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Transarterial chemoembolization using drug eluting beads and subsequent percutaneous MR-guided radiofrequency ablation in the therapy of intermediate sized hepatocellular carcinoma

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ABSTRACT

Objective: To evaluate safety, efficacy, survival and recurrence-free survival of transarterial chemoembolization (TACE) with drug eluting (DC) beads combined with MR-guided radiofrequency (RF) ablation for the treatment of hepatocellular carcinomas (HCC) larger than 3 cm.

Materials and methods: This retrospective study was approved by the institutional review board. 20 patients (69.6 years ±SD 8.8) with HCC underwent DC Bead TACE and subsequent MR-guided RF ablation. Treatment interval varied between 5 and 15 days. Mean HCC diameter was 39 mm ±SD 7 mm (range 31–50 mm). Rates of recurrence-free survival and overall survival were estimated using the Kaplan–Meier method.

Results: Technical success rate, primary and secondary technical effectiveness rate were 100%, 90% and 95%, respectively. Local tumour progression developed in one patient. Cumulative survival rates at 1, 3 and 5 years were 90% (Confidence Interval [CI]: 67%–97%), 50% (CI: 29%–70%), 27% (CI: 11%–51%) respectively. Median survival time was 37.4 months. During follow up (mean: 39.1 months ±SD 22.4; range 5–84 months), tumour progression in untreated liver developed in 14 cases. Cumulative recurrence-free survival rates at 1, 3 and 5 years were 48% (CI: 27–69%), 16% (5–39%), 16% (5–39%) respectively. Median recurrence-free survival time was 10.7 months. One major complication occurred due to misdiagnosed local recurrence.

Conclusion: In conclusion, we demonstrated that MR-guided RF ablation with subsequent DC Bead TACE is safe and effective in local tumour control in patients with intermediate sized HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common malignancy in the world, and the fifth most common cause of cancer mortality [1]. According to the Barcelona Clinic Liver Cancer (BCLC) Group, radiofrequency (RF) ablation is a recommended treatment option for patients with up to three (early stage) carcinomas with diameters below 3 cm [2]. However, it has been shown that RF ablation of larger tumours is critical as the limited size of coagulation necrosis fails to achieve complete ablation necrosis, therefore the local recurrence rate seems to increase in proportion to the size of the tumour [3,4]. Techniques such as the Pringle manoeuvre, balloon-occlusion of the hepatic artery and transarterial chemoembolization (TACE) have been combined with RF ablation to reduce the tumour blood flow resulting in larger ablation zones [5,6]. The combination therapy of conventional TACE based on lipiodol or gelatine sponge particles followed by RF ablation for treatment of larger tumours has been the particular subject of some studies, and the results are comparable to surgical hepatectomy [7–10]. A new drug delivery system for TACE has recently been described: drug-eluting (DC) Beads (Biocompatibles UK Ltd., Farnham, UK) are

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Table 1
Characteristics of patients and tumours.

Patients	$n = 20$ (100%)
Age, mean (years) ± SD	69.6 ± 8.8
Tumours size, mean ± SD	39 mm ± 7
Gender	
Male	19 (95%)
Female	1 (5%)
Aetiology	
Hepatitis B	2 (10%)
Hepatitis C	5 (25%)
Nutritive	7 (35%)
Haemochromatosis	2 (10%)
Others	4 (20%)
Number of treated tumours	
1	16 (80%)
2	4 (20%)
Pre-treatment	
Yes	5 (25%)
No	15 (75%)
Child-Pugh class	
A	18 (90%)
B	2 (10%)

based on polyvinyl alcoholic hydrophilic microspheres and can be loaded with cytotoxic drugs. Due to a high affinity for the drugs, the DC Beads enable a gradual release of the cytotoxic drugs into the tumour, allowing a longer intratumoral exposure and less systemic exposure of the drug, therefore reducing systemic toxicity [11–13].

In this study, we aimed to evaluate the safety, efficacy, survival and recurrence-free survival of TACE with DC Beads combined with RF ablation for the treatment of HCC larger than 3 cm.

