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Volumetric Analysis of Hepatocellular Carcinoma After Transarterial Chemoembolization and its Impact on Overall Survival

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Abstract. *Background/Aim: To evaluate the prognostic value of Response Evaluation Criteria In Solid Tumors (RECIST), modified RECIST and volumetric analysis in patients with hepatocellular carcinoma (HCC) treated by transarterial chemoembolization (TACE). Patients and Methods: This single-center prospective cohort study included a total of 61 patients with HCC treated by transarterial chemoembolization (TACE). The response of TACE was evaluated on preprocedural and postprocedural CT by two radiologists using RECIST/mRECIST and volumetric response to treatment. Each response assessment method was used to classify the response as progressive disease, stable disease, partial response and complete response. Kaplan-Meier analysis with log-rank test was performed for each method to evaluate its ability to help predict overall survival and progression free survival. Interobserver variability and reproducibility was determined by the Pearson and Spearman correlation coefficients. Results: The median overall survival was 17.1 months and the median progression-free survival was 11.1 months. Volumetric assessment was proved to be a prognostic factor for overall survival ($p<0.01$) and progression-free survival ($p<0.001$), contrasting with RECIST and mRECIST. All three methods featured very small interobserver variability ($p<0.001$ for Pearson and Spearman correlation coefficients). The patients classified as having stable disease had a 3.8-fold higher risk of death than the patients classified as having a complete/partial response (HR=3.82; 95% Confidence Interval (CI)=1.32-11.02; p=0.013) and a 4.5-fold higher risk of progression (HR=4.46; 95% CI=1.72-11.61; p=0.002). Conclusion: The prognostic value of volumetric analysis in patients with HCC treated by TACE appears to be superior to RECIST and mRECIST, with a real impact in everyday practice.*

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With more than 500,000 new cases diagnosed each year, hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and it is the third leading cause of cancer-related deaths. Chronic liver disease is the strongest risk factor for HCC; the most frequent causes are viral hepatitis (B and C) and alcohol abuse (1). HCC has a very poor prognosis due to minimal specific symptoms in the early stages of the disease. More than 60 % of patients are diagnosed with late-stage metastatic disease (2) with an overall 5-year survival rate <16% (3). According to the guidelines of the American Association for the Study of Liver Disease, one of the recommended therapies for unresectable intermediate HCC [Barcelona clinic liver cancer (BCLC) Stage B, multifocal HCC, or large carcinoma with no vascular invasion nor extra-hepatic metastasis and with a Child-Pugh score of A/B] is transarterial chemoembolization (TACE) (4, 5).

The standard criteria for evaluation of HCC response to treatment are still the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified Response Evaluation Criteria in Solid Tumors (mRECIST) (6-8). Their limitations, such as not differentiating necrosis from the viable part of tumor in RECIST (9) and unidimensional evaluation of irregularly shaped lesions in mRECIST, are well known (10-12). Such complexity is very commonly encountered after targeted therapy, *e.g.* transarterial chemoembolization (TACE).

New possibilities such as three-dimensional volumetric analysis or CT-perfusion were developed with advances in modern computer technologies (13, 14). Volumetric analysis can differentiate all the viable from the nonviable parts within a tumor. It facilitates volume calculation of the entire viable portion while disregarding the complexity of a lesion (Figure 1). Recent studies (15, 16) suggest that interobserver variability is smaller compared to the standard criteria.

As of now, published research articles still diverge over the correlation of the standard criteria with overall survival (OS) when assessing response to treatment. There is no apparent consensus; some authors have shown this reciprocity (17, 18), while others (19, 20) did not demonstrate a statistically significant relationship between RECIST and/or mRECIST and OS. In this regard, the aim of this study is to examine whether volumetric analysis is a predictive factor for OS and progression-free survival (PFS). The secondary aim is to determinate the interobserver variability of this method.

