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The impact of antiangiogenic therapy combined with Transarterial Chemoembolization on enhancement based quantitative tumor response assessment in patients with hepatocellular carcinoma

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ABSTRACT

Purpose: To investigate whether bevacizumab compromises early response assessment after Transarterial Chemoembolization (TACE) in patients with hepatocellular carcinoma by 3D quantitative European Association for the Study of the Liver (qEASL) criteria in comparison to other imaging-based criteria.
Materials and methods: Each of 14 patients receiving TACE and bevacizumab was matched with two patients receiving TACE alone. Baseline and Follow-up MRI was retrospectively analyzed regarding qEASL and other imaging-based criteria.
Results: Percentage-based qEASL achieved significant separation in both therapy arms ($p = 0.046$ and $p = 0.015$). Response and Overall Survival showed similar association among treatment groups ($p = 0.749$).
Conclusions: Anti-angiogenic therapy with bevacizumab does not impede early response assessment by qEASL.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1–3]. Most HCC patients present with intermediate or advanced stage disease, making curative treatments unattainable for most patients [4]. Trans-arterial chemoembolization (TACE) has meanwhile been established as the mainstay therapeutic option for many patients [4]. Recurrence following TACE is common, and a main cause is post-embolic tumor hypoxia leading to a surge of pro-angiogenic factors, such as the vascular endothelial growth factor (VEGF) [4–6]. Therefore, a strong rationale exists for investigating the use of bevacizumab, a humanized monoclonal antibody targeting VEGF, in combination with TACE, in order to contain tumor progression during and between TACE cycles [7].

Assessing tumor response is important for determining the course of patient treatment, and hence robust, precise, and reproducible criteria are essential for therapeutic success. Loco-regional embolization therapies like TACE cause tumor infarction, thus fundamentally changing the appearance of the targeted tissue on contrast-enhanced MRI by causing non-homogenous enhancement patterns [1,8]. In addition, early follow-up imaging after TACE usually does not demonstrate tumor shrinkage, making conventional diameter-based measurements obsolete. A plethora of published data demonstrates that uni-dimensional measurements such as Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST (mRECIST), as well as bi-dimensional measurements like the World Health Organization (WHO) and the European Association for the Study of the Liver (EASL) criteria, are unreliable in the

Abbreviations: TACE, Transarterial Chemoembolization; cTACE, conventional Transarterial Chemoembolization; HCC, hepatocellular carcinoma; EASL, European Association for the Study of the Liver Guidelines; qEASL, 3D quantitative European Association for the Study of the Liver criteria; BCLC, Barcelona Clinic Liver Cancer staging classification; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization; OS, Overall Survival; VEGF, vascular endothelial growth factor; ECOG, Eastern Cooperative Oncology Group score; ROI, region of interest; Bev, bevacizumab; SD, standard deviation; HKLC, Hong Kong Liver Cancer Stage; NASH, Nonalcoholic Steatohepatitis; INR, International Normalized Ratio; HR, hazard ratio; CI, Confidence Interval.

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setting of TACE at an early time point [1,9]. New 3D imaging biomarkers, such as the quantitative EASL [qEASL], have meanwhile been established to address the previously unmet need for robust tumor assessment techniques after TACE [1,8,10,11]. However, they have not yet been tested in the framework of TACE combined with systemic therapy using anti-angiogenic agents such as bevacizumab. All agents with similar molecular targets and comparable mechanism of action have been demonstrated to profoundly affect vascularity, pathologic vessel growth and tortuosity, as well as contrast agent permeability of the capillary bed of liver tumors. Little is known on the impact of bevacizumab on the role of tumor enhancement within the framework of imaging response.

Recently a number of studies have been done on bevacizumab in this context and while disagreeing on the safety and therapeutic success, they all struggled regarding appropriate early response assessment, with attempts ranging from subjective visual impression on MRI to diagnostic angiography [7,12,13]. Finding a not only early, but objective and reliable method could advance scientific knowledge on effective and safe bevacizumab application.

The purpose of our study is to investigate whether Bevacizumab compromises early response assessment after conventional TACE (cTACE) in patients with unresectable hepatocellular carcinoma (HCC) by 3D quantitative European Association for the Study of the Liver (qEASL) criteria in comparison to other imaging-based criteria.

