Research article

# Interventional oncology treatments for unresectable early stage HCC in patients with a high risk for intraprocedural bleeding: Is a single-step combined therapy safe and feasible?☆

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## ARTICLE INFO

## ABSTRACT

*Purpose:* This study was designed to assess the feasibility and safety of a single-step combined therapy using radiofrequency ablation and transarterial chemoembolization (RFA + TACE) in patients with hepatocellular carcinoma (HCC) and uncontrolled coagulopathy. The study also aimed to compare the effectiveness of this approach with TACE alone, performed in a control group.

*Material and methods:* One hundred and forty-three consecutive cirrhotic patients having a single HCC < 8 cm were enrolled in this observational prospective single-center study from January 2010 to June 2017 and were divided, according to coagulation tests, into three groups (A: low risk; B: intermediate risk and C: high risk of bleeding). The feasibility and safety of a single-step combined treatment (RFA followed by TACE) were evaluated in terms of technical success rate, periprocedural complications, and laboratory values variations. Tumor re-sponse obtained at 1-month CT follow-up for group C was compared with that of control group, composed by 16 matched patients with severe coagulopathy and single HCC < 8 cm, who underwent only TACE in a previous period, performed by the same operator.

*Results:* Technical success was achieved in all patients, without any major complications. Minor complications rate was significantly higher in group C after RFA; however, the patients were successfully treated with sub-sequent TACE therapy, without any differences between pre- and post-procedural laboratory values. One-month

complete response rates were similar in all the three groups; however, the response rates of group C were significantly higher as compared to that of the control TACE Group (p < .001).

*Conclusion:* The single-step RFA plus TACE therapy allows expansion of the indication for percutaneous thermal ablation, allowing to also include cases previously contraindicated due to the procedural high-risk of complications associated with bleeding, thus improving short-term patient outcome.

## 1. Introduction

The Barcelona Clinic Liver Cancer (BCLC) is the most commonly used staging system in the management of HCC. It incorporates tumor burden, liver functional reserve, and general performance status. The main advantage of this system is that it links tumor staging with treatment modalities and with an estimation of life expectancy based on the response rates of the therapy available. The BCLC staging system recommends curative treatments, such as resection, transplantation, and percutaneous ablation for patients with very early (single HCC up to 2 cm and Child-Pugh class A) and early-stage HCC (single HCC or up to 3 HCCs each < 3 cm and Child-Pugh class A–B) [1].

However, percutaneous thermal ablation therapies are contraindicated in patients with severe coagulation abnormalities, due to a high risk of intra-procedural bleeding involved. In this clinical scenario, transarterial chemoembolization (TACE) may be the only treatment option even in patients with early-stage HCC. However, differently, from resection and percutaneous ablation such as radiofrequency ablation (RFA), TACE is a palliative and not a curative treatment with a sustained complete response (CR) achieved only in 27% to 35% of the cases [2–5]. Based on this background, it would be useful to find a more effective approach for this subgroup of patients in order to offer a personalized medication that could improve outcome without increasing procedural complications and risks.

In recent years, a combination of interventional therapies has been proposed and widely applied in the treatment of HCC [6–13]. A possible strategy is based on the combination of the percutaneous approach, such as RFA, and of the intra-arterial locoregional approach, such as TACE. Recent studies have shown that the combined therapy with RFA and TACE in early or intermediate HCC stage could be more effective than TACE or RFA alone in local control of the disease and survival improvement [14,15]. Furthermore, transarterial chemoembolization performed after RFA can effectively and immediately treat any eventual RFA-induced hepatic bleeding; this approach could be useful in patients with a high risk of intraprocedural bleeding.

The primary aim of this study was, therefore, to assess the feasibility and safety of a single-step combined therapy using radiofrequency ablation and drug-eluting beads transarterial chemoembolization (RFA + TACE), in patients with HCC and uncontrolled coagulopathy. The study secondarily aimed to compare the effectiveness of this approach with that obtained in a matched population of patients having severe coagulopathy treated with drug-eluting beads transarterial chemoembolization (DEB-TACE) alone.

