CT volume of enhancement of disease (VED) can predict the early response to treatment and overall survival in patients with advanced HCC treated with sorafenib

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Abstract

Objectives To analyse the predictive value of the volume of enhancement of disease (VED), based on the CT arterial enhancement coefficient (ΔArt%), in the evaluation of the sorafenib response in patients with advanced hepatocellular carcinoma (HCC).

Methods Patients with sorafenib-treated advanced HCC, who underwent a multiphase contrast-enhanced CT before (T0) and after 60–70 days of starting therapy (T1), were included. The same target lesions utilised for the response evaluation according to modified Response Evaluation Criteria in Solid Tumors criteria were retrospectively used for the ΔArt% calculation ([HU_{arterial phase} − HU_{unenhanced phase}] / HU_{unenhanced phase} × 100). ΔArt% was weighted for the lesion volume to obtain the VED. We compared VED_{T0} and VED_{T1} values in patients with clinical benefit (CB) or progressive disease (PD). The impact of VED, ancillary imaging findings, and blood chemistries on survival probability was evaluated.

Results Thirty-two patients (25 men, mean age 65.8 years) analysed between 2012 and 2016 were selected. At T1, 8 patients had CB and 24 had PD. VED_{T0} was > 70% in 8/8 CB patients compared with 12/24 PD patients (p = 0.011). Patients with VED_{T0} > 70% showed a significantly higher median survival than those with lower VED_{T0} (451.5 days vs. 209.5 days, p = 0.032). Patients with VED_{T0} > 70% and alpha-fetoprotein_{T0} ≤ 400 ng/ml had significantly longer survival than all other three combinations. In multivariate analysis, VED_{T0} > 70% emerged as the only factor independently associated with survival (p = 0.037).

Conclusion In patients with advanced HCC treated with sorafenib, VED is a novel radiologic parameter obtained by contrast-enhanced CT, which could be helpful in selecting patients who are more likely to respond to sorafenib, and with a longer survival.

Key Points

- To achieve the best results of treatment with sorafenib in advanced HCC, a strict selection of patients is needed.
- New radiologic parameters predictive of the response to sorafenib would be essential.
- Volume of enhancement of disease (VED) is a novel radiologic parameter obtained by contrast-enhanced CT, which could be helpful in selecting patients who are more likely to respond to therapy, and with a longer survival.

Keywords Hepatocellular carcinoma · Sorafenib · Computer-assisted image analysis · Therapy · Treatment efficacy

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ΔArt%        | Arterial enhancement coefficient |
| AFP          | Alpha-fetoprotein |
| BCLC         | Barcellona Clinic Liver Cancer |
| CA           | Contrast agent |
| CB           | Clinical benefit |
| CR           | Complete response |
| HCC          | Hepatocellular carcinoma |
| HU           | Hounsfield units |
| mRECIST      | Modified Response Evaluation Criteria in Solid Tumors |
| PD           | Progressive disease |
| PR           | Partial response |

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group, although no radiologic evidence of response to therapy
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and Asia Pacific trials [5, 6], induced a modest but significant
Sorafenib HCC Assessment Randomized Protocol (SHARP)
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Introduction

Hepatocellular carcinoma (HCC) is the fourth cause of cancer
death in the world, with an increasing incidence, particularly
in Western countries [1]. Many patients present with advanced
stage disease, especially if the diagnosis is made outside of a
surveillance program [2–4]. Sorafenib is a multi-kinase inhib-
itor, which interferes with neo-angiogenesis [2]. Its use, in the
Sorafenib HCC Assessment Randomized Protocol (SHARP)
and Asia Pacific trials [5, 6], induced a modest but significant
increase in survival (3 months) with respect to the control
group, although no radiologic evidence of response to therapy
was reported [7]. Relevant side effects limit the use of this
drug [5–8], and it would be crucial to identify specific bio-
markers for therapy response prediction, currently not avail-
able, although several studies looked for computed tomogra-
phy (CT) or magnetic resonance (MR) parameters to antici-
pate the response to treatment [9–11]. The arterial enhance-
ment coefficient (ΔArt%) is a simple parameter, which pro-
vides information on the grade of tissue vascularisation by
arterial phase evaluation of a standard contrast-enhanced CT.
Choi et al [10] reported that changes in tumour vascularity
were the most specific indicators of treatment response in
patients with gastrointestinal stromal tumour on imatinib.
Smith et al [12] made similar remarks for metastatic renal cell
carcinomas on sorafenib or sunitinib. However, there are only
few reports in the context of HCC [13].

In this study, we retrospectively evaluated the possible pre-
dictive value of the volume of enhancement of disease (VED),
a new radiologic parameter based on ΔArt%, in predicting
early response to treatment and survival in a group of patients
with advanced HCC treated with sorafenib.

