Balloon-occluded percutaneous radio-frequency thermal ablation (RFA) plus transcatheter arterial chemoembolization (TACE): a new combined single-step therapy for treatment of unresectable hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fourth most common cancer in the world, responsible for an estimated 1 million deaths annually and carrying a poor prognosis due to its rapid infiltrating growth and complicating liver cirrhosis (1).

Although screening programs for high-risk patients have become more popular and many HCCs are now found in the early stages, some patients still present with large HCCs. Tumor diameter is an important prognostic factor in patients with HCC: prognosis worsens markedly when the maximum diameter is greater than 5 cm (2-8).

Consensus about a common treatment strategy for patients with HCC has not been reached worldwide, even if several proposals have been published. The most recent one is the Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment schedule.

Surgical approaches including liver resection and liver transplantation are regarded as potentially curative treatments for HCC (9-10). However, only a small minority of patients are suitable for surgical therapy due to their poor hepatic reserve resulting from underlying chronic liver disease, multifocal distribution of tumor nodules, extrahepatic metastases, early vascular invasion, shortage of donor organs, high complication rates and comorbidities (11-13).

In the last years, non-surgical alternative treatments, including transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), are promising additional tumor therapies for unresectable or multifocal tumors.

_TACE_ is safe and effective but it is a palliative treatment, with a limited survival (14-16), whereas previous studies have shown that _RFA_ is a useful therapeutic option, as effective as surgery for the treatment of unresectable small HCCs (17). However, its major weakness is related to the limited size of coagulation necrosis that can be obtained; as a matter of fact, a complete short-term necrosis can be achieved in less than 50-70% of lesions larger than 3 cm in diameter, even if the procedure is repeated (18). Another determinant of success is lesion location. Central lesions should be avoided because of the risk of central bile duct and vascular injury, whereas lesions bordering a large (>3 mm) vessel may not respond because of thermal protection provided by the adjacent blood flow, a phenomenon termed "heat sink". Blood flow promotes heat loss, and reducing or eliminating blood flow during the RFA procedure is known to increase the volume of the ablative zone (19). To increase the area of coagulation necrosis (ablation zone size), arterial occlusion such as balloon occlusion, embolization, and chemoembolization are combined with RFA (20).

Recent published studies suggest that a combined therapy with RFA and chemoembolization is superior to chemoembolization or RF ablation alone in patient
survival improvement, but it is not clear the best combination of these two procedures (21-22).

On the basis of this background, the purpose of our study was to evaluate the feasibility and safety of a new combined single-step therapy with balloon-occluded RFA followed by TACE in patients with unresectable hepatocellular carcinoma.
Methods and Materials

Study design

The ethical conduct of the study was approved by our departmental review board and was performed in agreement with the 1990 Declaration of Helsinki and subsequent amendments.

We tested a new single-step combined therapy with RF ablation of the main target lesion during balloon-occlusion of the hepatic artery supplying the tumor followed by selective chemoembolization; in case of other small nodules, the procedure was eventually completed by a segmental/lobar chemoembolization focused on their treatment.

Inclusion and exclusion criteria

Requirements for inclusion in our study were (a) no previous treatment of HCC, (b) a main HCC larger than or equal to 3 cm in diameter, (c) unilobar nodules, (d) liver cirrhosis classified as Child-Pugh class A or B, (d) no vascular invasion, and (e) no extrahepatic metastases.

The exclusion criteria were (a) Child-Pugh class C, (b) a platelet count of less than 40 000/µL and an international normalized ratio of greater than 1.5, (c) severe renal impairment or serum creatinine levels greater than 2 mg/dl.

Study population

Between April and September 2010, 10 consecutive patients (10 male; mean age: 68.7±8.6 years; range: 56-79 years) with multinodular (2-6 nodules) unilobar unresectable HCC and with a target main lesion larger than 3 cm, were enrolled in our single-center multidisciplinary pilot study. The mean height and weight of the patients were 169.6±6.8 cm (range: 160-184 cm) and 70.4±7.3 kg (range: 62-93 kg), respectively. The mean BMI was 29.2±4.8 kg/m2 (range: 23.5-35 kg/m2).