2. Materials and methods

2.1. Patients

This retrospective study was approved by our institutional review board. Between July 2006 and December 2010, 23 patients with HCC underwent combined treatment with TACE with DC Beads followed by MR-guided RF ablation. Inclusion criteria were: (1) one to three HCC with at least one HCC with a diameter over 3 cm, (2) an interval between TACE and RFA of below 16 days, (3) no extrahepatic manifestations, (4) Child-Pugh liver function class A or B. One patient who underwent combination therapy of a 17 mm HCC because of a sub-cardiac tumour location was excluded. Two other patients were excluded as the treatment interval exceeded 16 days. Nineteen men and one woman with a mean age ±standard deviation (SD) of 69.6 years ± 8.8 met the inclusion criteria. The diagnosis of HCC was based on histological results of image guided percutaneous needle biopsy in 10 cases, and based on the European Association for Study of the Liver Consensus conference criteria in 10 cases [14]. The decision for combined treatment was made in an interdisciplinary meeting. Sixteen patients were treated for a single HCC and four patients for two HCCs (of which one was above and one below 3 cm in diameter). Mean tumour size was 39 mm ± 7 mm (range: 31–50 mm). Fifteen patients received combination therapy as the initial treatment for HCC; five patients were pretreated for HCC in another location with conventional TACE plus RF ablation ($n = 3$) or RF ablation alone ($n = 2$). Interval between pre-treatment and combination therapy ranged from 2 to 65 months (mean 30.7 months) in these five patients. Patients' data and tumour characteristics are summarized in Table 1.

2.2. Transarterial chemoembolization

The informed consent for TACE and RF ablation was signed by all patients before treatment. All patients underwent pre-procedural contrast-enhanced multiphase computed tomography (Somatom Sensation 64 or Somatom Definition Flash; Siemens, Erlangen, Germany), or contrast-enhanced liver MRI (Siemens Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). After puncture of the right common femoral artery (19G needle, 4F sheath; Terumo, Leuven, Belgium), a 4F straight diagnostic catheter was introduced. Aortography was performed to assess anatomy of the hepatic arteries with Ultravist 370 (Bayer Schering Pharma, Zuerich, Switzerland), e.g. an abnormal left artery originating or a hepatomesenteric trunc. In case of a parasitic tumour supply e.g. originating from the inferior phrenic artery, these vessels were coiled before chemoembolization.

A 4F Cobra or Sidewinder catheter (Cordis Corporation, Bridgewater, NJ, USA) was placed in the coeliac trunk and coeliacography was performed. A 2.7F coaxial microcatheter was then advanced over a microguidewire (Progreat; Terumo, Shibuya, Japan) to assess vascularization of the HCC. After superselective catheterization, a suspension of 10–100 mg of epirubicin-loaded DC Bead particles (300–500 μm, Terumo) were slowly injected until stasis was achieved. Selective control angiography was performed after approximately 10 min and in case of residual tumour, loaded DC Beads were additionally injected to achieve full stasis.

2.3. RF ablation

All patients were treated using a wide-bore 1.5-T system (Siemens Magnetom Espree, Siemens Healthcare, Erlangen, Germany). A six-channel body array and an additional one-channel loop array placed at the puncture site were used. Analgesia and sedation were applied intravenously (i.v.) during the intervention (analgesia: piritramide i.v., total dose 8–15 mg; sedation: midazolam i.v., total dose 3–5 mg). Pulse rate and oxygen saturation were monitored during the procedure. Treatment included a MR planning examination, applicator placement using MR fluoroscopic sequences, repeated control imaging during the ablation procedure and contrast-enhanced post-interventional control imaging [15]. Three different commercially available MR-compatible RF systems were used for ablation: 13 procedures were performed using internally water-cooled bipolar applicators (Olympus Celon, Teltow, Germany); three applicators were used in 8 procedures and two applicators in 5 procedures, and active tip length varied between 3 cm and 4 cm. Five procedures were performed using one internally water-cooled monopolar cluster applicator (Valleylab, Covidien, Boulder, CO, USA) with an active tip length of 2.5 cm. Two patients were treated with an internally water-cooled monopolar RF system with a 17-gauge single applicator and a 4 cm active tip (Valleylab, Covidien, Boulder, CO, USA). Ablation progress was assessed during the procedure with MR control imaging and in case of suspicion of residual tumour or an insufficient safety margin, applicators were repositioned and ablation was continued until the procedure was complete. Applicator retraction was performed under coagulation. Post-interventional control examinations were performed immediately after ablation in the same MR scanner to evaluate the technical success and to exclude complications such as haematomas, active bleeding or cholestasis. T1- and T2-weighted transverse slices were acquired, followed by a T1-weighted, contrast-enhanced dynamic liver examination using a volumetric interpolated breath-hold examination (VIBE) sequence after intravenously injecting 0.1 mmol of gadobutrol per kg body weight (Gadovist, Bayer HealthCare, Leverkusen, Germany).

2.4. Follow-up imaging

Follow-up imaging scheme was based on liver MRI. The first examination was performed 4 weeks after RF ablation, and then every 3 months for 1 year and every 6 months for the next 3