Materials and methods

Patients

The ethics committee of our institution approved this retro-
spective study on 27 January (ref 2016-435; OSS. 16-260).
Each patient was assigned a numerical code to ensure the
anonymity of the clinical data. Written informed consent
was obtained for sorafenib treatment and for CT scans with
contrast agent (CA) administration, according to the principles
of the Declaration of Helsinki (revision of Edinburgh, 2000).
Patients with advanced HCC followed in the hepatology divi-
sion of our hospital and treated with sorafenib between

SD Stable disease

SHARP Sorafenib HCC Assessment Randomized Protocol

VED Volume of enhancement of disease

October 2012 and May 2016 were considered. They were
diagnosed with advanced HCC (BCLC-C) according to the
European guidelines [2]. Patients underwent treatment with
sorafenib at a dose of 400 to 800 mg/day. Only patients who
had undergone contrast-enhanced CT examination before
therapy (T0) and after 60–80 days of starting treatment (T1)
the local institution were considered. Patients with less than
45 days of treatment or patients with target lesion not evaluable (e.g. nodules < 1 cm) were excluded from the study.

CT acquisition

All CT exams were performed with a standard protocol, using
a 64-row detector scanner (Somatom Sensation CT, Siemens
Medical Systems). The images were obtained in the cranial–
caudal direction with breath-hold helical acquisition. The
scanning parameters were 1.2 × 24 collimation, 120 kV
(peak), 140–240 mAs (using automated dose modulation),
5.0 mm slice thickness with a reconstruction interval of 2.0
mm, pitch 1.2 and 0.5 s gantry rotation time. All patients
received intravenous non-ionic CA (Ultrasound 370, Bayer
HealthCare Pharmaceuticals; 370 mg of iodine/1 ml), at a
volume of 1.4 ml/kg of body weight, by a bolus at 3 ml/s,
using a mechanical power injector (Medrad Stellant CT
Injection System), followed by a 40 ml saline flush through
a 20-G catheter inserted into an antecubital vein. After
unenhanced CT, the time-to-peak aortic enhancement was
evaluated by an automatic bolus tracking technique (CARE
Bolus CT, Siemens Medical Systems) to determine the opti-
mal scanning delay for the arterial phase. The single-level
monitoring low-dose scanning (20 mAs) was initiated 5 s after
CA injection, and arterial phase scanning was started automatic-
ally 15 s after the trigger threshold (increase of 120
Hounsfield units (HU)) had been reached at the level of su-
prarenal abdominal aorta. Portal venous (extended to the chest
and lower abdomen) and equilibrium-phase acquisitions were
obtained at 70 s and 180 s, respectively.

Evaluation of the response to sorafenib

The anonymised images were evaluated in consensus by
two abdominal radiologists (10-year experienced), and if
discordant, a consensus was reached through a joint re-
view with the study coordinator (30-year experienced).
Following the modified Response Evaluation Criteria in
Solid Tumors (mRECIST) criteria, the patient’s baseline
level was established, annotating the characteristic of el-
gible lesions as “target” and “non-target” [14]. Selection
criteria of the target lesion(s) were diameter > 1 cm, eas-
ily measurable and well-defined margins, with
intratumoural arterial enhancement; HCC lesions previ-
ously treated with locoregional treatments were selected
if the lesion showed a well-delineated area of viable

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tumour (at least 1 cm in longest diameter) on the arterial phase; in the presence of multiple HCC nodules, a maximum of two target lesions was selected; all other lesions or sites of disease were considered non-target lesions, including malignant portal vein thrombosis and lymph nodes detected at the porta hepatitis with short axis > 20 mm. At T1, overall patient response was a result of the combined assessment of target lesions, non-target lesions and new lesions [14]. We considered new intrahepatic lesion, the nodules ≥ 1 cm with arterial enhancement with or without washout. The appearance of one or more new lesions indicated progressive disease (PD) regardless of the result of the comparison of target and non-target lesions. For the purpose of this study, only two groups were considered: PD and clinical benefit (CB), the latter comprising complete response (CR), partial response (PR) and stable disease (SD) [14].

