European Journal of Radiology 90 (2017) 73–80

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Early response evaluation using CT-perfusion one day after transarterial chemoembolization for HCC predicts treatment response and long-term disease control

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ARTICLE INFO

Article history:
Received 9 December 2016
Received in revised form 17 February 2017
Accepted 20 February 2017

Keywords:
Hepatocellular carcinoma
Chemoembolization
Perfusion
Response assessment
Computed tomography

ABSTRACT

Purpose: To determine the value of CT perfusion (CTP) for early response assessment after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).
Materials and methods: Between April 2013 and April 2015, 41 HCC (16 patients) were included in this study. CT perfusion was performed before and one day after TACE. Blood flow (BF), blood volume (BV), time to start (TTS), arterial liver perfusion (ALP), portal liver perfusion (PVP) and hepatic perfusion index (HPI) were measured. Quantitative perfusion values before and after TACE were compared to the response assessed using mRECIST criteria six weeks after TACE and long-term outcome was assessed.
Results: Twenty-one lesions (51%) had complete remission (CR) and five (12%) had partial response (PR) six weeks after TACE. CTP parameters were significantly reduced after TACE in responders (PR, CR, $p < 0.001$) while no difference was observed in non-responders. ALP_{post} was superior in the prediction of CR compared to BF_{post} and BV_{post} ($p < 0.001$) with a sensitivity, specificity, PPV, NPV, and accuracy of 90%, 90%, 91%, 90%, and 91%, respectively. Only 3/21 lesions with CR recurred, with a mean local-recurrence-free survival of 19.6 months.
Conclusion: CT perfusion detects lesions with complete response one day after TACE, and is a feasible tool for early response assessment.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common liver tumour and is currently ranked as the number five cause of cancer-related mortality [1]. HCC usually occurs in the setting of chronic liver disease and cirrhosis [2] and treatment is influenced not only by tumour stage, but also by liver function [3]. For patients with intermediate-stage HCC (multifocal tumours without extrahepatic or macrovascular involvement), transarterial chemoembolization (TACE) is the preferred treatment according to current practice guidelines [4].

HCCs are largely hypervascularized tumours, which is evident on both imaging [5], as well as histopathology. On multidetector CT (MDCT), the typical image appearance is described by a clear hypervascularity in the arterial phase and by rapid washout in the venous and parenchymal phases. Based on this criteria, the diagnosis of HCC can be made non-invasively [2]. After TACE, only a partially enhancing lesion will remain in cases of incomplete embolization. This fact is attributed to in the modified response criteria (mRECIST), which have been developed to assess treatment response in hypervascular lesions [6], like HCC. These criteria are currently

Abbreviations: ALP, arterial liver perfusion; BF, blood flow; BV, blood volume; CR, complete response; CTP, CT perfusion; HCC, hepatocellular carcinoma; HPI, hepatic perfusion index; MDCT, multidetector computed tomography; mRECIST, modified response criteria in solid tumours; NR, no response; OS, overall survival; PD, progressive disease; PR, partial response; PVP, portal liver perfusion; ROI, region of interest; SD, stable disease; TACE, transarterial chemoembolization; TTS, time to start; VOI, volume of interest.

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http://dx.doi.org/10.1016/j.ejrad.2017.02.032
0720-048X/

used as a surrogate parameter to assess changes in tumour vascularity after embolization. The disadvantage is that only the size of the enhancing part is measured and no real quantitative evaluation of tumour perfusion is performed. Furthermore, HCCs can divert from those imaging features, and might be isodense in the arterial phase, which would not allow a sufficient differentiation from the liver parenchyma [7].

As a consequence of those limitations, CT Perfusion (CTP) has an emerging role in oncologic imaging [8]. The experience with prediction and assessment of response after various oncologic treatments is preliminary at this stage [9]. However, CTP might be an attractive modality for the assessment of treatment response in HCC and other hypervascular liver tumours since the response to treatment is often related to early changes in perfusion [10,11]. It has already been shown that CTP is more sensitive than conventional MDCT in the prediction of response after anti-angiogenic treatment for advanced HCC [1,12], but little information is available about the potential of CTP in assessing response very early after TACE and whether this method can predict sustainable, long-term disease control.

Thus, we conducted a prospective study to determine whether CTP can predict response one day after TACE for HCC, compared to the reference standard of response assessment six weeks after TACE, using mRECIST criteria. Furthermore, the implications on long-term outcome were studied.

2. Materials and methods

2.1. Study design

This prospective study was approved by the local institutional review board (IRB No. 1669/2013), and written informed consent was obtained from all participants. Patients who were scheduled for TACE at our institution between April 2013 and April 2015 were prospectively evaluated for inclusion in the early treatment response protocol.