Table I. *Basic characteristics of patients (n=61) - categorical data.*

Characteristics	Category	n	%
Child-Pugh score	A	47	77.0%
	B	9	14.8%
	C	5	8.2%
Type of cirrhosis	No cirrhosis	12	19.7%
	Toxonutritive hepatitis	21	34.4%
	Hepatitis C	9	14.8%
	Other*	19	31.1%
Total of TACE undergone	1	11	18.0%
	2	15	24.6%
	3	9	14.8%
	4	8	13.1%
	5 and more	18	29.5%
RECIST	CR+PR	11	18.0%
	SD	32	52.5%
	PD	18	29.5%
mRECIST	CR+PR	32	52.5%
	SD	19	31.1%
	PD	10	16.4%
Volumetric analysis	CR+PR	21	34.4%
	SD	29	47.5%
	PD	11	18.0%
Sorafenib	No	43	70.5%
	Yes	18	29.5%

*Hepatitis A, hepatitis B, primary biliary cirrhosis, unknown or combined etiology. CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Patients and Methods

Study design. This cohort prospective study was reviewed and approved by the Ethics Committee of the University Hospital Brno. It is registered with ClinicalTrials.gov, using identifier NCT04780789.

673 TACE procedures were performed on 230 patients at the University Hospital Brno from February 2016 to December 2020. The study population included 61 adult patients (52 men, 9 women) diagnosed with HCC. All patients were treated by at least one session of TACE with drug-eluting beads DC Bead™ (Biocompatibles UK Ltd, a BTG group company, Farnham, UK). Patients were not required to give informed consent for this study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. The date of the first chemoembolization performed is established as the baseline for overall survival. The basic characteristics of the patients are summarized in Table I.

The inclusion criteria were: diagnosis of HCC by a radiologist according to the European Association for the Study of the Liver (EASL) criteria or confirmed histologically, at least one TACE undergone at the University Hospital Brno, initial/ follow-up CT (Brillance 64, Philips, Netherlands; contrast enhancement 125 mL Iomeron 400, Bracco, Germany), and follow-up on or before December 31, 2020.

TACE. The treatment management of all patients was approved by the Multidisciplinary Tumor Board at the University Hospital Brno. A consistent process was followed in accordance with our standard institutional protocol. TACE was performed under local anaesthesia *via* the common femoral artery using a 5F sheath. Iodine contrast agent (Xenetix350, Guerbet, France) was used to visualize the arteries. Catheterization of the coeliac trunk and arteries supplying the liver was then performed under fluoroscopic guidance. A pathological vascularization pattern was identified and chemoembolization material consisting of DC beads was injected by the performing physician superselectively using 2.4F-2.8F microcatheters (Renegade, Boston Scientific). DC beads were successively applied during a 20-30 min period and control visualization with contrast agent was made approximately every 5 min. The punction point was treated by a closing device (MynxGrip, Cardinal Health). The procedure was repeated after 4 weeks if necessary according to a follow-up CT which was performed after 1-3 TACE sessions according to the extent of the lesion, 3 weeks after the last procedure. Patients with complete response were scheduled for an imaging follow-up every 3 months, allowing evaluation of the effect of treatment. In case of response to the treatment, another session of TACE was indicated. Chemoembolization sessions were performed as inpatient procedures, with a mean hospitalization time of 4 days.

Methods of assessing response to treatment. All measurements using RECIST, mRECIST and volumetric analysis were completed by two independent radiologists (a resident with 4 years of experience and a board-certified radiologist with 10 years of experience) employing the computer program Portal Intellispace v5.0 (Philips, Amsterdam, Netherlands) with semi-automatic slice-based segmentation for