VED calculation

After the definition of the response to therapy, in a second session 15 days apart, the readers reviewed the images to calculate the volume of the liver target lesions, their arterial enhancement rate and the VED. If the reviewers were disagreeing, they reached a consensus through a joint review of the recorded images together with the coordinator. The same liver target lesions utilised for the assessment of response according to mRECIST criteria were used for the VED calculation. If more than two lesions were present, the largest were chosen to evaluate a quantity of disease in any case greater than 80%. The volume of the entire lesion, including necrotic areas, was calculated using OsiriX, an open-source Digital Imaging and Communications in Medicine (DICOM) viewer (Fig. 1). The degree of

![Fig. 1 VED calculation. a-d In the 2D viewer, the ROI is marked on several arterial phase images with the “closed polygon” ROI tool (from the most caudal to the most cranial part of the lesion). Selecting the “ROI/ROI volume/Generate missing ROIs,” ROIs from the slices not included in the previous selection were generated. e After adjusting the contours of the lesion, if necessary, the “ROI/ROI volume/Compute volume” tool is used to obtain the 3D reconstruction, the volume and the mean density in the arterial phase (HU arterial phase) of the selected lesion, by summing the areas of all the ROIs, both selected and generated. After this, the operator copies the ROI of each arterial phase image and pastes it on the same-level unenhanced image. So, the estimation of the mean density at unenhanced phase (HU unenhanced phase) is obtained (not shown in the figure)
arterial enhancement was assessed at T0 and T1 time points according to the following formula:

\[ \Delta Art\% = \left( \frac{(HU_{\text{arterial phase}} - HU_{\text{unenhanced phase}})}{HU_{\text{unenhanced phase}}} \right) \times 100 \]

Therefore, to weight the \( \Delta Art\% \) of each lesion for the volume of the lesion itself, the new parameter, i.e. the VED, was calculated as follows: volume lesion \( \times \Delta Art\% \) / volume lesion. While for a single target lesion \( \Delta Art\% = \text{VED} \), when two target lesions were present, to take into account the possibility of heterogeneous behaviour of them, the VED was calculated according to the following formula:

\[ \frac{(V1 \times \Delta Art\%_1 + V2 \times \Delta Art\%_2)}{(V1 + V2)} \times 100 \]

where \( V1 \) is volume lesion 1, \( \Delta Art\%_1 \) is enhancement coefficient lesion 1, \( V2 \) is volume lesion 2 and \( \Delta Art\%_2 \) is enhancement coefficient lesion 2.

The VED was calculated for each patient, both at baseline (VE\( \text{D}_{T0} \)) and after therapy (VE\( \text{D}_{T1} \)).

To evaluate the possible changes in mean enhancement of disease during sorafenib treatment, we calculated the \( \Delta \text{VED} \), applying the following formula: \( \Delta \text{VED} = \text{VE}\text{D}_{T1} - \text{VE}\text{D}_{T0} \). The patients were classified as \( \Delta \text{VED}_{(\text{pos})} \), if \( \text{VE}\text{D}_{T1} > \text{VE}\text{D}_{T0} \), and as \( \Delta \text{VED}_{(\text{neg})} \), if \( \text{VE}\text{D}_{T1} < \text{VE}\text{D}_{T0} \). Finally, we compared the volume and VED values between CB and PD patients at T0 and T1 time points. To avoid the possible reproducibility bias due to CA administration rate variation, HU arterial/unenhanced phase values of cancer-free parenchyma have been calculated from an average of 3 circular ROIs (1 cm in diameter) inserted on 3 consecutive slices on the parenchyma surrounding the lesion. So, the \( \Delta Art\% \) of the parenchyma was evaluated at T0 and T1 time points, for each patient.

Ancillary imaging findings and blood chemistries

The presence of malignant portal vein thrombosis, distant metastases and the diameter of enlarged lymph nodes were assessed in all patients. Lymph nodes located at the level of the hepatic hilum were considered as metastatic in the case of a minor axis \( > 2 \) cm [14]. The values of the alpha-fetoprotein (AFP) and other serum parameters (total bilirubin, alkaline phosphatase, platelets, gamma glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, international normalised ratio) were evaluated prior to and after therapy for CB and PD patients.

Prediction of the therapy outcome and patient survival time

Survival time was evaluated for the study population and for each patient group. We tried to detect a \( \text{VE}\text{D}_{T0} \) cutoff value that allowed us to classify the patients in CB and PD groups, with significantly different survival days. Finally, we evaluated the \( \text{VE}\text{D}_{T0} \) cutoff values, ancillary imaging findings and laboratory parameters that could influence survival.

