G Chir Vol. 37 - n. 5 - pp. 206-210
September-October 2016

original article

Follow-up of multicentric HCC according to the mRECIST criteria: role of 320-Row CT with semi-automatic 3D analysis software for evaluating the response to systemic therapy

M. TELEGRAFO[1], G. DILORENZO[1], G. DI GIOVANNI[1], I. CORNACCHIA[1], A.A. STABILE IANORA[1], G. ANGELELLI[1], M. MOSCHETTA[2]

SUMMARY: **Follow-up of multicentric HCC according to the mRECIST criteria: role of 320-Row CT with semi-automatic 3D analysis software for evaluating the response to systemic therapy.**

M. TELEGRAFO, G. DILORENZO, G. DI GIOVANNI, I. CORNACCHIA, A.A. STABILE IANORA, G. ANGELELLI, M. MOSCHETTA

Aim. *To evaluate the role of 320-detector row computed tomography (MDCT) with 3D analysis software in follow up of patients affected by multicentric hepatocellular carcinoma (HCC) treated with systemic therapy by using modified response evaluation criteria in solid tumors (mRECIST).*

Patients and methods. *38 patients affected by multicentric HCC underwent MDCT. All exams were performed before and after iodinate contrast material intravenous injection by using a 320-detection row CT device. CT images were analyzed by two radiologists using multi-planar reconstructions (MPR) in order to assess the response to systemic therapy according to mRECIST criteria: complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD). 30 days later, the same two radiologists evaluated target lesion response to systemic therapy according to mRECIST criteria by using 3D analysis software. The difference between the two systems in assessing HCC response to therapy was assessed by the analysis of the variance (Anova Test). Interobserver agreement between the two radiologists by using MPR images and 3D analysis software was calculated by using Cohen's Kappa test.*

Results. *PR occurred in 10/38 cases (26%), PD in 6/38 (16%), SD in 22/38 (58%). Anova Test showed no statistically significant difference between the two systems for assessing target lesion response to therapy ($p > 0.05$). Inter-observer agreement (k) was respectively of 0.62 for MPR images measurements and 0.86 for 3D analysis ones.*

Conclusions. *3D Analysis software provides a semiautomatic system for assessing target lesion response to therapy according to mRECIST criteria in patient affected by multifocal HCC treated with systemic therapy. The reliability of 3D analysis software makes it useful in the clinical practice.*

KEY WORDS: HCC - Therapy - CT - Computed tomography - 3D analysis.

Introduction

Hepatocellular carcinoma (HCC) represents the first primitive hepatic malignancy, the 5th most frequent cancer among men, the 7th among women, and the 2nd cause of cancer death worldwide. Chronic liver disease due to hepatitis B virus (HBV) or hepatitis C virus (HCV) accounts for the majority of HCC cases. Minor and upcoming risk factors include alcoholic chronic liver disease, obesity, diabetes, non-alcoholic fatty liver disease (NAFLD), host genetic factors (1). HCC is classified into nodular, solitary or multicentric, and infiltrative basing on macroscopic features and into well differentiated, moderately differentiated and poorly differentiated basing on histological features (2, 3). Nodular lesions are commonly well differentiated, have an expansive growth pattern and grow slowly as compared with infiltrative forms, which are poorly differentiated and have an invasive growth pattern (2, 3).

Various types of treatment, curative and non curative have been developed and are nowadays available for HCC. Curative approaches include hepatic transplant, resection and percutaneous radiofrequency ablation (PRA) while non curative include TACE (transarterial chemoembolization), brachytherapy and systemic therapies (ormonal therapy, chemotherapy, biological and molecular therapies) (3).