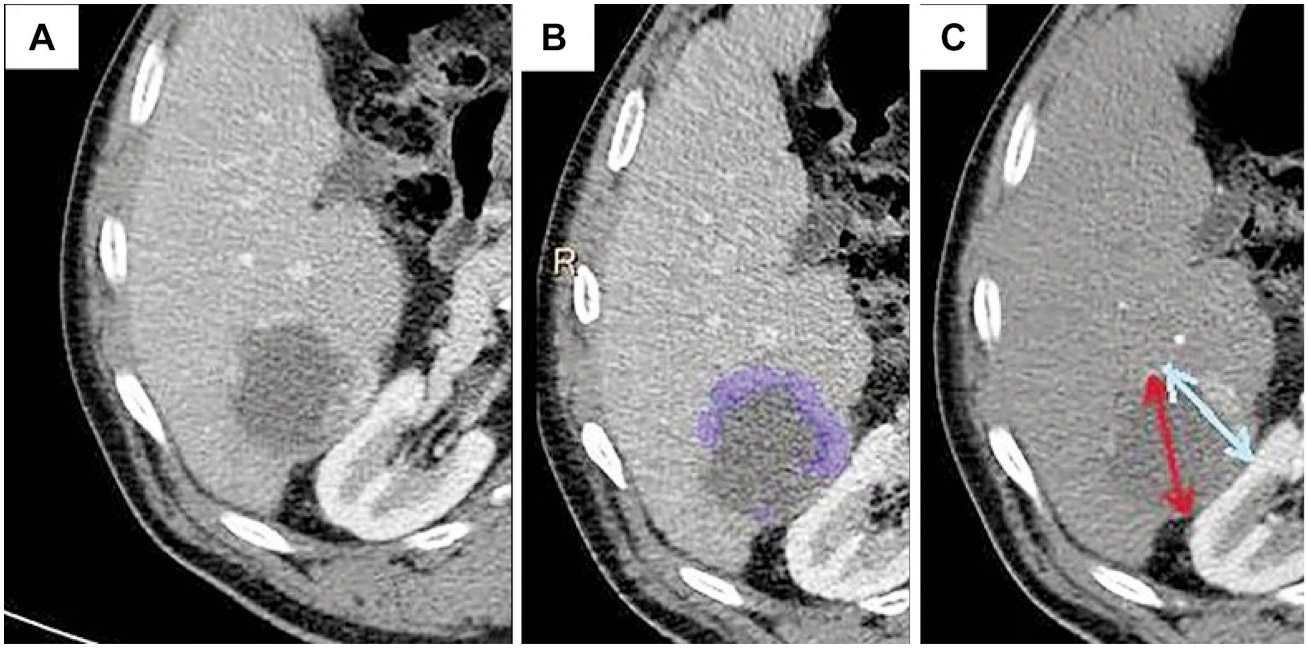

Figure 1. *Hepatocellular carcinoma after a single session of TACE. (A) CT scan 3 weeks after the procedure. (B) Measurement using volumetric analysis. (C) Measurement using RECIST (red arrow) and mRECIST (blue arrow).*

Table II. *Assessment of target lesion response: RECIST and mRECIST assessment for HCC (6) and volumetric assessment for HCC (7).*

	RECIST	mRECIST for HCC	Volumetric assessment
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions	Disappearance of all target lesions
PR	At least a 30% decrease in the sum of target lesions diameters, taking the sum of the diameters as reference	At least a 30% decrease in the sum of viable (enhancement in the arterial phase) target lesions diameters, taking the sum of the diameters as reference	Volume of all target lesions decreased by more than 65% and no new lesions
SD	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
PD	At least a 20% increase in the sum of target lesions diameters, taking as reference the smallest sum detected since treatment initiation	At least a 20% increase in the sum of viable (enhancing) target lesions diameters, taking as reference the smallest sum detected since treatment initiation	Volume increase of at least 44%

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

volumetric analysis. The evaluation was performed on the initial (prior the first TACE) contrast enhanced CT scans and all the follow-up scans. The variability between the two examiners was evaluated using the mean of differences between the measurements with the associated 95% limits of agreement. Correlation coefficients (Pearson, Spearman) are supplied to evaluate the reproducibility of the measurement.

The total volume of lesions and the volumes of their viable parts (enhancing with minimum difference of 25 HU) were measured from 5mm reconstructed slices. The viable portion/ total volume ratio was calculated as a potential factor of response to treatment. The best response to treatment was determined as the lowest volume achieved. Tumor response to treatment was categorized into four groups according to RECIST, mRECIST 1.1, and the final volume of the viable portion (Table I, Table II). The cut-off values for volumetric assessment were determined by extrapolation of RECIST, *i.e.* extrapolation of the diameter of a lesion to the volume of an ideal lesion of a regular spherical shape (7). Considering the size of tumor measured using RECIST a diameter r, we use it to calculate the spherical volume of the lesion $V=(4/3)\pi r^3$. For example, if the measured diameter decreases by 30%, an extrapolated spherical volume reduces by 65%.

Statistical analysis. Standard statistics were used in the descriptive analysis of the patients. Categorical variables were described by absolute and relative frequencies. The mean supplemented by 95% confidence interval, median, and range were taken as continuous variables.