Statistical analysis

Data were analysed using the SPSS® v.24.0 statistical analysis software (IBM Corp., 131; formerly SPSS Inc.) and Stata/IC 11 (StataCorp). For each variable, normality was evaluated using the Kolmogorov–Smirnov test. Since all the variables were not normally distributed, non-parametric tests (Mann–Whitney \( U \) test and Kruskal–Wallis statistical test for independent samples, Wilcoxon signed-rank test for correlated sample, McNemar’s test for paired proportions) were used to compare the distributions between subgroups or between subjects at T0 and T1 time points. Receiver operating characteristic (ROC) curves were used to find the best cutoff value of \( \text{VE}\text{D}_{T0} \) to discriminate CB from PD patients. The area under the ROC curve was used as predictive power of the test. For different \( \text{VE}\text{D}_{T0} \) cutoff values (from 10 to 110, in steps of 10), we evaluated patients’ survival, at T0 and T1 time points. Kaplan–Meier curves were used to graphically depict survival probabilities. Survival in different groups (\( \text{VE}\text{D}_{T0} > 70; \text{VE}\text{D}_{T0} \leq 70 \)) was compared, using the log-rank test. Moreover, given that AFP serum levels \( > 400 \text{ng/ml} \) are considered as diagnostic and specific for HCC [15], we compared the survival with the log-rank test in the following patient groups: AFP \( \leq 400 \) and \( \text{VE}\text{D}_{T0} > 70 \), AFP \( \leq 400 \) and \( \text{VE}\text{D}_{T0} \leq 70 \), AFP \( > 400 \) and \( \text{VE}\text{D}_{T0} > 70 \), AFP \( > 400 \) and \( \text{VE}\text{D}_{T0} \leq 70 \), and AFP \( \leq 400 \) and \( \text{VE}\text{D}_{T0} \leq 70 \). Univariate and multivariate linear regression analyses were used to evaluate the predictive value of VED and AFP (independent variables) for survival (outcome variable). Specifically, both independent variables were dichotomous for VED (\( > 70 \) or \( \leq 70 \)) and for AFP (\( > 400 \) or \( \leq 400 \)). For each analysis, a \( p \) value \( \leq 0.05 \) was considered statistically significant.

Results

Patients’ characteristics and evaluation of the response to treatment

Forty-eight patients with advanced HCC treated with sorafenib were initially assessed for eligibility (Fig. 2), and a total of 32 patients were included (11 patients with 1 nodule and 21 patients with 2 or more nodules). Characteristics of the 32 patients enrolled in the study are shown in Table 1. A maximum of 2 nodules was selected as target lesion for each patient, for a total of 53 nodules in 32 patients. The median duration of sorafenib therapy was 117 days (range, 45 to 255). The main adverse events during treatment were fatigue (16 patients), diarrhoea (13), hand–foot syndrome (13) and...
major worsening of liver function (3). At T1 control, the expert reader advice was required for 3 patients. No patients showed a CR, and 1 patient had a PR to therapy, with clear reduction in both size and enhancement (Fig. 3). The CB group included the latter, and 7 patients with SD. Twenty-four patients were in the PD group: ten PD patients showed a greater than 20% increase in the sum of the diameters of viable target lesions, one with 1 target lesion and 9 with 2 target lesions. In the other 14 patients, the sum of these diameters did not reach the 20% threshold as requested by mRECIST criteria to define a PD. However, in this subgroup, disease progression was due to appearance of new lesions and/or appearance or progression of neoplastic portal vein thrombosis (5 patients), lymph node involvement (5 patients) and distant metastases (4 patients).

**Tumour volume and VED**

In CB patients, we found a reduction of about 15% in mean volume, while in PD patients, a significant increase in the volume of the target lesions was found, with an average increase of about 84% (Table 2). Patients with CB had higher baseline VED values than those with PD (Fig. 4) although the significance level of this difference was only borderline, due to the high variability. However, in CB patients, the VED values at the T1 time point were significantly lower than those at T0 ($p = 0.018$) (Fig. 4). When the $\Delta VED$ parameter was analysed, all CB patients fell into the $\Delta VED_{neg}$ class, while this behaviour was observed in only 9 out of 24 (38%) patients with PD. $\Delta Art\%$ values of cancer-free parenchyma for the PD and CB groups patients did not show statistically significant differences comparing the two time points.

**Ancillary imaging findings and blood parameters**

At the T0 time point, 10 patients had portal vein thrombosis, 11 had lymph node involvement and 4 had metastases (3 with lung involvement and 1 with bone involvement). Comparing the presence/absence of the findings, no statistically

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**Table 1** Characteristics of the 32 patients enrolled in the study

| Characteristic                           | Median (IQR) or n (%) |
|------------------------------------------|-----------------------|
| Age (years)                              | 65.8 (63–78)          |
| Gender (male)                            | 25 (78.1)             |
| Aetiology of chronic liver disease       |                       |
| HCV                                       | 12 (37.5)             |
| HBV                                       | 6 (18.8)              |
| Alcohol                                   | 6 (18.8)              |
| HBV-HDV                                   | 2 (6.2)               |
| Cryptogenic                               | 2 (6.2)               |
| Primary biliary cholangitis               | 1 (3.1)               |
| Non alcoholic steatohepatitis            | 3 (9.4)               |
| Child–Pugh Score                         |                       |
| A5                                        | 11 (34.4)             |
| A6                                        | 21 (65.6)             |
| MELD Score                                | 9 (7–11)              |
| Extrahepatic spread (present)            | 4 (12.5)              |
| Lymph node involvement                   | 11 (34.4)             |
| Portal vein thrombosis                   | 10 (31.3)             |
| Duration of therapy (days)               | 180 (90–270)          |
significant differences were found between the 2 time points (Table 3). Blood parameters and their temporal trends are summarised (Table 4). Only the median values of aspartate aminotransferase were significantly different comparing the pre/post-therapy values. In PD patients, both aminotransferase and bilirubin values were significantly different.