## 2. Material and methods

### 2.1. Study design

Ethical approval for the study was obtained from the Institutional Review Board which was in agreement with the 1990 Declaration of Helsinki and subsequent amendments. Written informed consent was obtained from all the patients. Patients with cirrhosis and unresectable single HCC, fulfilling the inclusion and exclusion criteria were enrolled in this observational prospective single-center study conducted from January 2010 to June 2017. Inclusion criteria were: patients older than 18 years; unresectable BCLC early HCC stage with single nodule smaller than 8 cm in size; treatment with single-step combined RFA + TACE performed; liver cirrhosis classified as Child-Pugh score A or B7; no

vascular invasion or extrahepatic metastases; no previous treatment of HCC. Exclusion criteria were: history of severe allergy or intolerance to any contrast media or chemotherapeutic drugs not controlled with medication; Child-Pugh score B ≥ 8 or C; serum creatinine levels > 2.0 mg/dL; refractory ascites.

The control group was comprised of a cohort of cirrhotic patients having severe coagulopathy, who underwent drug-eluting beads transarterial chemoembolization in our center, and retrospectively assembled during the period January 2008-December 2009. All these patients were excluded from surgical resection due to one or more of the following reasons: severe portal hypertension, surgery unfeasible or hazardous due to the site of the lesion or concurrent severe co-morbidities, and the 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].

All the patients included were divided into three groups based on coagulation profiles: Group A- bleeding time < 10 min, activated plasma thromboplastin time (APTT) 1–1.2, INR < 1.7, platelet (PLT) count > $150 \times 10^9$/L–low risk; Group B- bleeding time > 10 min and < 15 min and/or APTT ratio 1.2–2, and/or INR 1.7–2.3, and/or PLT count > $50 \times 10^9$/L and < $150 \times 10^9$/L–average risk; Group C-bleeding time > 15 min and/or APTT ratio > 2 and/or INR > 2.3 and/or PLT count < $50 \times 10^9$L–high risk.

### 2.2. Pre-treatment work-up

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 US, based on non-invasive criteria (coincidental findings by two imaging techniques - multiphase multidetector CT scan or dynamic contrast-enhanced MRI - or alternatively one imaging technique along with AFP levels above 400 ng/ml) and/or pathology (percutaneous biopsy) [16, 17]. Two weeks prior to the treatment, all patients underwent physical examination, laboratory tests, and imaging studies with diagnostic and staging purposes including liver ultrasound (US), bone scintigraphy, contrast-enhanced thorax and abdomen computed tomography (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). The coagulation studies were performed prior to the treatment in all patients and included measurement of bleeding time, PLT count, APTT, and INR, according to standard procedures.

### 2.3. Treatment

All combined treatments were performed in a single-step approach by the same interventional radiologist, using antibiotic prophylaxis, patient monitoring and anesthesiologist assistants (AA), using the same technique and devices, as also previously published (ref – our previous published paper). In the pretreatment regimen, fresh frozen plasma, Vitamin K, and/or platelet transfusion was performed in case of abnormal parameters.

Immediate post-RFA angiographic control was performed in order to detect or exclude eventual bleeding or vascular complications. DEB-TACE was then performed within 5 min of RFA completion. The endpoint of combined treatment was the disappearance of tumor enhancement, observed in hepatic arteriography performed immediately

after chemoembolization. The final angiographic check was performed to evaluate treatment response as well as to detect or exclude eventual bleeding or vascular complications.

As regards the control group, DEB-TACE was performed by the same operator, with the same technique and the same devices as previously described (ref – our previous published paper). Furthermore, based on coagulation parameters, fresh frozen plasma, Vitamin K, and/or platelet transfusion was also performed during pretreatment in all the patients included.

