RESPONSE EVALUATION OF AR-67 FROM A PHASE-2 RECURRENT GLIOBLASTOMA TRIAL BY ARTIFICIAL INTELLIGENCE-ASSISTED TUMOR VOLUMETRIC ESTIMATION: COMPARISON WITH THE SUM OF THE PERPENDICULAR DIAMETERS PRODUCTS

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Abstract # CTNI-45

BACKGROUND

The Modified Radiographic Response Assessment in Neuro-Oncology ("mRANO") based on calculating the Sum of the Perpendicular Diameters Products (SPDP) of tumor images, forms the basis for assessing treatment response in glioblastoma. This 2-D analytical approach is subject to inconsistencies because of issues that may include sampling bias, irregularities in tumor shape, and inability to capture other critical aspects of tumor biology, such as cell density, level of blood supply/vessel leakage and diffusion. These limitations can lead to difficulty in differentiating between pseudo- and true disease progression. Volumetrics image analysis using artificial intelligence (AI), a 3-D analytical approach, may overcome these limitations and improve our ability to detect changes earlier and more accurately.[1] Here, we compared the two analytical methods using images from a subset of patients with recurrent GBM who received an investigational drug, AR-67, in a Phase 2 clinical study [2]

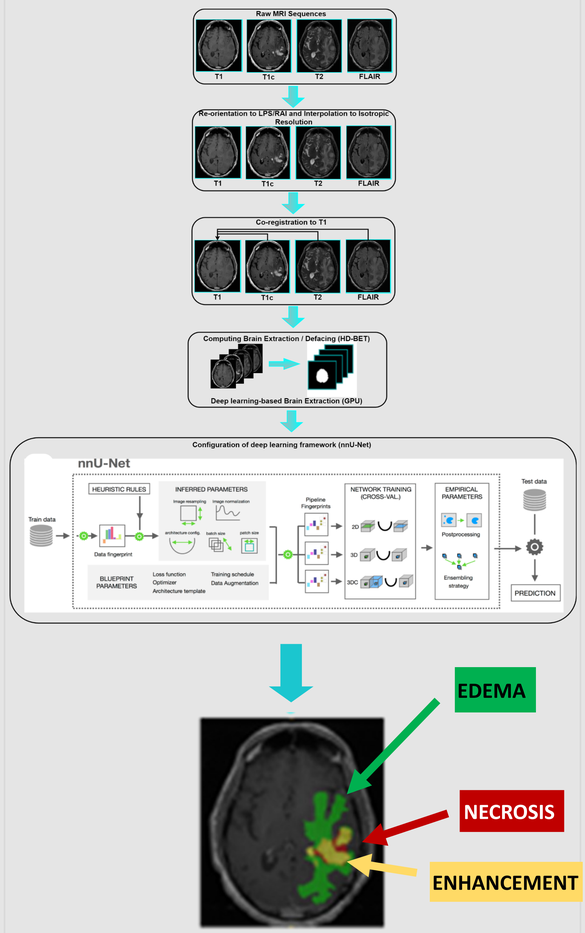
EDUCATIONAL OBJECTIVES

1. Using AI-assisted (AI-A) image analysis technology for measurement of volumetrics of enhancing tumor in neuro-oncology trials may provide a more sensitive and accurate tool than mRANO bi-directional measurements to detect response rate, particularly for large lesions.
2. Volumetrics and SPDP cannot be used interchangeably and in 18% of the cases showed discrepancy in the directionality of the changes, which may result in erroneous estimations of treatment response.
3. SPDP estimations are highly correlated with the respective volumes but tend to consistently overestimate the tumor burden if we consider volumetric as the reference standard.

METHODS

Images from 8 of 45 patients in a Phase 2 recurrent GBM study of Vivacitas Oncology's drug, AR-67[2], were re-assessed using Image Analysis Group's (IAG) AI-assisted volumetric measurements proprietary platform Dynamika™. A median of 5 time points from each patient were included. The response was determined by mRANO central reading and tumor volumetric measurement. Statistical significance was set at p<.0001.