Prediction of the response to therapy and patient survival time

To evaluate the significance of VED in the prediction of the outcome of therapy, ROC curves (Fig. 5) showed that a VED\textsubscript{T0} cutoff value of 70% had the highest sensitivity and specificity (100% and 54.2%, respectively) in discriminating CB from PD patients. Survival time from the beginning of sorafenib therapy was highly variable (from 4 months to more than 2 years), and it was significantly longer in CB vs. PD patients (\(p = 0.001\), Table 2). Separating the patients according to different cutoff values of VED\textsubscript{T0}, those with VED\textsubscript{T0} > 70% showed a significantly longer survival time than those with lower VED\textsubscript{T0} (506 ± 306 days vs. 266 ± 133 days, \(p = 0.032\); Fig. 6, Table 5). Additionally, patients with ΔVED\textsubscript{(neg)} showed a tendency to an average survival time longer than those with ΔVED\textsubscript{(pos)} (493 ± 319 days vs. 328 ± 201 days, \(p = 0.189\)). At T0, the presence of portal vein thrombosis, lymph nodes or metastases did not significantly influence survival (\(p = 0.411\), \(p = 0.327\) and \(p = 0.564\), respectively). Among blood parameters, only AFP at T0 significantly influenced survival time. Twenty-one patients with AFP\textsubscript{T0} \(\leq\) 400 ng/ml showed an average survival of 478 ± 282 days, while in 11 patients with AFP\textsubscript{T0} > 400 ng/ml, survival was 299 ± 243 days (\(p = 0.02\)). When VED\textsubscript{T0} values and AFP levels were combined, median survival was significantly longer in patients with VED\textsubscript{T0} > 70% and AFP\textsubscript{T0} \(\leq\) 400 ng/ml than in all other combinations (Fig. 6). A multivariate linear regression analysis clarified the role and the weight of the baseline VED and AFP, in predicting survival. The results showed that VED\textsubscript{T0} >

![Representative images from a 51-year-old man with advanced HCC and partial response to sorafenib.](image)

**Table 2** Volume of the target lesions at T0 and T1 time points, and survival time of the patients

|                  | T0\(^a\) \(^b\) | T1\(^a\) | \(p^a\) |
|------------------|----------------|--------|------|
| Volume (cm\(^3\)) |                |        |      |
| All (\(N = 53\)) | Mean ± SD 61.6 ± 24.4 | 96.7 ± 28.7 | < 0.001 |
|                  | Median 28.7 | 44.5   |      |
|                  | Range 0.9–1912.3 | 0.5–2572.4 |      |
| CB (\(N = 14\))  | Mean ± SD 65.3 ± 11.5 | 54.2 ± 9.1 | 0.331 |
|                  | Median 47.6 | 44.5   |      |
|                  | Range 8.1–1150.3 | 0.5–522.5 |      |
| PD (\(N = 39\))  | Mean ± SD 61.4 ± 28.7 | 112.8 ± 54.2 | < 0.001 |
|                  | Median 22.4 | 54.2   |      |
|                  | Range 0.9–1912.3 | 0.9–2572.4 |      |
| Survival time (days) |                |        |      |
| All (\(N = 32\)) | Mean ± SD 416.3 ± 279.0 |        |      |
|                  | Median 325.5 |        |      |
|                  | Range 116–1166 |        |      |
| CB (\(N = 8\))   | Mean ± SD 687.2 ± 351.3 |        |      |
|                  | Median 817.5 |        |      |
|                  | Range 180–1166 |        |      |
| PD (\(N = 24\))  | Mean ± SD 326.0 ± 182.5 |        |      |
|                  | Median 289.5 |        |      |
|                  | Range 116–792 |        |      |

\(CB\) clinical benefit, \(PD\) progressive disease

\(^a\) For volumes: Mann–Whitney \textsubscript{U} test for the independent samples (CB vs. PD): \(p = 0.391\) and \(p = 0.558\)

\(^b\) For survival time: Mann–Whitney \textsubscript{U} test for the independent samples (CB vs. PD): \(p < 0.001\)

\(^c\) Wilcoxon signed-rank test for the paired samples (T0 vs. T1 values)
70% predicts a longer survival ($\beta = 209.6; p = 0.037$), while AFP lost its predictive role ($p = 0.216$).

