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Computed tomography perfusion imaging for monitoring transarterial chemoembolization of hepatocellular carcinoma

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ABSTRACT

Purpose: To prospectively monitor changes in tumor perfusion of hepatocellular carcinoma (HCC) in response to doxorubicin-eluted bead based transarterial chemoembolization (DEB-TACE) using perfusion-CT (P-CT).

Methods and materials: 24 patients (54–79 years) undergoing P-CT before and shortly after DEB-TACE of HCC were prospectively included in this dual-center study. Two readers determined arterial-liver-perfusion (ALP, mL/min/100 mL), portal-venous-perfusion (PLP, mL/min/100 mL) and the hepatic-perfusion-index (HPI, %) by placing matched regions-of-interests within each HCC before and after DEB-TACE. Imaging follow-up was used to determine treatment response and to distinguish complete from incomplete responders. Performance of P-CT for prediction and early response assessment was determined using receiver-operating-characteristics curve analysis.

Results: Interreader agreement was fair to excellent (ICC, 0.716–0.942). PLP before DEB-TACE was significantly higher in pre-treated vs non-treated lesions ($P < 0.05$). Mean changes of ALP, PLP and HPI from before to after DEB-TACE were −55%, +24% and −27%. ALP and HPI after DEB-TACE were correlating with response-grades ($r = 0.45/0.48$; both, $p < 0.04$), showing an area-under-the-curve (AUC) of 0.74 and 0.80 respectively for identification of complete response.

Conclusion: High arterial and low portal-venous perfusion of HCC early after DEB-TACE indicates incomplete response with good diagnostic accuracy.

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent form of liver cancer, representing the fifth most common cancer in men and the seventh in women worldwide [1]. Several treatment strategies have been developed to manage HCC at its different stages. Among them, transarterial chemoembolization has become the standard technique for treatment of unresectable HCC in patients with preserved liver function [2]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend TACE for Child–Pugh A and B patients with large or multifocal HCC with no cancer related symptoms, macrovascular invasion or extrahepatic invasion [3]. Median survival, which ranges around 82% in the first year after TACE treatment, has been reported to depend on lesion size [4] and liver function [5] which are thus important prognostic factors of therapy response. Modern TACE procedures consist in the application of doxorubicin eluting beads (DEB) with the ability to release the antitumoral drug in a controlled fashion, increasing local concentration and diminishing the amount of drug reaching the systemic circulation [6]. In comparison to the conventional TACE technique, which includes the application of a radio-opaque lipiodol based drug emulsion, DEB-TACE allows for visualization of tumor necrosis and direct assessment of the post-treated lesion by contrast-enhanced CT. The former standard of response analysis − response evaluation criteria in solid tumors (RECIST)

Abbreviations: HCC, hepatocellular carcinoma; DEB-TACE, doxorubicin-eluted bead based transarterial chemoembolization; P-CT, perfusion-CT; ALP, arterial liver perfusion; PLP, portal venous perfusion; HPI, hepatic perfusion index; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; HIPAA, Health Insurance Portability and Accountability Act; DEB, doxorubicin eluting beads; MIP, maximum intensity projection; ROC, receiver operating characteristic; AUC, area under the curve; ICC, intraclass correlation coefficient; RECIST, response evaluation criteria in solid tumors

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criteria − have shown significant shortcomings as changes in tumor volume did not reflect the biological reaction of tumor cells to therapy [7]. In recent years, the European Association of the Study of the Liver (EASL) therefore recommended modified RECIST criteria, which also rely on lesion vascularity in terms of contrast media uptake during the arterial phase to distinguish residual tumor from tumor necrosis [8]. Standard imaging follow-up after DEB-TACE is commonly one month or longer. However, even after this period the delineation of residual tumor versus peritumoral hyperemia or shunting is difficult, which is crucial for subsequent therapeutic planning ranging from re-treatment to wait-and-watch strategies. Accordingly, earlier assessment of treatment response by specific imaging biomarkers is highly desirable for a more personalized and faster initiation of treatment regimens.

CT perfusion (P-CT) provides quantitative information about the haemodynamic characteristics of the liver parenchyma [9] and it has shown great potential for monitoring cancer treatment [10–13]. In liver metastases, the arterial liver perfusion (ALP) has been shown to be a good biomarker for both prediction and assessment of treatment response at transarterial radio-embolization [14], whereas changes in the relation of ALP and portal-venous liver perfusion (PLP), as expressed by the hepatic perfusion index (HPI), has been shown to be valuable for response assessment ≥1 month after TACE of HCC [15]. However, the value of P-CT before and directly after TACE for early treatment response assessment − i.e. before the standard follow up at ≥1 month usually performed in clinical routine − has not yet been determined [16].