### 2.4. Post-treatment and follow-up studies

Perioperative morbidity and mortality included major/minor complications and death occurring within seven days from treatment. A major complication was defined as an event that engendered substantial morbidity and disability, an increased level of care, or substantially lengthened hospital stay. All other complications were considered minor [18]. Major bleeding was defined as a requirement for blood transfusion, radiological or surgical intervention. Minor bleeding was defined as ≥1.0 g/dl fall in post-procedure hemoglobin. Post-procedure coagulation parameters were evaluated at 3 and 12 h. Further investigations were undertaken only if clinically indicated.

Multiphasic CT study was performed one month after the procedure to evaluate treatment results at the level of the target lesion using m-RECIST criteria [19] and to detect/exclude new lesions. CT-examinations were evaluated by 2 experienced abdominal radiologists "in consensus".

### 2.5. Statistical analysis

All data were reported as mean ± standard deviation. Differences between groups were evaluated using Student's *t*-test and Fisher's exact test. P-values were determined to be significant if they were less than 0.05. All analyses were conducted using SAS software (SAS Institute Inc, USA).

## 3. Results

### 3.1. Study population

A total of 143 consecutive cirrhotic patients (106 males; mean age 69.3 ± 4.5 years, range 46–86 years), having a single HCC, smaller than 8 cm in size, were enrolled in the study. Mean diameter of the HCC was 4.2 ± 1.6 cm (range 2–7.8 cm). Based on pre-treatment coagulation risk assessment, three groups of patients were identified: group A – low risk, comprising 46 patients, group B – intermediate risk, 76 patients, and group C – high risk, 21 patients.

DEB-TACE Group was composed of 16 patients (12 male; mean age 63.1 ± 6.2 years, range 48–78 years) with single HCC smaller than 8 cm in size who underwent TACE matched with group C patients (high risk for bleeding). The main features of patients and tumors are reported in Table 1.

Based on pretreatment coagulation parameters, all group C (21 patients) and control group (16 patients) patients underwent platelet transfusion (one single donor unit) whereas, to correct coagulopathies secondary to clotting factor deficiency, 10 ml/kg of fresh frozen plasma (FFP) was administered in only 5 out of 21 (5/21, 23.8%) and 3 out of 16 (3/16, 18.7%) patients of group C and control group, respectively. Hemostatic agents were administered one hour before the treatment, without repeating coagulation tests.

### 3.2. Intraprocedural/immediate post-treatment results

Technical success was achieved in all patients. Hepatic angiography performed at the end of the combined therapy depicted the complete disappearance of the tumor neovasculature and/or tumor stain in all cases. No major complications or death were registered.

Minor complications were detected in 49 patients (49/143, 34.3%) including intraprocedural (8/143, 5.6%) as well as immediate post-procedural events (43/143, 30.1%) (Table 2). Intraprocedural events were represented by post-RFA active bleeding; patients were then treated with subsequent selective chemoembolization using the standard technique, and without any change in the planned treatment in any of the patients. A complete disappearance of active bleeding was observed at the final angiographic control (Fig. 1). When considering subgroup distribution of intraprocedural bleeding complications, a significantly higher rate was detected in Group C (high risk, 5/21, 23.8%) as compared to both Group A (low risk, 1/46, 2.4%) and Group B (average risk, 2/76, 2.6%), respectively (p < .05). However, there were no significant differences between the pre- and post-procedural values of PLT count, INR, and Hemoglobin level in any of the three subgroups of patients.