Table III. *Evaluation of overall survival (OS) by individual factors – categorical data.*

Characteristics	Category	OS after TACE			
		n	Mean of survival months (95% CI)*	HR (95% CI)	*p*-value
All patients	-	61	17.1 (11.6; 21.8)	–	–
RECIST	CR+PR	11	34.4 (17.0; -)	–	–
	SD	32	14.4 (9.9; 23.1)	2.42 (0.82; 7.10)	0.108
	PD	18	11.7 (5.0; 20.6)	2.98 (0.97; 9.20)	0.058
mRECIST	CR+PR	32	20.6 (14.4; 30.5)	–	–
	SD	19	9.2 (6.8; 36.3)	1.56 (0.73; 3.33)	0.249
	PD	10	14.4 (2.2; 20.7)	1.25 (0.54; 2.89)	0.602
Volumetricanalysis	CR+PR	21	51.7 (17.0; -)	–	–
	SD	29	11.8 (9.2; 21.8)	3.82 (1.32; 11.02)	**0.013**
	PD	11	11.7 (2.4; 20.7)	5.94 (1.83; 19.26)	**0.003**
Sorafenib	No	43	17.0 (10.2; 23.1)	–	–
	Yes	18	20.3 (8.5; 23.8)	0.89 (0.46; 1.72)	0.719

*95% CI could not be evaluated in some cases (marked as -). Bold values denote statistical significance.

Table IV. *Evaluation of progression free survival (PFS) by individual factors – categorical data.*

Characteristics	Category	PFS after TACE			
		n	Mean of PFS months (95% CI)*	HR (95% CI)	*p*-value
All patients	-	61	11.1 (8.4; 14.6)	–	–
RECIST	CR+PR	11	16.9 (9.0; 46.4)	–	–
	SD	32	11.1 (6.4; 21.7)	1.81 (0.73; 4.46)	0.201
	PD	18	9.5 (2.9; 11.3)	2.57 (0.99; 6.68)	0.053
mRECIST	CR+PR	32	14.4 (9.0; 23.7)	–	–
	SD	19	8.0 (2.5; 11.7)	1.82 (0.91; 3.65)	0.091
	PD	10	10.6 (2.2; 14.8)	1.57 (0.73; 3.41)	0.252
Volumetric analysis	CR+PR	21	41.0 (14.6; -)	–	–
	SD	29	9.0 (6.1; 11.5)	4.46 (1.72; 11.61)	**0.002**
	PD	11	7.9 (2.2; 11.3)	7.00 (2.40; 20.40)	**<0.001**
Sorafenib	No	43	14.3 (9.0; 16.9)	–	–
	Yes	18	9.6 (5.4; 11.5)	1.24 (0.67; 2.32)	0.492

*95% CI could not be evaluated in some cases (marked as -). Bold values denote statistical significance.

OS and PFS following TACE (considering the date of the first TACE as the baseline) were visualized using the Kaplan-Meier methodology. Statistical significance of difference in survival among groups of the patients was tested by the log-rank test. The univariate Cox proportional hazards models were used and relationships between OS and PFS and other factors (both continuous and categorical) were described by the hazard ratio (HR) with 95% confidence interval (CI). Although continuous variables were initially evaluated as continuous, they were then divided into binary variables while taking median as threshold. The measurements of the more experienced radiologist were used in the analyses. The level of statistical significance in all analyses was p=0.05. All alternative hypotheses were two-sided. The analyses were performed using IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA).

Results

Overall survival. The evaluation of OS by individual factors is summarized in Table III. Mean OS of all the patients was 17.1 months (95% CI=11.6-21.8 months). However, statistical significance of correlation with OS has only been proved for the assessment by volumetric analysis (p=0.005*)*: The patients classified as SD had a 3.8-fold higher risk of death than the patients classified as CR/ PR (HR=3.82; 95% CI=1.32-11.02; p=0.013) and the patients classified as PD had a 5.9-fold higher risk of death than the patients classified as CR/ PR (HR=5.94; 95% CI=1.83-19.26; p=0.003). The median OS was 51.7 months (17.0, – still alive) for the CR/ PR group,