The evaluation of response to treatment represents a key aspect in cancer therapy and is widely performed

[1] DIM - Interdisciplinary Department of Medicine, Section of Diagnostic Imaging, "Aldo Moro" University of Bari Medical School, Bari, Italy
[2] DETO - Department of Emergency and Organ Transplantations, University of Bari Medical School, Bari, Italy

Corresponding author: Marco Moschetta, e-mail: marco.moschetta@gmail.com

by using such imaging techniques as computed tomography (CT) and magnetic resonance imaging (MRI) (4-9). The Response Evaluation Criteria In Solid Tumors (RECIST) allow the radiologists to perform an accurate evaluation of cancer response to therapy on imaging techniques, basing on dimensional criterion; however, in case of HCC, therapy-induced response consists of the tumour necrosis which is often not accompanied by tumour shrinkage. For this reason, in 2008, American Association for the Study of Liver Diseases (AASLD) introduced modified RECIST (mRECIST) by integrating RECIST assessment with the concept of tumor viability, that is the intra-tumoral tissue showing uptake in arterial phase of contrast enhanced radiologic imaging techniques (10-17).

The aim of this study is to evaluate the role of 320-detector row computed tomography (CT) with 3D analysis software in follow up of patients affected by multicentric HCC treated with systemic therapy by using mRECIST and to compare the obtained results with measurements on MPR images.

Patients and methods

Patients and CT protocol

Between December 2012 and June 2015, 38 male patients (mean age 66; range 48-79) affected by multicentric HCC and treated with systemic therapy (Sorafenib) underwent CT examination once before and every six months after treatment. The mean duration of systemic treatment was of 13 months for a total of three CT examinations.

Our sample included patients with well-defined target lesions, accurately measured in at least one dimension as 1 cm or more and with intra-tumoral arterial enhancement on contrast-enhanced CT. Patients affected by infiltrative, ill-defined border and hypovascular HCC were excluded from our study. Institutional review board approval was obtained for our retrospective study.

CT examinations were performed by using a 320-row multi detector device (Aquilion One, Toshiba Medical Systems, Otawara, Japan), and the following acquisition parameters were used: slice thickness 0.5 mm, and increment 0.5 mm, rotation time 0.5 s; 120/200 kVp/mAs. An automatic dose modulation system was used in all cases.

Images were acquired before and after intravenous injection of iodinate contrast material (Iodixanol 320mgI/mL, Visipaque, GE Healthcare) in a quantity of 1.5 mL/kg of body weight at a flow rate of 3.5 mL/s. Scans were performed with a triphasic technique in the arterial, portal venous and delayed phases, with a mean delay respectively of 35s, 65s and 90s from the contrast material injection. The baseline CT examination included thorax.

Image analysis

CT data were transferred to and analyzed on a workstation (HPXW8600) equipped with software dedicated to image reconstruction (Vitrea FX 2.1, Vital Images, Minneapolis, MN, USA).

For each patient, two target lesions were selected on the basis of their size (those with longest diameter), were retrospectively and separately analyzed on multi-planar (MPR) images (Fig. 1A) by two radiologists with 10 years experience in the field of abdominal CT. Thirty days later, the two radiologist evaluated the same target lesions using 3D Analysis software measurements (Fig. 1B).

By using the two different measurement systems (MPR and 3D analysis) therapy response was classified, basing on mRECIST criteria, into:

- Complete Response (CR): disappearance of any arterial enhancement in all target lesions.
- Partial Response (PR): at least 30% decrease in the sum of diameters of viable (contrast-enhanced in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
- Stable Disease (SD): any cases that do not qualify for either PR or PD.