**Discussion**

After its approval in 2008, sorafenib remained the only first-line treatment for advanced HCC, until the recent approval of lenvatinib [16]. Clinical experience accumulated during these years [17–19] indicates that sorafenib improves overall survival of patients with HCC, in the absence of objective response, and that tumour progression is better used as a surrogate of survival. However, to achieve the best results with sorafenib treatment of advanced HCC, a strict selection of patients is needed. Therefore, considerable efforts have been made to identify baseline factors that could predict the response to sorafenib. Minor advances were made with a few biohumoral factors weakly associated with a good response to therapy, while no molecular markers of response were identified [20–22]. Patients undergoing sorafenib therapy are often elderly, and the therapy is associated with important side effects, yet affording a limited survival advantage over untreated patients.

In this study, we identified the VED, a parameter based on the degree of arterial enhancement of HCC nodules, weighed by the volume of the target lesion(s), as a relevant factor in the

**Table 3** Presence of portal vein thrombosis, lymph nodes and metastases, at T0 and T1 time points

| Accessory imaging          | T0, N (%) | T1, N (%) | p (McNemar’s test for paired proportions) |
|---------------------------|-----------|-----------|-----------------------------------------|
| All patients              |           |           |                                         |
| Portal vein thrombosis    | 10 (31.3) | 12 (37.5) | 0.500                                   |
| Lymph nodes               | 11 (34.4) | 13 (40.6) | 0.500                                   |
| Metastases                | 4 (12.5)  | 6 (18.8)  | 0.500                                   |
| CB patients               |           |           |                                         |
| Portal vein thrombosis    | 2 (25)    | 2 (25)    | 1.000                                   |
| Lymph nodes               | 3 (37.5)  | 3 (37.5)  | 1.000                                   |
| Metastases                | 0         | 0         | 1.000                                   |
| PD patients               |           |           |                                         |
| Portal vein thrombosis    | 8 (33.3)  | 10 (41.7) | 0.500                                   |
| Lymph nodes               | 8 (33.3)  | 10 (41.7) | 0.500                                   |
| Metastases                | 4 (16.7)  | 6 (25)    | 0.500                                   |

*CB* clinical benefit, *PD* progressive disease
prediction of the response to sorafenib. Several data from our study support the potential utility of this new parameter in the management of patients with HCC. We observed that CB patients tended to have a higher mean VED at baseline and a significant decrease in VED was found at the T1 time in CB patients, as compared with PD, suggesting that a positive outcome of sorafenib therapy is associated with a reduction in this parameter. Importantly, all CB patients fell in the group with higher VEDₜₒ, i.e. > 70%. These data are strongly supported by the analysis of survival in the different groups. In fact, median survival in the VEDₜₒ > 70% group was almost twice longer than that in patients with lower VED as baseline. In contrast, none of the patients with a VEDₜₒ ≤ 70% had a CB from sorafenib therapy. Therefore, this parameter might be especially useful to identify the patients who are not likely to respond, characterised by low basal VED. Conversely, among patients with VEDₜₒ > 70%, 12 out of 20 still did not respond to treatment.

Our results support the hypothesis that low-vascularised HCC nodules are poorly sensitive to sorafenib therapy. This assumption is biologically plausible based on the pharmacological properties of sorafenib,