Post-procedural minor complications were represented by serum level of transaminase that increased as compared to the basal value (18

**Table 1**
Summary of patient and tumor characteristics.

| | TOTAL | GROUP A | GROUP B | GROUP C | Control Group |
|---|---|---|---|---|---|
| Patients | 143 | 46 | 76 | 21 | 16 |
| Age (years) | 69.3 ± 4.5 (46-86) | 71.6 ± 3.8(56-86) | 67.3 ± 6.2 (46-83) | 65.7 ± 5.6 (51-74) | 63.1 ± 6.2 (48–78) |
| Male (%) | 106 (74.1) | 34 (73.9) | 57 (75) | 15 (71.4) | 12 (75%) |
| Cirrhosis etiology | | | | | |
|   Hepatitis B | 36 (25.2%) | 11 (23.9%) | 21 (27.6%) | 4 (19%) | 4 (25%) |
|   Hepatitis C | 71 (49.6%) | 24 (52.2%) | 39 (51.3%) | 11 (52.4%) | 9 (56.2%) |
|   Alcohol-related | 28 (19.6%) | 9 (19.6%) | 14 (18.4%) | 5 (23.8%) | 2 (12.5%) |
|   Cryptogenic | 8 (5.6%) | 3 (6.5%) | 4 (5.3%) | 1 (4.8%) | 1 (4.8%) |
| Child-Pugh Class | | | | | |
|   A | 94 (65.7%) | 32 (69.6%) | 49 (64.5%) | 13 (61.9%) | 10 (62.5%) |
|   B | 49 (34.3%) | 14 (30.4%) | 27 (35.5%) | 8 (38.1%) | 6 (37.5%) |
| Diameter (cm) | 4.2 ± 1.6 (2-7.8) | 4.3 ± 1.8 (2.4-7) | 4 ± 1.9 (3.4-7.8) | 3.9 ± 1.5 (2-6.5) | 4.2 ± 1.3 (2.5-7.5) |
| 2-3 cm (%) | 16 (11.2) | 5 (10.9) | 9 (11.8) | 2 (9.5) | 2 (12.5) |
| 3-5 cm (%) | 74 (51.7) | 24 (52.2) | 39 (51.3) | 11 (52.4) | 9 (56.2) |
| > 5 cm (%) | 53 (37.1) | 17 (37) | 28 (36.9) | 8 (38.1) | 5 (31.2) |
| Platelets (x10⁹/L) | 210 ± 201 (24-774) | 471 ± 152 (151-774) | 101 ± 26* (50-148) | 35 ± 7* (24-48) | 31 ± 9 (22-41) |
| INR | 1.2 (0.9-2.4) | 1.1 (0.9-1.6) | 1.2 (0.9-1.5) | 1.4 (1.2-2.4) | 1.3 (1.2-2.3) |
| Hb (g/dL) | 12.7 (7.9-16.6) | 12.5 (8.3-15.5) | 13.1 (8.9-16.6) | 11.7 (7.9-14.5) | 11.9 (7.8-13.9) |
| MELD | 10 (6-23) | 9 (6-19) | 10 (7-19) | 13 (9–23) § | 12 (9-19) |

  * Significantly lower than that obtained in Group A.

  \* Significantly lower than that obtained in both Group B and C; § significantly higher than that obtained in both Group A and B.

**Table 2**
Summary of intraprocedural laboratory tests.

| | GROUP A | GROUP B | GROUP C |
|---|---|---|---|
| PLT (x10$^9$/L) | | | |
| Pre | 471 ± 152 (151-774) | 101 ± 26 (50-148) | 35 ± 7 (24-48) |
| Post | 448 ± 138 (124-656) | 89 ± 36 (42-134) | 33 ± 11 (22-41) |
| Differential | − 23 ± 21 | − 12 ± 15 | − 2 ± 11 |
| INR | | | |
| Pre | 1.1 (0.9-1.6) | 1.2 (0.9-1.5) | 1.4 (1.2-2.4) |
| Post | 1.2 (0.9-1.6) | 1.2 (0.9-1.6) | 1.3 (1.1-2.1) |
| Differential | 0.1 | 0 | − 0.1 |
| Hb (g/dL) | | | |
| Pre | 12.5 (8.3-15.5) | 13.1 (8.9-16.6) | 11.7 (7.9-14.5) |
| Post | 12.3 (8.0-15.5) | 12.8 (8.8-14.5) | 11.6 (7.9-13.8) |
| Differential | − 0.2 | − 0.3 | − 0.1 |

patients, 12.6%), post-embolization syndrome that was defined as transient elevation in body temperature, pain in the abdomen, nausea and/or vomiting, leukocytosis and elevated liver enzymes (20 patients, 14%), transient cholecystitis (3 patients, 2.1%), and mild subcapsular hematoma that resolved spontaneously without treatment (2 patients, 1.4%). No significant differences were observed between subgroups of patients in terms of post-procedural minor complications.