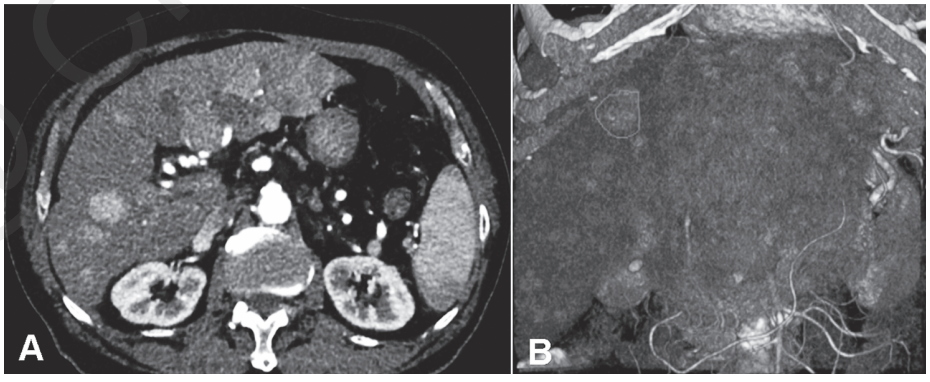

Figure 1 - Multicentric HCC. A. CT transverse scan of target lesion in the arterial phase. B. Same lesion assessed by 3D analysis software.

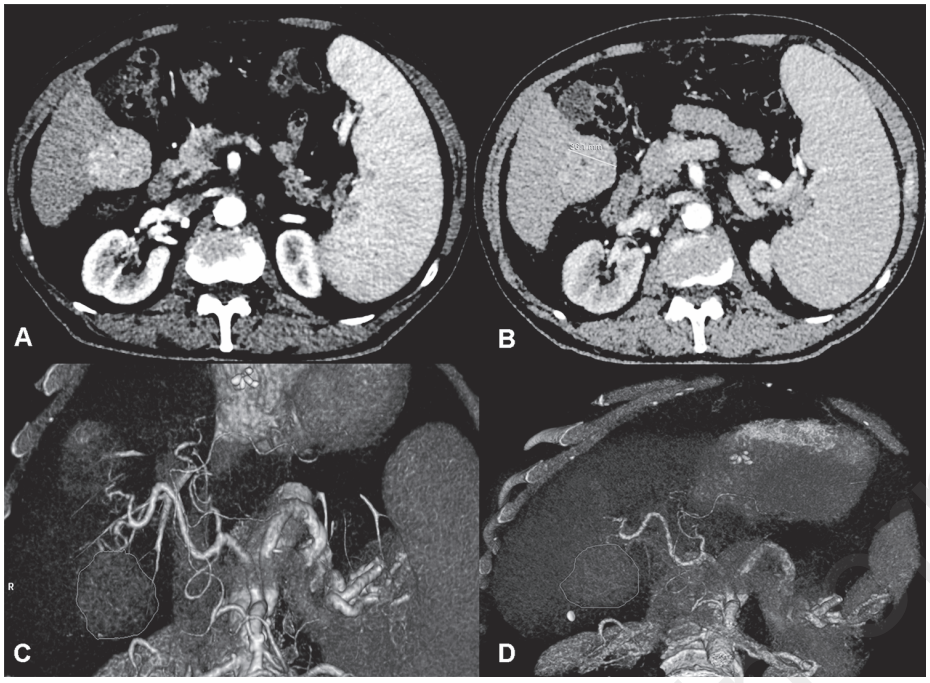

Figure 2 - A case of partial response as assessed by MPR CT images on the transverse plane (A: before treatment; B: after treatment) and by 3D analysis software (C: before treatment; D: after treatment).

- Progressive Disease (PD): increase of at least 20% in the sum of the diameters of enhanced target lesions, referred to the smallest sum of the diameters of viable target lesion since the treatment began. It corresponds to a volumetric growth of about 73% of target lesion (14).

Statistical analysis

The differences between MPR and 3D Analysis software measurement system were assessed by using the analysis of the variance (Anova Test).

Inter-observer agreement was calculated by Cohen's Kappa. Cohen's kappa (k) test was for evaluating diagnostic reliability of the two measurement system in the assessment of cancer therapy response. A k value of more than 0.81 was considered to represent near perfect agreement, and values of 0.61–0.80 and 0.41–0.60 to represent substantial and moderate agreement, respectively.

All calculations were performed using NCSS2007® statistical software.

Results

In 36 out of 38 (95%) patients, HCC affected only liver and in the remaining 2 patients cancer involved lung parenchyma (n=1) and right adrenal gland (n=1).

