of esophageal varices # F2 or gastric varices, and/or splenomegaly with platelet count < 100,000/mL, and/or previous ascites successfully treated with diuretics), surgery unfeasible or hazardous due to lesion location or concurrent severe comorbidities, and refusal of surgery. The diagnosis of cirrhosis was established by means of histological and/or clinical findings (laboratory parameters, ultrasound [US] and/or computed tomography [CT] signs).

The ethical conduct of the study was approved by our Institutional Review Board and was performed in agreement with the 1990 Declaration of Helsinki and subsequent amendments. Written informed consent was obtained from all patients.

Pre-treatment Work-up

All patients underwent within 2 weeks before treatment physical examination, laboratory tests, and imaging studies with diagnostic and staging purposes including liver US, bone scintigraphy, contrast-enhanced thorax and abdomen CT performed with a multiphasic protocol (flow-rate: 4 mL/s; unenhanced, arterial, portal and late phases; slice thickness: 0.625-mm) using a 64-multidetector-row CT scanner (Lightspeed VCT, GE Medical Systems). According to the guidelines in force at the time of enrollment, the diagnosis of HCC was made in the presence of a nodule detectable on ultrasound showing the typical features of HCC on contrast-enhanced CT (hypervascular in arterial phase with washout in portal-venous phase) (16). Eventual parasitic vascular supplies of the lesion were evaluated on pre-treatment contrast enhanced CT.

Treatment

All combined treatments were performed in a single-step approach by the same interventional radiologist, using antibiotic prophylaxis, patient monitoring and anesthesiologic assistance. An hepatic artery angiography was performed through a right common femoral approach to map liver vascular anatomy, check for arteriovenous shunts
and identify the arterial tumor supply. A 0.014-inch guide wire (Choice, Boston Scientific, USA) was advanced into the segmental hepatic artery feeding the lesion, enabling an optimal guidance of the low-profile monorail PTA-balloon (4-5x20mm, Muso, Terumo, Tokyo, Japan).

RFA was then performed using US-guidance with the patient under sedation with Fentanyl citrate (0.1-0.2 mg, Phentanest; Daiichi Sankyo, Tokyo, Japan) and local anesthesia. An internally cooled electrode with 3-cm exposed tip (Cool-Tip RF Ablation System, Covidien, Valleylab, USA) was introduced into the nodule and the occlusion balloon in the hepatic artery was filled with a mixture of saline solution and contrast material. The RF generator was activated, and the power needed to maintain a temperature of 90°C-115°C at the exposed tip was delivered for 12 minutes. At the end of the procedure, the electrode was withdrawn, the occlusion balloon was deflated, and the immediate results were evaluated with angiography.

After RFA, DEB-TACE was performed. The time elapsed between RFA completion and DEB-TACE performance was less than 5 minutes. A superselective chemoembolization of the lesion was performed using a coaxial technique and placing a 2.7-Fr microcatheter (Progreat; Terumo, Tokyo, Japan) in the distal segmental hepatic artery feeding the HCC. Slow injection of the 100-300µm DC-Bead (Terumo, Tokyo, Japan) loaded with Epirubicin (Farmorubicin® 50mg Powder) followed until the complete intended dose was administered and slow flow was observed.

**Post-treatment and Follow-up Studies**

Perioperative morbidity and mortality included major/minor complications and death occurring within 7 days from treatment. Major complication was defined as an event that engenders substantial morbidity and disability, an increased level of care, or substantially lengthens hospital stay. All other complications were considered minor (17). The endpoint of combined treatment was the disappearance of tumor enhancement at hepatic arteriography performed immediately after chemoembolization.

Multiphasic CT study was performed one month after the procedure and every 3 months to evaluate the treatment result at the level of the target lesion using m-RECIST criteria (18) and to detect occurrence of new lesions.

**Control Group**

Patients submitted to combined treatment were compared to a control group of cirrhotic patients with unifocal HCC and without ascites treated with DEB-TACE alone during the period 2008-2012 (DEB-TACE group). These patients did not undergo DEB-TACE + RFA because they were treated before the beginning of the present study or because RFA was judged unfeasible due to tumor location or inadequate clotting parameters (platelet count < 40,000/µL and/or international normalized ratio >1.5).
Fig. 1: A single large HCC nodule in VIII hepatic segment (4.5 cm in diameter) was confirmed on selective digital subtraction angiography (DSA) (a). RFA electrode is placed into the lesion under US-guidance (b) and the RF generator was activated during balloon-occlusion (circle in b) of the tumor arterial supply. DSA image performed after RFA showed the immediate result with a complete central devascularized area and peripheral reactive hyperemia (c). After RFA, a superselective chemoembolization of the lesion demonstrated a complete devascularization of the lesion (d).

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**Fig. 2:** Axial contrast-enhanced CT images before combined treatment showed a right lobe HCC lesion of 4.5 cm in size (a: arterial phase; b: late-phase).

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**Fig. 3:** At 1-year follow-up axial contrast-enhanced CT images after combined treatment displayed a complete necrosis of the lesion without local tumor progression (c: arterial phase; d: late-phase).