Hepatic impairment was evaluated using Child-Pugh scores: 7 patients (70%) class A cirrhosis, 3 patients (30%) class B cirrhosis. The underlying biopsy-proven cirrhosis was related to hepatitis C in 5 patients (50%), hepatitis B in 2 patients (20%), alcohol use in 1 patient (10%), and cryptogenic in 2 patients (20%).

The mean diameter of the largest lesion was 4.1±0.5 cm (3.5-6cm). One patient had a single HCC larger than 3 cm in maximum diameter whereas the other 9 patients had multiple HCCs. In detail, three patients had one large HCC (target lesion) and another HCC smaller than 3 cm whereas 4 and 2 patients had less or more than 5 associated unilobar lesions smaller than 3 cm in diameter, respectively.
Pre-treatment Work-up

A routine physical examination, laboratory tests, and imaging studies, including ultrasonography (US), unenhanced and contrast medium-enhanced CT performed with a multiphasic protocol (contrast 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) were performed before treatment in all patients. The US and CT studies were performed within 2 weeks before chemoembolization.

Treatment

Antibiotics were administered prophylactically before and 1-2 days after procedures.

All procedures were performed in an angiographic suite which had the structural characteristics of an opening room, using patient monitoring and anesthesiologic assistance.

Diagnostic angiography was always performed under local anesthesia (10mL of 1% lidocaine) using the Seldinger technique through a right common femoral approach, by placing a 6-Fr angiographic introducer. The selective celiac catheterism was performed with a 6Fr-guiding catheter (C1 or C2 curve, 65cm in length). A 0.014-inch guide wire (Choice, Boston Scientific) was advanced into the hepatic artery that was feeding the target main lesion, enabling an optimal guidance of the low-profile monorail PTA-balloon (4-5x20mm, Muso, Terumo, Tokyo, Japan). RF ablation was then performed with US-guidance with the patient under sedation and local anesthesia in the area where the electrode was placed. Fentanyl citrate (0.1-0.2 mg, Phentanest; Daiichi Sankyo, Tokyo, Japan) was used for analgesia; lidocaine (Xylocaine; AstraZeneca International, Osaka, Japan) was used for local anesthesia.

An internally cooled electrode with 3-cm exposed tip (Cool-Tip RF Ablation System: Valleylab, Covidien) was then introduced into the target 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 hook tips 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, TACE was immediately performed. In detail, a superselective chemoembolization of the main lesion was performed using a coaxial technique and placing a 2.7-Fr microcatheter (Progreat; Terumo, Tokyo, Japan) in the distal segmental hepatic artery that was feeding the main lesion previously ablated.
In all cases, an emulsion of carboplatin (Carboplatin) and iodized oil (Lipiodol Ultra Fluid; Mitsui, Tokyo, Japan) was infused, followed by embolization performed with gelatin sponge particles (Gelfoam; Pfizer, Tokyo, Japan). The treatment was eventually completed by selective segmental or lobar chemoembolization of others associated nodules. A total of 450mg of Carboplatin was always infused (fig. 1).

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

Perioperative morbidity and mortality, including major/minor complications and death, respectively, occurring during the first 7 days were registered.

For evaluation of perioperative complications, all patients underwent hemoglobin, serum aminotransferase, and Child-Pugh-related liver tests within 24 hours after the procedure and US within 48-72 hours after the procedure.

Multiphasic spiral CT studies (64-row CT Lightspeed VCT scanner, GE Medical Systems; contrast flow rate 4 mL/s; unenhanced, arterial, portal and late phases; slice thickness 0.625 mm) were performed one month after the procedure to evaluate responses to combined therapy (BO-RFA+TACE).

After therapy, lesions may not change in size or may become smaller or larger. Lesions also may become more heterogeneous in density or signal intensity. On arterial phase images, residual tumor tends to be hyperdense compared with the surrounding liver and necrotic portion. On portal/late venous phase images, tumor can be hypodense relative to the liver but become more enhanced than the necrotic portion. The tumor also can be isodense or hyperdense relative to the liver.

On CT-follow-up exams, when considering the main lesion, we examined the size of the lesions, the necrosis and enhancement pattern, as well as the presence, distribution, and maximum thick of peripheral lipiodol uptake (safety margin).