CT signs of cirrhosis and portal hypertension were found in all cases, ascites in 28/38 cases (74%), portal thrombosis in 22/38 cases (58%). Target lesions' mean diameter was of 1.6 cm (diameter ranging between 1 and 4 cm).

In 10/38 cases (26%) partial response (PR) (Fig. 2), in 6/38 cases (16%) progressive disease (PD), in 22/38 cases (58%) stable disease were respectively found. There were no complete responders (CR) among our patients.

The analysis of variance showed no statistical difference between the two measurement systems ($p > 0.05$). Inter-observer agreement (k) was of 0.62 for MPR images and 0.86 for 3D Analysis software, with a significant increase in semi-automatic evaluation performed with 3D Analysis software.

Discussion

The accurate evaluation of response to treatment represents a crucial aspect in HCC therapy and provides useful information in terms of patient prognosis. World Health Organization (WHO) in 1979 and National Cancer Institute in 2000 introduced Response Evaluation Criteria In Solid Tumors (RECIST) relying on lesion greatest diameter measurement for objective assessment of HCC response (10-14). Even if RECIST allow an effective evaluation of response to cytotoxic agents, they result unreliable in cases of molecular-targeted therapies or other interventional procedures which influence not only lesion size but also lesion vascularisation; these therapeutic approaches induce tumor necrosis and the extension of intra-tumoral necrosis is independent from lesion dimensions. As a result, tumour response to

systemic treatment could be underestimated (14-17). For these reasons, in 2008, American Association for the Study of Liver Diseases (AASLD) introduced modified RECIST (mRECIST) by integrating RECIST assessment with the concept of tumor viability, that is the intra-tumoral tissue showing uptake in arterial phase of contrast enhanced radiologic imaging techniques (10-17). The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response: complete response in case of disappearance of any intratumoral arterial enhancement in all target lesions; partial response in case of at least a 30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions; progressive disease in case of an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since the treatment started; stable disease in case of any cases that do not qualify for either partial response or progressive disease. Several studies demonstrated that mRECIST result more reliable criteria than RECIST, in particular in patients treated with sorafenib (10-12). In our study, the semiautomatic software 3D Analysis was applied on CT images of patients affected by multicentric hepatocellular carcinoma (HCC), treated with systemic therapy by using mRECIST. 3D Analysis software represents a semi-automatic software commonly used for the study of arterial plaque composition; in case of multicentric HCC, it provides 3D reconstructions of hyper-vascular nodules, indicating, in semi-automatic way, their volume, area and maximum diameter. In our series, we used only the HCC maximum diameter provided by 3D analysis software because it is widely reported in the medical literature that one dimensional measurement of tumour maximum diameter may be sufficient to assess change in solid tumours. The use of 3D analysis software for evaluating therapy response in HCC has shown no statistically significant difference as compared with MPR assessment with a p value of more than 0.05. However, the higher inter-observer agreement obtained by using 3D Analysis software could make it a reliable tool for objectively evaluating therapy response. In fact, the proposed software directly works on the viable portion of the target lesions providing a semiautomatic evaluation of response to therapy. The higher agreement obtained in our series could be due to the fast and objective measurements obtained by the used software as compared with the manual measurements performed on MPR images.

The obtained results are also consistent with medical literature in terms of HCC response rates to sorafenib because only in 6% of cases there was a progressive disease, meaning an increasing trend in long term survival in patients affected by HCC (12).

Our study has some limitations mainly represented by the relative small number of the enrolled patients, the limited statistical evaluation, the lack of a histological control of lesions in all cases.

Conclusions

3D analysis software provides a semiautomatic system for assessing target lesion response to therapy according to mRECIST criteria in patient affected by multicentric HCC treated with systemic therapy. The reliability of 3D Analysis software makes it useful in the clinical practice.

Conflicts of interest

All authors have no conflicts of interest nor financial or personal relationships regarding this paper.

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