Table 4  Blood parameters at T0 and T1 time points

|              | T0          | Median | Range       | T1          | Median | Range       | p*         |
|--------------|-------------|--------|-------------|-------------|--------|-------------|------------|
|              | Mean ± SD   |        |             | Mean ± SD   |        |             |            |
| All          |            |        |             |            |        |             |            |
| AFP          | 26,127.1 ± 122,419.9 | 32.3   | 0.9–695,203 | 8539.0 ± 19,161.7 | 25.7   | 2–73,604.2  | 0.213      |
| BLR          | 1.3 ± 0.7   | 1.29   | 0.37–2.92   | 1.8 ± 1.4   | 1.17   | 0.06–6.2    | 0.079      |
| ALP          | 165.8 ± 87.0 | 132.5  | 64–432      | 190.3 ± 101.1 | 167.0  | 53–480      | 0.299      |
| PLT          | 155,687.5 ± 115,830.6 | 112,000 | 51,000–587,000 | 153,843.7 ± 115,739.7 | 105,000 | 47,000–569,000 | 0.891      |
| GGT          | 187.3 ± 147.4 | 132    | 40–648      | 205.4 ± 148.0 | 160.5  | 40–589      | 0.334      |
| ALT          | 52.4 ± 23.4 | 52     | 10–103      | 71.8 ± 84.3 | 55     | 15–504      | 0.072      |
| AST          | 78.6 ± 38.8 | 71.5   | 27–209      | 119.6 ± 115.3 | 77     | 2–544       | 0.042      |
| INR          | 1.3 ± 0.4   | 1.17   | 0.9–3       | 1.3 ± 0.5   | 1.16   | 0.9–3.44    | 0.750      |
| CB           |            |        |             |            |        |             |            |
| AFP          | 87,324.9 ± 245,622.6 | 17.6   | 0.9–695,203 | 247.6 ± 5614.6 | 17.7   | 2–16,013    | 0.463      |
| BLR          | 1.4 ± 0.7   | 1.4    | 0.6–2.7     | 1.1 ± 0.6   | 1.0    | 0.4–2.1     | 0.092      |
| ALP          | 184.2 ± 105.7 | 151    | 98–432      | 162.7 ± 68.3 | 163.5  | 53–277      | 0.484      |
| PLT          | 186,500 ± 104,793.7 | 176,000 | 59,000–337,000 | 138,500 ± 119,734.2 | 99,000 | 47,000–426,000 | 0.093      |
| GGT          | 207.4 ± 143.4 | 141.5  | 81–502      | 199.5 ± 149.9 | 166    | 67–538      | 0.866      |
| ALT          | 54.1 ± 22.3 | 55     | 30–103      | 63.2 ± 25.8 | 59.5   | 34–98       | 0.161      |
| AST          | 75.6 ± 25.9 | 72     | 1.1–1.3     | 69.9 ± 20.7 | 70.5   | 38–111      | 0.362      |
| INR          | 1.2 ± 0.1   | 1.2    | 1.1–1.3     | 1.2 ± 0.1   | 1.2    | 1–1.4       | 0.673      |
| PD           |            |        |             |            |        |             |            |
| AFP          | 5727.8 ± 100,052.5 | 44.4   | 3.6–32,701  | 10,559.8 ± 21,638.9 | 40.5   | 3.8–73,604.2 | 0.230      |
| BLR          | 1.2 ± 0.7   | 1.2    | 0.37–2.92   | 2.0 ± 1.5   | 1.4    | 0.06–6.17   | 0.018      |
| ALP          | 159.3 ± 81.5 | 126    | 64–375      | 199.4 ± 109.5 | 167.5  | 60–480      | 0.107      |
| PLT          | 145,416.7 ± 119,586.2 | 101,500 | 51,000–587,000 | 158,958.3 ± 116,544.6 | 114,000 | 50,000–569,000 | 0.254      |
| GGT          | 180.6 ± 151.1 | 132    | 40–648      | 207.3 ± 150.6 | 160.5  | 40–589      | 0.273      |
| ALT          | 51.8 ± 24.2 | 49     | 10–96       | 74.7 ± 96.6 | 55     | 15–504      | 0.244      |
| AST          | 79.6 ± 42.6 | 71.6   | 27–209      | 136.1 ± 129 | 109    | 2–544       | 0.010      |
| INR          | 1.3 ± 0.4   | 1.1    | 0.9–3       | 1.3 ± 0.5   | 1.1    | 0.9–3.44    | 0.395      |

*Wilcoxon signed-rank test for the correlated sample
whose main mechanism of action is the reduction of neo-angiogenesis, inhibiting the activity of vascular endothelial and platelet-derived growth factors [23]. In the treatment of other neoplastic diseases, high expression of these factors and/or increased activity of their cognate receptors makes the drug more likely to be effective [24–27]. Thus, a high pre-therapy VED may be viewed as a proxy for a high pro-angiogenic activity targeted by sorafenib. In agreement, CB patients had a significant reduction in VED at T1.

Our study also provides additional evidence for the negative prognostic role of AFP elevation [28]. In fact, patients with AFP > 400 ng/ml had a significantly shorter survival than the others. Combining the VED and AFP values at T0 allowed us to stratify the patients, where those with VED$_{T0}$ > 70% and AFP$_{T0}$ < 400 ng/ml were more likely to respond, showing an average survival of 17 months (vs. less than 10 months of the other groups) (Fig. 6).

The VED parameter is non-invasive, economic, fast and easy to calculate in standard CT acquisitions, even without specific hardware and software, and it could provide a semi-quantitative and reliable evaluation of the volume of the disease and its perfusion. The reproducibility of VED computation is influenced by various factors, such as the concentration, amount and flow rate of CA administered, in association with the characteristics of each patient, mainly cardiac function. Therefore, it is important to underline that in our study, the dynamic CT was acquired with the bolus tracking technique to ensure that enhanced phases were as comparable as possible among patients. The lack of statistically significant variation of the $\Delta$Ar% value in the non-focal parenchyma at T0 and T1 time points supports the high reproducibility of this method.

The possible predictive role of MR diffusion and perfusion techniques in sorafenib-treated patients was evaluated [29–36]. Perfusion CT allows quantitative analysis of various parameters related to the micro-vascularisation of a neoplasm [37–39] and seems able to disclose significant differences between tumour tissue and surrounding parenchyma [30, 40]. However, perfusion CT is poorly reproducible and requires a software program which is not widely available, and the radiation dose administered is considerably higher than that of standard CT acquisitions. Also, dynamic contrast-enhanced ultrasound was investigated in evaluating the effectiveness of anti-angiogenic drugs on tumour perfusion in patients with HCC with encouraging results [41–45].