### 3.3. Control group: intraprocedural/immediate post-treatment results

Technical success was achieved in all patients. No major complications or death were registered in any of the patients. Minor immediate post-procedural complications were detected in four patients (4/16, 25%), represented by post-embolization syndrome in three patients and transient cholecystitis in the last one. No hepatic bleeding or femoral hematoma was observed in any of the patients.

### 3.4. Short-term results

No patient showed a worsening of the Child-Pugh score at one month from treatment. One-month CT showed a mean necrotic diameter of 5.4 ± 1.2 cm (range: 3.8–7.8 cm). Based on m-RECIST criteria, a CR (Complete Response) was achieved in 109/143 (76.2%) patients (CR group) whereas a PR (Partial Response) was obtained in the last 34 patients (33.8%) (residual tumor < 30%: 29 patients, between 30% and 50%: five patients) (PR group). No significant differences were observed between the three subgroups of patients in terms of tumor response, whereas the high-risk Group C achieved a

significantly higher CR rate as compared to the DEB-TACE control Group (p < .001) (Table 3).

## 4. Discussion

Image-guided techniques for local tumor treatment have emerged as a viable therapeutic option for non-surgical patients with limited hepatic malignant disease. Furthermore, in the last two decades, percutaneous treatments for malignant liver tumors have extensively progressed; it is well-known that RFA is a useful therapeutic option for the treatment of unresectable, small HCCs < 3 cm, with the possibility of combination with intra-arterial procedures for the treatment of larger nodules, measuring up to 8 cm in size and for achievement of better results than that obtained with TACE or RFA alone [6–13]. Percutaneous ablation treatments are well-tolerated, have low complication rates and bear few absolute contraindications (mostly concerning patients at a high risk of bleeding). In particular, patients with severe coagulation abnormalities are usually excluded from percutaneous ablation treatments [20–22]. Percutaneous Ethanol Injection (PEI) is performed using fine Chiba or dedicated needles and could be an option for these high-risk patients; however, it is effective only for nodules measuring up 2 cm in size [23–25]. For HCCs larger than 2 cm in size, in patients with serious coagulation abnormalities, the only option would be TACE, which is a palliative treatment, being characterized by low rates of complete tumor necrosis. Therefore, it would be beneficial to find an alternative approach for this subgroup of patients in order to offer a tailored treatment for each patient, based on the technical possibilities offered by new innovative biotechnologies. When considering single-step combined treatment, transarterial chemoembolization performed after RFA can effectively and immediately treat any eventual RFA-induced hepatic bleeding. As a matter of fact, RFA in a combined approach can be potentially used to safely treat "complex patients" with a high risk of bleeding complications without requiring blood transfusion or other prophylactic treatment. Thus, in order to assess the feasibility and safety of a single-step combined therapy (RFA + TACE) in patients with a single HCC ranging from 2 to 8 cm in size and severe coagulopathy, the authors have evaluated all patients prospectively enrolled in our study who underwent combined treatment in our department over a 7-year period, considering three different subgroups based on coagulation profiles. This study showed that combined treatment is feasible and safe, also in patients with a high risk for bleeding (bleeding time > 15 min, APTT ratio > 2, INR > 1.5, PLT count < 50 × 10$^9$/L). In particular, the higher risk of bleeding justifies the significantly higher rate of post-RFA active bleeding that was found



**Fig. 1.** A 58 yo patient with a single HCC nodule 36 mm in diameter in the V segment (a), not amenable to RFA alone due to the low platelet count (45.000/ mm$^3$). In order to keep the patient in the transplantation list, our multidisciplinary group decided to treat the patient with a combined approach. At first RFA was performed under US guidance with 17 G needle and during occlusion of the feeding artery with PTA balloon (b). At the end of the ablation, the angiography shows the peri-lesional hyperemia but also a small peripheral blush of contrast medium (c) as also demonstrated on US (e). The bleeding was promptly trated with chemoembolization with resolution of the intra-procedurale complication as shown at the ultrasound check after 48 h hours (f).