Thus, the goal of this dual-center study was to monitor changes in tumor perfusion of HCC in response to DEB-TACE and to evaluate diagnostic value of P-CT for prediction and early assessment of treatment response.

2. Materials and methods

2.1. Patients

This prospective dual-center study (Karolinska Institutet, Stockholm; University Medical Center Mannheim, Mannheim) was approved by the institutional review board of both centers and complies both with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA). Written informed consent was obtained for all participating patients prior to the first P-CT study.

Between June 2013 and February 2015 a total of 24 patients (15 men; 9 women; mean age 69 years; range, 54–79 years) with liver cirrhosis and HCC (N = 35) undergoing clinically indicated DEB-TACE were prospectively included. Patient demographics are given in Table 1.

Inclusion criteria were biopsy proven liver cirrhosis with unresectable or multinodular HCC at intermediate stage qualifying for DEB-TACE according to the Barcelona Clinic Liver Cancer (BCLC) criteria [17]. The diagnosis of HCC was imaging-based in all patients using CT in 7 patients (29%) and MRI in 17 patients (71%). Criteria for HCC was lesion size larger than 1 cm in diameter in combination with a HCC-specific enhancement pattern including arterial-enhancement and contrast wash-out and underlying liver cirrhosis as defined by the AASLD [3] and the European Association for the Study of the Liver (EASL). Lesions with atypical imaging characteristics including hypovascular HCC were accordingly excluded from the study

Further exclusion criteria were previous radiofrequency ablation of the selected lesion, or systemic (e.g. anti-angiogenetic therapy) treatment; preceding DEB-TACE treatment of the selected lesion within the last 3 months, and general contraindications for contrast-enhanced CT (pregnancy, previous hypersensitivity reaction to intravenous contrast agent, renal impairment − defined as eGFR below 45 mL/min). Lesions with atypical enhancing characteristics in the diagnosis imaging were also excluded from our data.

In all patients P-CT examinations were performed before and directly after the DEB-TACE treatment, with a mean interval of 12 ± 24.74 h (range 1–48 h) between both P-CT examinations. In case of several consecutive DEB-TACE sessions, patients were only included in the first session. In 21/24 (88%) patients one HCC was treated, whereas in the other 3/24 (12%) patients two HCC were treated with DEB-TACE at the same session. To avoid potential data clustering only the largest HCC was included in those three patients. Accordingly, 3 HCC in three patients were excluded resulting in 24 HCC in 24 patients undergoing statistical evaluation. Treatment response was assessed on routine imaging follow-up according to EASL criteria. EASL response grades include complete response (disappearance of all viable lesions), partial response (≥50% decrease in the sum of the product of bi-dimensional diameters of all viable lesions), stable disease (≥25% increase in the sum of the diameter of viable lesions) and progressive disease (any case that do not qualify for either partial response or progressive disease). In addition, patients were sub classified into complete responders (no residual tumor) and incomplete responders (residual tumor), the latter summarizing patients with partial response, stable disease and progressive disease and those patients that need to undergo further (DEB-TACE) treatment. Imaging follow-up for response assessment after DEB-TACE was successfully performed in 22/24 patients (92%) using multi-phase contrast-enhanced CT (N = 12) or, MRI (N = 10), whereas 2/24 (8%) patients were lost to follow up. The mean imaging follow-up was 47 ± 22 days (range, 24–90 days).

Table 1
Patient demographics.

Gender	
Male	15
Women	9
Mean age ± SD (range)	69.6 ± 7 (54–79)
Causes of liver cirrhosis	
Hepatitis B	2
Hepatitis C	7
Alcohol abuse	4
Hemochromatosis	1
Cryptogenic liver disease	1
Liver disease of mixed etiology	3
Previous liver treatment (not necesarily on the selected lesion)	
DEB-TACE	12
Liver surgery	3
Radiofrequency ablation	1
Mean time for follow-up in days (range)	47 ± 22 (24–90)

2.2. DEB-TACE procedure

A standard DEB-TACE protocol was used in all patients. After sedation, a catheter was introduced using femoral access and conducted through the aorta to the branch of the hepatic artery supplying blood to the tumor. Tumor feeding arteries was identified by angiogram, and a micro catheter was sub–sub segmentally placed in their lumen, where 300–500 μm DEB were finally injected. When sub–sub segmental treatment was not possible, DEB-TACE was performed at a sub segmental level. The treatment end point was determined by the complete stasis of intratumoral arteries (demonstrated by angiography) or when reaching the maximum doxorubicin dose of 150 mg. When the maximum dose was reached before complete stasis of the selected vessels, a small amount of none-drug-eluting particles (one or two sizes bigger than the previously injected beads) were injected to reach complete embolization.

2.3. Perfusion CT imaging

All patients were examined with a second-generation 64-slice dual-source CT system (SOMATOM Definition Flash, Siemens Healthcare,