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Table 1: Tab. 1 - Study Population * RFA+DEB-TACE (Total population) vs DEB-TACE **RFA+DEB-TACE: Group A vs Group B Abbreviations: RFA: radiofrequency ablation, DEB-TACE: drug eluting beads-transarterial chemoembolization, HCC: hepatocellular carcinoma, NA: not applicable; ALT: alanine aminotransferase; AFP: alphafetoprotein

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Results

RFA+DEB-TACE group

Study population:

Between November 2010 and June 2012, 40 consecutive cirrhotic patients with single HCC larger than 3 cm were enrolled. The main features of patients and tumors are reported in Table 1. Mean HCC diameter was 4.7±1.1 cm (range 3.2-7.5 cm), and according to the HCC size, the patients were further divided in Group A (23 patients with HCC # 5 cm, mean diameter 3.9±0.5 cm, range 3.2-5.0 cm) and Group B (17 patients with HCC > 5.0 cm, mean diameter 5.7±0.7 cm, range 5.2-7.5 cm). Apart from tumor size, no significant differences were found between these two groups (Table 1).

Intraprocedural/early post-treatment results

Technical success was achieved in all patients. A mean procedural time of 68±12 minutes was registered. No major complications were registered. On 1-month CT, based on m-RECIST criteria, a CR was achieved in 32/40 (80%) patients whereas a PR was obtained in the remaining 8 patients (residual tumor < 30%: 6 patients, 30-50%: 2 patients). In group A CR and PR were achieved in 20/23 (87%) and 3/23 (13%) tumors, respectively. In group B CR and PR were reached in 12/17 (70.6%) and 5/17 (29.4%) tumors, respectively. When comparing CR rates, the difference between Groups A and B was significant (p=0.009). According to the 1-month CT results, a repeated locoregional treatment was performed in 8 patients (3 in Group A and 5 in Group B) to achieve complete necrosis. During follow-up CR was maintained in 25 patients (25/40, 62.5%). In detail, at the time of last response assessment, in Group A (mean follow-up: 24±8 months) a CR was still present in 16/23 patients (69.6%) (Fig. 2), including two patients who underwent liver transplantation 4 and 8 months after treatment and showed complete necrosis of the tumors at explant analysis, whereas in Group B (mean follow-up: 23±7 months) long term CR was observed in 9/17 patients (53%) (p=0.008). At the time of censoring, 15 patients (37.5%) showed HCC recurrence: of them, 7 were in group A (30.4%) and 8 in group B (47%). In Group A, 3 LTP (two treated with percutaneous ethanol injection, the other with one session of DEB-TACE) and 4 IDR (two treated with RFA, and the other two with one session of DEB-TACE) were observed. In Group B, 5 LTP (two treated with percutaneous ethanol injection, the other three with one session of DEB-TACE) and 3 IDR (one treated with RFA, the other two with one session of DEB-TACE) were detected. Both 1- and 2-year LTP cumulative rates (5.6% and 22.5% vs 18.1 and 40.3%) and 1- and 2-year cumulative HCC recurrence rates (19.2% and 39.2% vs 30.7 and 59.6%) were lower in Group A than in Group B but these differences did not reach significance (p 0.214 and 0.337, respectively) (Fig 3). Three deaths (4%) occurred because of neoplastic disease progression (one in Group A and two in Group B). The cumulative 1- and 2-year overall survival rates were 94.7% - 91.1% in the whole
population, 92.5%-92.5% in Group A, and 94.1%-84.7% in Group B. The difference between Groups A and B was not significant (p 0.389).

DEB-TACE group

Short-term Results

On 1-month CT, based on m-RECIST criteria, CR and PR were achieved in 8/20 (40%) and 12/20 (60%) patients, respectively. Compared to the DEB-TACE+RFA Group, the rate of patients achieving a short term CR was significantly lower (p<0.001). In patients with PR, a repeated TACE was performed in 7 cases.

Long term Results

During follow-up (mean duration: 24±17 months), CR was maintained in 4/20 patients (20%) and this rate was significantly lower than that achieved in RFA+DEB-TACE Group (p<0.001). At the time of censoring, a total of 16 patients (76%) showed HCC recurrence: 8 showed both LTP and IDR recurrence, 6 showed just LTP recurrence, 2 showed just IDR recurrence. Seven deaths (33%) occurred because of neoplastic disease progression or liver function failure. Compared to RFA+DEB-TACE Group, DEB-TACE Group showed significantly higher 1- and 2-year HCC recurrence rates (45.5% and 78.2% vs 24.3% and 48.1%, p<0.001), and significantly lower 1- and 2-year overall survival rates (67.4% and 60.6% vs 94.7 and 91.1%, p 0.004).
Conclusion

Our study demonstrates that single-step balloon-occluded-RFA plus DEB-TACE, is a safe and effective treatment of unifocal HCC larger than 3 cm detected in compensated cirrhotic patients and not amenable to surgical treatment. Combined treatment seems to provide better results than DEB-TACE alone. Tumor size is an important factor associated with sustained HCC control as a significantly higher rate of long term CR was observed in patients with lesions smaller than 5cm.
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