**Table 3**
Tumour response (mRECIST).

| | ALL | GROUP A | GROUP B | GROUP C | Control Group |
|---|---|---|---|---|---|
| Complete response (CR) | 76.2% (109/143) | 34 (73.9%) | 59 (77.6%) | 16 (76.2%) | 5 (31.25%)* |
| Partial response (PR) | 23.8% (34/143) | 12 (26.1%) | 17 (22.4%) | 5 (23.8%) | 10 (62.5%) |
| Stable Disease (SD) | 0% | 0% | 0% | 0% | 1 (6.25%) |
| Progression Disease (PD) | 0% | 0% | 0% | 0% | 0% |

\* Significantly lower than that obtained in all other groups.

in this subgroup of patients (23.8% vs. 2.4% and 2.6% observed in low and intermediate risk group, respectively). However, all these complications were promptly and effectively treated with subsequent selective chemoembolization, performed using standard technique, without any alteration in the planned treatment. It is worthy to highlight that due to prompt embolization of the bleeding vessel, no significant differences between the pre and post-procedural values of platelet count, INR, and Hemoglobin level were recorded in all three subgroups of patients, and none of the patients with the bleeding complication required any additional treatment. Furthermore, the benefit of combined therapy was not counteracted by any relevant side effects or worsening of liver function; in detail, no patient experienced any increase in Child-Pugh score at one month follow-up. It is also worthy to note that the use of combined treatment allowed the authors to provide to high-risk patients, the same therapeutic benefit as that offered to low and intermediate risk patients. A CR rate of about 75% was obtained in the overall population without any significant differences between the three subgroups of patients. These results are particularly interesting if compared to the rate of CR obtained in the matched population with severe coagulopathy treated with DEB-TACE alone (76.2% vs. 31.25%). It is also important to point out that among the 21 high-risk patients, there were two patients with unresectable HCC of less than 3 cm in size; if only TACE would have been performed the patients would have received only palliative therapy instead of a curative treatment despite the size. The use of combined treatment allowed the authors to offer a curative option to these patients, probably changing the long-term prognosis of their HCC. Considering the high rate of CR obtained in a single step, this approach may also allow to decrease the number of therapeutic procedures performed per patient, with a potential decreased risk of liver function failure due to the treatment-related injury of non-neoplastic liver tissue.

The main limitation of the study is the small number of high-risk patients enrolled; therefore, further multicenter investigations with larger patient populations and longer follow up periods are warranted. Furthermore, as we didn't perform coagulation tests after hemostatic agent administration, we were unaware of intraprocedural values of platelets and INR. Based on this limitation we are not able to identify eventual correlation between intraprocedural bleeding and response to treatment with platelet transfusion and fresh frozen plasma in Group C as well as control group. This information could potentially allow us to better select patients who would need to undergo combined treatment instead of ablation or chemoembolization only. In addition, future clinical studies are also necessary to assess if the use of combined treatment could allow to reduce the dose or avoid the hemostatic agent administration without increasing the bleeding risk and complication rate, in patients with coagulation abnormalities.

In conclusion, the study demonstrates that single-step RFA plus DEB-TACE is a safe and effective treatment for single HCC measuring up to 8 cm in size, detected in cirrhotic patients with severe coagulopathy, who are not amenable to surgical treatment or percutaneous thermal ablation alone, due to procedural high-risk of bleeding complications, expanding indication to curative treatments thus improving short-term patient outcome.

## Declarations of interest

None.

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