AI-A TUMOR VOLUME ESTIMATION



Segmentation Image Superimposed on T1ce Image

The AI-based automatic brain tumor segmentation pipeline

RESULTS

Four patients showed responses, two patients showed stable disease, and two patients showed progressive disease. Tumor volume was significantly correlated (r=0.97) with SPDP but this was driven by high coefficients in large lesions. Using Bland-Altman analysis, we could detect systematic overestimation of the tumour tissue using the SPDP technique in larger tumors and hence, discrepancies in response rates. ***For example, the mean response rate based on IAG's volumetric criteria was +22% compared with +17% using the SPDP technique.*** Eight out of 45 time-points differed in the directionality of responses (e.g., increase vs. decrease) with SPDP underestimating the positive effects of AR-67 compared to the AI-based volumetric approach.

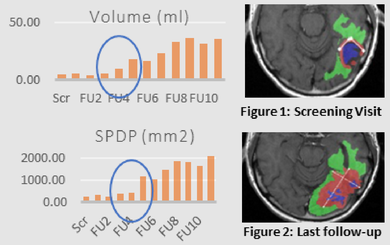


Figure 1: Screening Visit

Figure 2: Last follow-up

Figs 1-2. The tumor shape in the screening visit makes it notoriously difficult to estimate objectively the residual tumor burden. Using tumor volumetric measurements, however, offers a robust, reproducible tumor estimation. As evident on the bar graphs, SPDP didn't detect the increase in the tumor volume between the 4th and the 5th time points (TPs), which was precursor of the later unfavorable response, while this was picked up later at the 6th TP as overprportional, compared with the volumetry tumour increase.

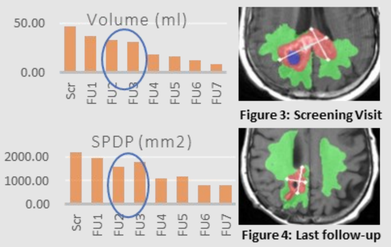


Figure 3: Screening Visit

Figure 4: Last follow-up

Figs 3-4. The SPDP-based estimation of the tumor in the screening visit is obviously erroneous due to the inclusion of the necrotic area (in blue). This problem is easily addressed by the AI-assisted volumetry approach. There is clear directionality of decreasing tumor load during treatment, evidenced on the volumetry. This fact is not reflected on the SPDP-based approach, where there are transient fluctuations on the estimated disease burden, giving also the impression of possible pseudoprogression on follow-up 3.

DISCUSSION

AI-assisted tumor volumetric analysis is feasible and may be more sensitive for treatment-related response rates than the standard SPDP methodology.[1] It may also allow for more accurately differentiating between pseudo- and true disease progression in terms of enhancing tumor, as it did in one of the 8 patients studied here (Table 1). In addition, functional imaging biomarkers such as diffusion and perfusion in the volumetric estimation is expected to enhance diagnostic accuracy. Overall, the findings from the AI-driven volumetric re-analysis confirm and extend our understanding of AR-67's therapeutic potential.

Patient ID#	Original Assessment Best Response – Reponse at EOS	AI-A Tumor Volumetric Assessment
301	N/A – N/A	Response
340	N/A - PD	No Response
536	PD - PD	No Response
637	N/A – N/A (taken off study, reasons unknown)	Response
734	SD – PD (taken off study due to PD assessment)	SD (evidence of potential pseudo-progression)
844	PR - PD	Response
845	PR - PR	Response
846	SD - PD	No Response

PD = Progressive Disease; SD = Stable Disease; PR = Partial Response; N/A = Not Available

TABLE 1. Comparison of Assessments

CONCLUSIONS

AI-assisted tumor volumetric analyses of images from a subset of reGBM patients treated with AR-67 in a Phase 2 trial reveal that standard analytical methods (SPDP) likely underestimated the positive response rate to drug in the original study .

In practical terms, AI-assisted image analyses may distinguish between pseudo– and true progression such that premature removal of subjects from a trial may be reduced or avoided altogether.

REFERENCES

1. Bakas et al. 2018. Identifying the Best Machine Learning Algorithms for Brain Tumor Segmentation, Progression Assessment, and Overall Survival Prediction in the BRATS Challenge. Computer Vision and Pattern Recognition: arXIV: 1811.02629
2. Kumthekar et al. 2019. Neuro-Onc 21 (Supp 6): vi22 (ACTR-40)