2. Materials and methods

2.1. Study design and patient selection

This is a retrospective single-institution Health Insurance Portability and Accountability Act–compliant and institutional review board–approved study. Informed consent was waived. Study design was in agreement with the Standards for Reporting of Diagnostic Accuracy guidelines. Enrolled were all 16 consecutive patients receiving cTACE and bevacizumab combination therapy between September 2006 and December 2008 during a Phase II clinical trial at one of the two institutions conducting the trial, which is described in detail in prior literature [12]. Patients without follow-up MR imaging (N = 2) were excluded; the remaining 14 patients were analyzed.

The clinical study inclusion protocol required patients to demonstrate sufficient platelet count (≥50,000/nl), adequate liver and kidney function, Child-Pugh Class A or B, and Eastern Cooperative Oncology Group score (ECOG) 0–2 [12]. Exclusion criteria included risk factors for severe bleeding, major vessel or heart disease [12]. For each cycle the patients received 10 mg/kg bevacizumab intravenously 7 days prior to TACE, followed by subsequent biweekly administration. During the course of the study, the therapy regimen was adjusted to administer bevacizumab 14 days prior to TACE, due to prolonged recovery after the procedure which interfered with the next biweekly injection. Patients received up to 3 cycles of cTACE and bevacizumab therapy [12]. Further detail regarding the protocol used, is provided in the cited article addressing safety and efficacy [12].

To improve comparability, a control group was included consisting of patients who received TACE without bevacizumab. For this purpose, a prospectively acquired patient database was retrospectively used to randomly include TACE-naïve patients who received cTACE between May 2004 and April 2006 (before the enrolment period of the prospective trial) [14]. Inclusion and exclusion criteria for the control group were identical to those for the prospective trial group. For each patient receiving the combination therapy, two patients with matching Child-Pugh Class and Barcelona Clinic Liver Cancer stage (BCLC) as well as similar tumor size and number (±10% in largest lesion diameter) were included into the control group (Fig. 1). An additional 1:1 control group matching was performed for basic consistency check.

2.2. TACE protocol

After decision by consensus agreement of a multidisciplinary tumor board for each patient, TACE was performed by an interventional radiologist (XX) with 19 years of experience. The Seldinger technique was used to gain access to the femoral artery and a catheter was advanced into the aorta under angiographic guidance. Following confirmation of the patient's vessel anatomy, access was gained to the hepatic artery through the coeliac trunk, or the replaced hepatic through the superior mesenteric respectively. Lobar or superselective embolization was performed with a solution containing 50 mg of doxorubicin and 10 mg of mitomycin C in a 1:1 mixture with iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France) under the guidance of intraprocedural imaging. This was followed by the application of microspheres with a diameter of 300–500 μm (Embospheres; Merit Medical Systems, South Jordan, Utah).

2.3. MR imaging

For early assessment during treatment, contrast-enhanced multiphasic breath-hold MRI with T1-weighted sequences was acquired 2 ± 3 weeks prior to embolization (baseline MR), and 3 ± 3 weeks afterwards (follow-up MR) using a 1.5 Tesla MR scanner (Siemens Magnetom Avanto, Erlangen, Germany). Imaging was acquired prior to the intravenous administration of Gadolinium-base contrast agent (pre-contrast phase) and at multiple time points afterwards (arterial, portal venous, and delayed phases).

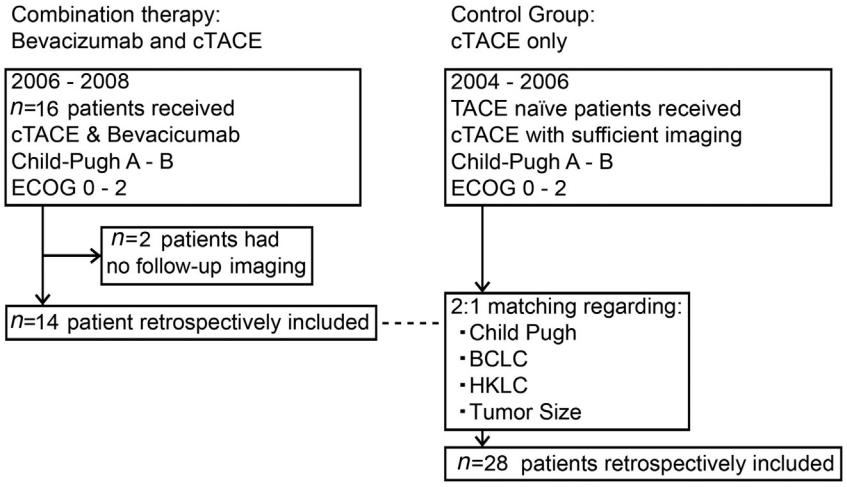

Fig. 1. Flowchart of inclusion and matching of the control group.