Some limitations of this study should be acknowledged. Firstly, the patients are few, and extension of these results to a larger series is warranted; however, each one was followed till his death. Also, the study has been conducted in a single centre, and reproducibility in other non-specialised facilities should be assessed. Then, to classify CB vs. PD patients, we could not use LI-RADS v2018 (not dealing with the evaluation of the response to systemic treatment). Thus, we chose mRECIST [14], even if we were conscious of some bias related to these criteria (non-volumetric evaluation, non-percentage assessment of the enhancement, incomplete evaluation reliability for systemic therapy) [8, 14, 16, 46–49], and that a revision of this system has been recently published by the same authors [50]. Furthermore, in this series, the VED was calculated for a maximum of 2 target lesions, which accounted for more than 80% of the overall disease burden. It should be pointed out that VED measurement may be difficult in some patients, especially when multifocal and infiltrative disease, with poor margins and different degrees of enhancement, is present. Finally, although all patients have been investigated with the same protocol and the same CT scanner, the retrospective nature of our work is an additional weakness.

In conclusion, this study identified the VED as a novel parameter obtained by a standard CT, which could be helpful, if confirmed by larger series in a prospective fashion, in predicting the response to treatment, identifying patients who are less likely to respond to sorafenib.
Fig. 6 Survival analysis. Kaplan–Meier plots by the level of VED T0 (> 70, ≤ 70) (a) and by the level of AFT (> 400, ≤ 400) and VED T0 (> 70, ≤ 70) (b). For a, log rank (Mantel–Cox) = 0.007, Breslow (generalised Wilcoxon) = 0.024 and Tarone–Ware = 0.013. For b, log rank (Mantel–Cox) = 0.030, Breslow (generalised Wilcoxon) = 0.019 and Tarone–Ware = 0.024. In particular, survival time (mean) is as follows: if VED T0 > 70% and AFT T0 ≤ 400 ng/ml, 582 days, and AFT T0 > 400 ng/ml, 208 days; and if VED T0 ≤ 70% and AFT T0 ≤ 400 ng/ml, 213 days, and AFT T0 > 400 ng/ml, 213 days.

Table 5 Survival time by different cutoff values of VED, at T0 and T1 time points

| VED cutoff values | T0              | T1              |
|-------------------|-----------------|-----------------|
|                   | N               | Survival time (mean ± SD) | p* | N               | Survival time (mean ± SD) | p* |
| > 110             | 13              | 469.1 ± 342.1 | 0.791 | 10              | 293.3 ± 122.3 | 0.269 |
| ≤ 110             | 19              | 380.2 ± 229.5 | 0.667 | 22              | 472.3 ± 313.1  | 0.366 |
| > 100             | 14              | 463.9 ± 329.3 | 0.478 | 12              | 335.7 ± 208.8  | 0.261 |
| ≤ 100             | 18              | 379.3 ± 236.1 | 0.478 | 20              | 464.7 ± 308.5  | 0.366 |
| > 90              | 15              | 471.7 ± 318.8 | 0.478 | 17              | 345.8 ± 206.0  | 0.261 |
| ≤ 90              | 17              | 367.5 ± 237.8 | 0.478 | 15              | 496.3 ± 333.1  | 0.366 |
| > 80              | 18              | 485.3 ± 309.5 | 0.180 | 22              | 346.6 ± 218.7  | 0.060 |
| ≤ 80              | 14              | 327.7 ± 213.1 | 0.478 | 20              | 509.7 ± 344.3  | 0.060 |
| > 70              | 20              | 506.5 ± 306.2 | 0.032 | 24              | 387.8 ± 251.6  | 0.334 |
| ≤ 70              | 12              | 266.0 ± 133.9 | 0.032 | 8               | 502.0 ± 354.3  | 0.334 |
| > 60              | 22              | 491.5 ± 295.3 | 0.018 | 26              | 411.1 ± 288.2  | 0.588 |
| ≤ 60              | 10              | 250.9 ± 142.7 | 0.018 | 6               | 439.0 ± 257.8  | 0.588 |
| > 50              | 28              | 442.5 ± 287.1 | 0.169 | 26              | 411.1 ± 288.2  | 0.588 |
| ≤ 50              | 4               | 233.5 ± 107.9 | 0.169 | 6               | 439.0 ± 257.8  | 0.588 |

*Mann–Whitney U test for the independent samples
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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Stefano Colagrande.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise (Chiara Lorini, Department of Health Science, University of Florence).

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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