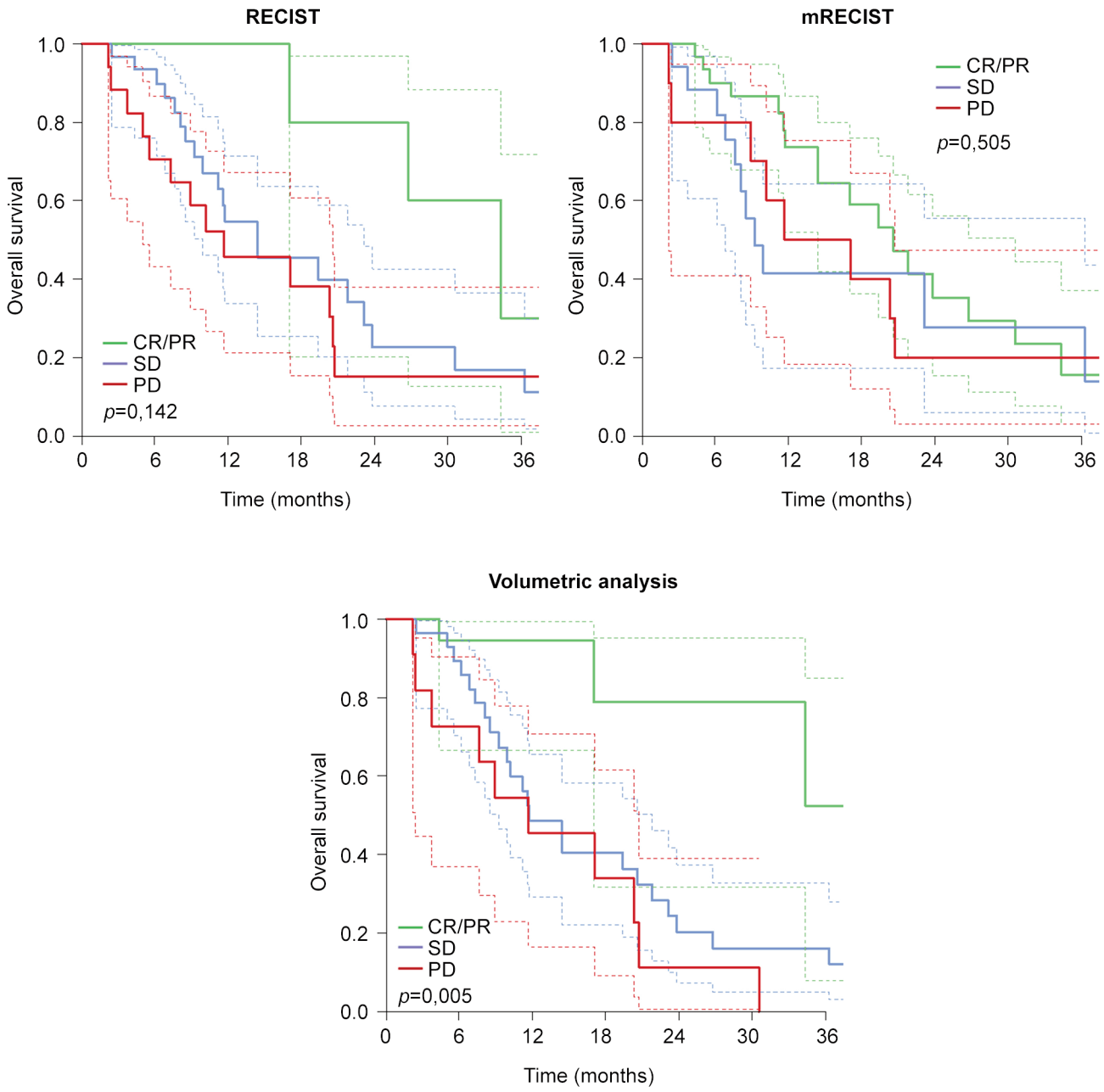

Figure 2. *Bland and Altman plots showing the means and differences between measurement 1 and 2.*

11.8 months (9.2-21.8) for the SD group, and 11.7 months (2.4-20.7) for the PD group. RECIST and mRECIST showed no correlation with OS (Figure 2; p=0.142 and 0.505, respectively). Neither of the other monitored parameters proved to correlate with OS, nor did they correlate with PFS at the level of statistical significance.

Progression free survival. The evaluation of PFS by individual factors is summarized in Table IV. PFS of all the patients was 11.2 months (95% CI=8.4-14.6 months). Statistical significance of correlation with PFS has only been shown for volumetric assessment (Figure 3, p<0.001). The patients classified as SD had a 4.5-fold higher risk of progression than the patients classified as CR/ PR (HR=4.46; 95% CI=1.72-11.61; p=0.002) and the patients classified as PD had a 7-fold higher risk of progression than the patients classified as CR/ PR (HR=7.00; 95% CI=2.40-20.40; p<0.001).