2.2. Eligibility criteria

The decision for TACE was made at the weekly multidisciplinary tumour board and patients were screened for eligibility based upon that treatment recommendation.

We included consecutive patients with either primary or recurrent early HCC of at least 1 cm in size with adequate liver function who were either unresectable or not amenable to local ablative therapy (Barcelona Clinic Liver Cancer stage A) or intermediate HCC (Barcelona Clinic Liver Cancer stage B). The diagnosis of HCC was either confirmed by a biopsy or according to criteria defined by the European Association for the Study of the Liver [4] in the context of underlying liver cirrhosis.

Exclusion criteria were: Poor performance status (Eastern Cooperative Oncology Group Performance Score 2 and higher), renal impairment (calculated glomerular filtration rate <30 ml/min), history of severe adverse reaction to the contrast material used (IOMERON® 400; Bracco, Milan, Italy), liver-directed therapy including selective internal radiation therapy within four weeks prior to inclusion and recent anti-angiogenic medication (e.g. bevacizumab or sorafenib, etc.)

The selection process is outlined in Fig. 1, the final cohort amenable for outcome analysis consisted of 41 lesions in 16 patients.

2.3. Early response assessment protocol

On the day before TACE, a CT-perfusion baseline study was conducted as described below (CTPb). If not performed earlier, a diagnostic staging CT was performed two-to-four hours later in order to allow for TACE planning and as a baseline study (CTb) for response assessment according to mRECIST. On the day after TACE, patients received another CTP study (CTPpost). Patients were clinically managed according to standard operating procedures and were discharged upon the discretion of the treating physician. Six weeks after TACE, patients received a follow-up diagnostic biphasic staging CT of the abdomen for routine response assessment (CTfu), which served as the reference standard (Fig. 2). No patients with more than two TACE cycles were included in the early response protocol.

Patients were followed up at three-month intervals with either CT or MRI until progression, and any event (death, progression) was recorded in the clinical files. Four patients were censored after an orthotopic liver transplantation.

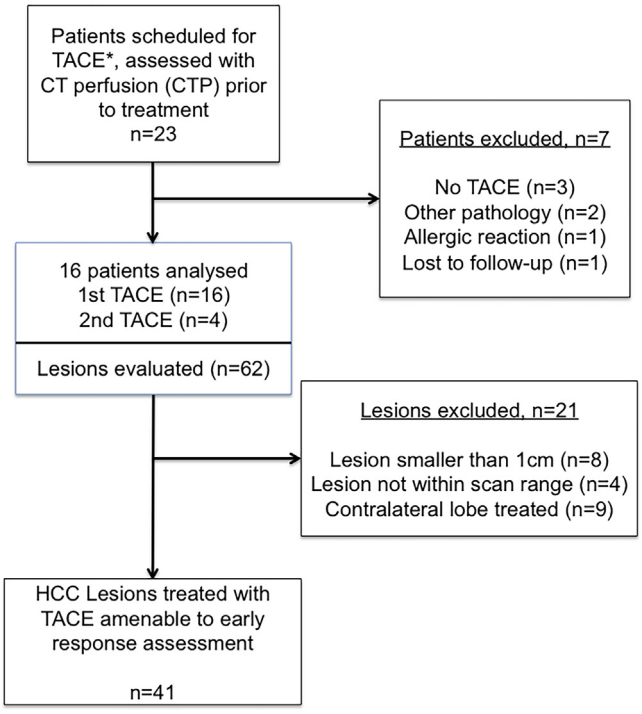

Fig. 1. Flow diagram of the patient selection process.

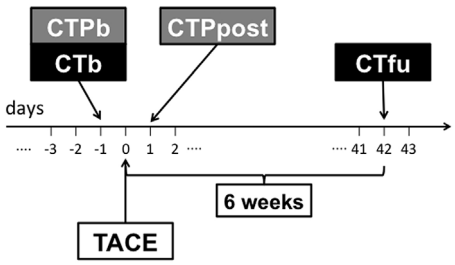

Fig. 2. Early response assessment protocol.
CTPb and CTPpost, CT-perfusion before and after TACE (index test); CTb and CTfu, staging CT before and six weeks after TACE (reference standard); TACE, transarterial chemoembolization.

2.4. CT perfusion technique

All CTP studies were performed using the same scanner (Siemens Definition Flash, 2 × 128 row dual source CT, Siemens AG, Erlangen, Germany). Initially, a non-contrast study of the upper abdomen was obtained to localize the tumour(s). The standard coverage for the 4D spiral mode in the z-axis was 10 cm. The