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

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ABSTRACT

Background: Our aim was to evaluate the effectiveness of the single-step combined therapy with radiofrequency ablation and drug-eluting beads transarterial chemoembolization in single hepatocellular carcinoma (HCC) larger than 3 cm. Secondary aim was to compare the results with those obtained in a matched population treated with drug-eluting beads transarterial chemoembolization alone.
Methods: 40 consecutive cirrhotic patients with single HCC were prospectively enrolled and treated. Twenty-three patients had tumours between 3 and 5 cm (Group A), and 17 larger than 5 cm (Group B). Twenty cirrhotic patients with single HCC treated only with chemoembolization formed the control group.
Results: Complete response at 1 month was achieved in 32/40 tumours (80%). During follow-up, complete response was maintained in 25 patients (25/40, 62.5%), and this rate was higher in Group A (69.6% vs 53%, $p = 0.008$). The group treated with combined therapy showed a significantly lower 2-year recurrence (48.1% vs 78.2%, $p < 0.001$) and significantly higher survival (91.1% vs 60.6%, $p = 0.004$) than the group treated with chemoembolization alone.
Conclusions: Balloon-occluded-radiofrequency ablation plus drug-eluting beads transarterial chemoembolization is an effective treatment of HCC larger than 3 cm not amenable to surgical resection, providing better results than transarterial chemoembolization alone. The best results are achieved in tumours up to 5 cm.

1. Introduction

Despite the implementation of screening programmes for early diagnosis, about half of the cirrhotic patients still present with single large hepatocellular carcinomas (HCC) at diagnosis, and only 30% of them benefit from curative therapies [1–4]. Resection may provide excellent long-term results in these patients [5]. However, in patients who are not good surgical candidates, radiofrequency ablation (RFA) is not a good treatment option as the better results are achieved in tumours up to 3 cm large [6]; furthermore, studies performed on explanted livers obtained from patients treated with RFA before transplantation show that the rate of complete necrosis ranges between 13% and 43% in tumours larger than 3 cm [7]. On the other hand, despite transarterial chemoembolization

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(TACE) is the current standard of care for patients with large HCC not amenable to surgery, a sustained complete response (CR) is achieved in only 27–35% of cases [8]. An improvement in TACE technique has been attained after the introduction of drug-eluting beads (DEB-TACE): these particles are able to bind and then elute doxorubicin in a predictable manner, thus allowing a more standardized approach and less drug-related toxicity [9]. However, even though DEB-TACE induces extensive tumour necrosis in more than 70% of tumours, less than 20% of the patients achieve a CR [10–12]. The main goal of the research in this field should be to increase the number of patients with single HCC larger than 3 cm suitable for non-surgical curative treatment; for these patients, a reasonable approach is 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's size affects the follow-up response [13–15].

Therefore, 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.

2. Materials and methods

2.1. Study design/study population

A prospective single-centre 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 oesophageal 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's 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 the study was performed in agreement with the 1990 Declaration of Helsinki and subsequent amendments. Written informed consent was obtained from all patients.

2.2. Pre-treatment work-up

Within 2 weeks before treatment, all patients underwent physical examination, laboratory tests, and imaging studies with diagnostic and staging purposes, including liver US, radionuclide bone scan, contrast-enhanced chest and abdominal 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 enrolment, the diagnosis of HCC was made in the presence of a nodule detectable on US and 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.

2.3. Treatment

All combined treatments were performed in a single-step approach by the same interventional radiologist, using antibiotic prophylaxis, patient monitoring, and anaesthesiological assistance. An hepatic artery angiography was performed through a right common femoral approach to map liver vascular anatomy, as well as to check for arteriovenous shunts, and identify the arterial tumour 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 (4–5 × 20 mm, 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 anaesthesia. An internally cooled electrode with a 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 90–115 °C at the exposed tip was delivered for 12 min. 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 min. 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 100–300 μm DC-Bead (Terumo, Tokyo, Japan) loaded with Epirubicin (Farmorubicin® 50 mg powder) followed until the complete intended dose was administered and slow flow was observed.

2.4. Post-treatment and follow-up studies

Perioperative morbidity and mortality included major/minor complications and death occurring within 7 days from treatment. A major complication was defined as an event that engenders substantial morbidity and disability, requires 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 tumour enhancement at hepatic arteriography performed immediately after chemoembolization.

The multiphasic CT study was performed one month after the procedure and then every 3 months both to evaluate the treatment result at the level of the target lesion using m-RECIST criteria [18], and to detect the occurrence of new lesions. CR was defined as the absence of enhancing tissue and a non-enhancing area at the tumour site larger than that of the tumour pre-treatment. In case of partial response (PR) of the target lesion, another session of combined treatment or TACE was performed; specifically, a combined treatment was preferred in case of nodular residual tumour larger than 3 cm.

Local tumour progression (LTP) was defined as the appearance of nodular, irregular enhancement around or within the treated area in tumours previously assessed as completely necrotic. Intrahepatic distant recurrence (IDR) was defined as the appearance of new HCCs in the untreated liver or extrahepatic sites. All the patients with relapsing or progressive tumours were treated with the best possible options (combined therapy, percutaneous ethanol injection, RFA, TACE, or supportive care), depending on tumour staging, liver function assessment, and patient's clinical condition.