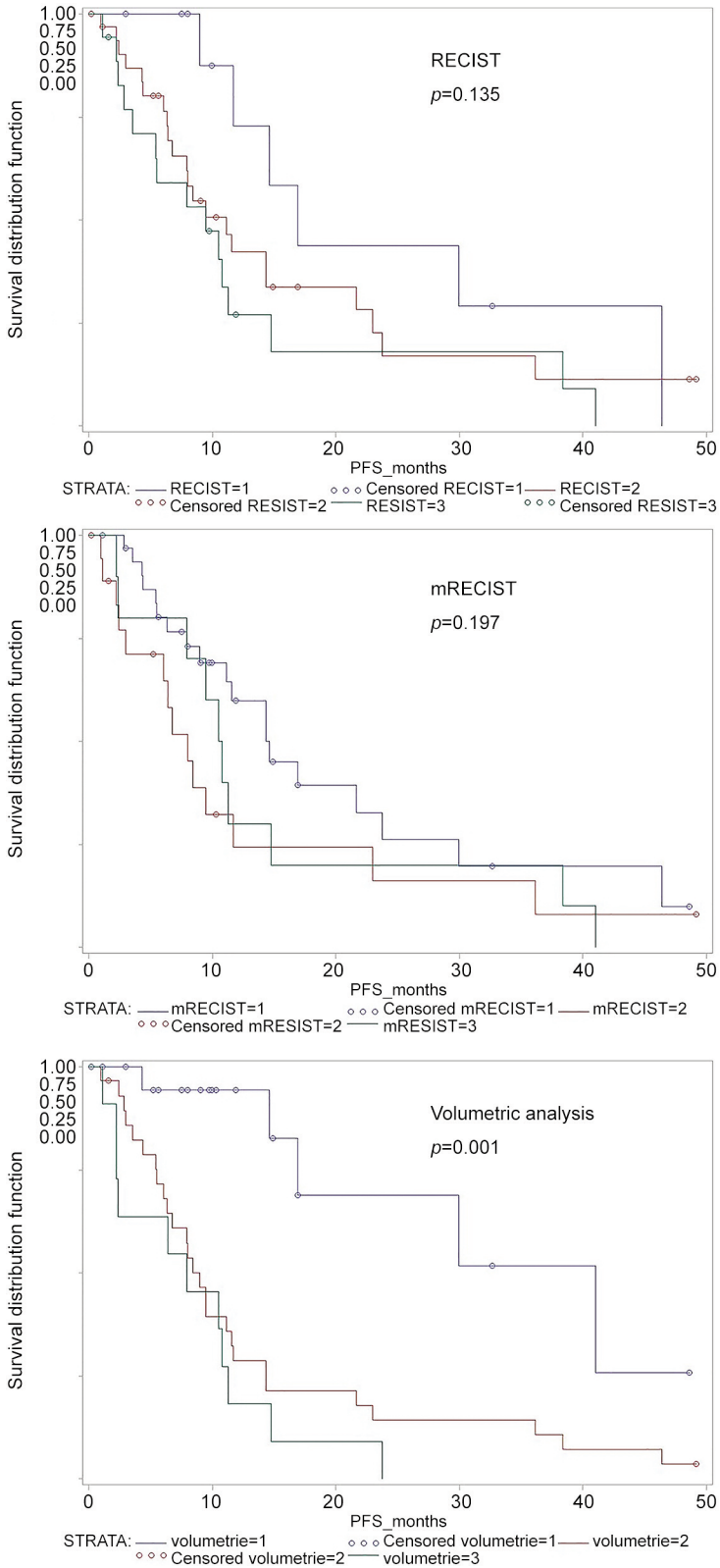

Figure 3. *Kaplan Meier plots of overall survival (OS). OS of patients with HCC after TACE with p-value of the log-rank test according to RECIST (p=0.142), mRECIST (p=0.505) and volumetric analysis (p=0.005). The green line corresponds to CR+PR, the blue line corresponds to SD, the red line corresponds to PD. 95% confidence interval is presented by the dashed line.*