When considering the concomitant nodules, we evaluated the presence of complete lipiodol captation with eventual necrosis/enhancement pattern.

Complete response, partial response, stable disease, or progressive disease was calculated according to RECIST criteria (23). In detail, complete response was defined as complete devascularization of the lesion during the arterial phase. Necrosis was defined as no enhancing tissue. Complete necrosis of a lesion was considered complete response.

Partial response required an at least 30% increase in the percentage of lesion necrosis.

Stable disease consisted of insufficient change in lesion necrosis to be classified as complete or partial response. Progressive disease is at least 20% increase or appearance of new lesions.
According to our ethical committee, all the patients with relapsing or progressive tumors were treated with the best possible options (other percutaneous therapies such as repeated TACE, supportive care; etc.).
Results

Intraprocedural/Immediate Post-treatment Results

Technical success was achieved in all 10 patients (100%).

Hepatic angiography performed at the end of RF ablation depicted complete disappearance of the tumor neovascuature and/or tumor stain in all cases. No hepatic arterial thrombosis occurred.

Patients were discharged between 72-96h.

No major complications were registered. With regard to minor complications, self-limited subcapsular hematoma was observed in 2 patients and hypertransaminasemia in 7 patients, not requiring any treatment.

The #-fetoprotein levels decreased in all patients who had elevated pretreatment values - to within the normal range in 7 patients, to 20-100 µg/L in 2, and from 1,528 to 975 µg/L in one, with a significant decrease from the baseline values (P<0.05).

Short-term Results: 1-month CT follow-up

On 1-month CT exams, when considering the target lesion, a nonenhancing area corresponding in shape to the previously identified HCC (mean necrotic diameter: 3.42 ± 0.41cm, range: 3-4.5cm), with a circonferential peripheral lipiodol uptake, as safety margin of lesion, of at least 1.02 ± 0.71cm (0.3-2.8cm) was always obtained, with a final mean diameter of treated lesion (necrotic plus safety margin) of 4.53±0.53cm (range: 3.6-5.5cm).

When considering the main target lesion, a complete response was achieved in 7/10 (70%) patients, with a partial response obtained in the last 3 patients (residual tumor <30%: 1 patient; 30-50%: 2 patients; >50%: 0 patients), without any progressive disease.

Whereas, when considering the concomitant nodules, a complete lipiodol captation was obtained in 8/9 patients (88.9%), without progressive disease or new lesions observed (0%).
Conclusion

Balloon-occlusion of the tumor arterial supply seems to increase the area of coagulation necrosis (ablation zone size) obtained with RF ablation, reducing arterial blood flow and minimizing heat loss ("heat sink").

On the other hand, transarterial chemoembolization seems to increase the local effect of RF ablation, working on the large zones of sublethal heating created during RFA application in tissues surrounding the electrode. In detail, the chemotherapy drug should be concentrated in a relatively small volume of residual viable neoplastic tissue, characterized by a reduced cell resistance to the drug due to the previous exposure to sublethal heating. Furthermore, the administration of chemotherapy drug should also be enhanced by the reactive hyperemia induced by RFA application, with a facilitate delivery of the drug.

In conclusion, our pilot study demonstrates that Balloon-occluded-RFA plus TACE seems to be a safe and effective combined therapy for the treatment of advanced unresectable HCC lesions, allowing to:

- obtain a high complete local response rate also in large lesions (mean diameter of the target lesion: 4.1±0.5 cm): complete necrosis or residual tumor <30% obtained in 80% of patients
- treat large hypovascular lesions, not responders to TACE alone (post-RFA reactive hyperemia)
- treat multiple lesions with a single-step procedure  (fig. 2)
- treat "complex lesions", i.e. hepatic tumors adjacent to the diaphragm with a consequent high risk of thermal injury: post-RFA chemoembolization could treat the part of the lesion strictly adjacent to the diaphragm (safety margin)  (fig. 3)
- treat "complex patients", with high risk for bleeding complications: transarterial chemoembolization performed after RFA could prevent eventual iatrogenic hepatic bleeding, with a consequent potential reduction of bleeding complications compared to RFA alone  (fig.4).
References


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