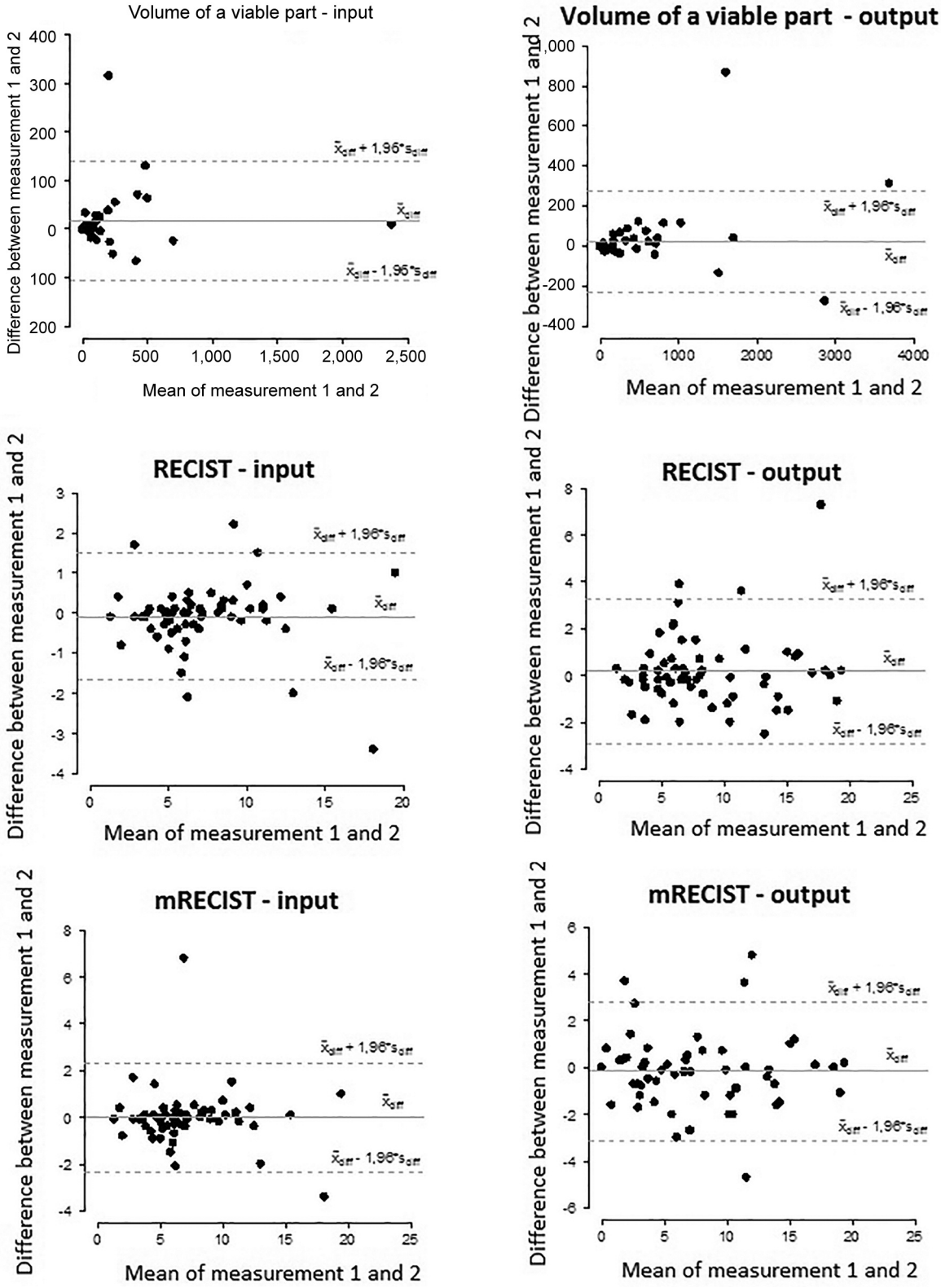

Figure 4. *Kaplan Meier plots of progression free survival (PFS). PFS of patients with hepatocellular carcinoma after TACE with p-value of the log-rank test according to RECIST (p=0.135), mRECIST (p=0.197) and volumetric analysis (p<0.001). The green line corresponds to CR+PR, the blue line corresponds to SD, the red line corresponds to PD.*

Interobserver variability. According to the total of outlier observations (n=2-7 for all the methods of assessment, *i.e.* 3.3-11.5% of the measurements) there is no significant difference in accuracy of the measurement of the two examiners using RECIST, mRECIST, and volumetric analysis (Figure 4). p-values for Pearson and Spearman correlation coefficients are <0.001 for all parameters. The mean Rs coefficient for input and output values is 0.952 for RECIST, 0.941 for mRECIST and 0.994 for volumetric analysis.

Discussion

RECIST and mRECIST are methods with well-known limitations and are imprecise especially for tumors after targeted therapies such as TACE, transarterial radioembolization, or targeted treatment with sorafenib. Numerous authors have pointed out that, because of the complexity of the lesions, the unidimensional measurement currently used as the standard method of evaluation is not accurate (10, 11, 13). This is due to the ischemic, cytotoxic, or cytostatic effect of the therapy which leads to tumor necrosis instead of reduction in its size (12).

With the introduction of new automatic and semi-automatic software for image segmentation (15), volume measurements have become quicker and widely available. Volume measurement is well reproducible with excellent interobserver agreement; our results are in accordance with previous studies (12, 15, 16, 21). Volumetric analysis was the only evaluation method the results of which correlated with OS and PFS in this study. The SD and PD categories showed the highest HR (3.82 and 5.94 for OS; 4.46 and 7.00 for PFS, respectively) showing that volumetric analysis is the optimal method for evaluating the potential benefit in terms of OS/PFS. This correlation has been demonstrated in other recent studies (22, 23). However, it should be noted that some of those studies differentiated patient groups only as responders *vs*. nonresponders.

The median OS after TACE was 17.1 months in our study. The result is comparable with larger studies where this parameter varied from 16 to 20 months (24, 25). The slightly worse outcome may be explained by the small number of participants and by setting the date of the first chemoembolization as the baseline which usually coincides with the date of HCC diagnosis in similar studies.

One major difficulty with this approach is comparing diameter with volume. Simple extrapolation of diameters to spherical volumes (used in our study as well) doesn't take in consideration the naturally irregular shape of the tumors. This problem is demonstrated when calculating the volume of a sphere (V=4/3 πr^3) where an enlargement in the radius (r) correlates with a much extensive incremental change in volume. For example, if the radius expands from 4 to 5, the calculated volume of a sphere doubles ($5^3/4^3$=125/64 ≈ 2/1). Likewise, volumetric measurements tolerate a greater margin of error and variability in comparison with linear measurements (26). In previous studies, two approaches have been used: volumetric spherical (7) and volumetric ellipsoid, an alternative criteria designed in 2012 (27), which found out that relating RECIST to an ellipsoid instead of spherical volume better corresponded with survival. The cut-off values for ellipsoid volumetric criteria were numerically the same as for RECIST: partial response (30% decrease in volume), stable disease, or disease progression (20% increase in volume). However, since the volumetric spherical approach is used in almost all the previous studies, we opted for this in order to make our research comparable.

This study had some limitations. It was a single-center study and the sample size was relatively small (especially if divided into CR+PR/SD/PD groups), which may cause a selection bias. We only used one software platform – but the same platform was used by both radiologists with excellent interobserver variability and the aim of the study was not to compare different software. Further studies on larger populations performed on different software may confirm our results.

According to the BCLC staging system, TACE is recommended for stage B patients, an extremely heterogeneous population mostly because of varying tumor size, tumor number and liver function. Prognosis and suitability for treatment can be variable and careful patient selection is pivotal to the success of TACE. Thus, using volumetric analysis rather than RECIST could potentially alter clinical decision-making in therapy.

Conclusion

The volumetric analysis proved to be the only method correlating with OS and PFS in contrast to the standard criteria (RECIST, mRECIST). This study showed significant differences between the categories of CR+PR/SD/PD, not just between the responders *vs*. nonresponders. Because of its excellent reproducibility and prognostic value of volumetric analysis in patients with HCC treated by TACE, it appears to be superior to the standard criteria, with a real impact in everyday practice.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Monika Hajkova: Conceptualization, Methodology, Writing – Original draft preparation; Tomas Andrasina: Conceptualization, Methodology, Resources, Writing – Reviewing and Editing; Petra Ovesna: Methodology, Data analysis; Tomas Rohan: Conceptualization, Methodology, Writing – Original draft preparation; Marek Dostal – Methodology, Writing – Reviewing and

Editing; Vlastimil Valek: Writing – Reviewing and Editing, Supervision; Lenka Ostrizkova: Resources; Stepan Tucek: Resources; Jiri Sedo: Resources, Writing – Reviewing and Editing; Igor Kiss: Writing – Reviewing and Editing, Supervision.

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