Is edema zone volume associated with Ki-67 index in glioblastoma patients?

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Abstract

Purpose: Despite all the progress with genetic mapping and multimodal treatment, the prognosis of GBM remains poor, with median overall survival (OS) of only 12 to 15 months. Several studies showed correlations between clinical features and prognosis, however the same don`t occurs with radiological features. The purpose of this study is to determine possible correlations between the volumetric analysis of glioblastoma compartments and the proliferation index represented by Ki-67.

Methods: We performed a retrospective analysis of MRI studies of 70 patients with glioblastoma multiforme acquired up to one week before surgery. The tumor compartments were divided in enhancing zone; edema zone and tumor total zone. Each compartment was submitted to volumetric analysis using Horos Project software. Linear regression model was used to assess correlations between ki-67 index and volume of each compartment with p value of 0,05.

Results: Male/female ratio in our study was 1.7:1, at a mean age of 60.7 ± 14.6 years. Tumor predominant location was the temporal lobe with 25% of cases and cystic morphology was present in 17%. The median of Ki-67 was 40%. The average tumor compartment volume was 40.8 cm^3 for contrast-enhancing zone, 62.7 cm^3 for edema zone and 103.5 cm^3 for total tumor volume. A significant association between Ki-67 index and edema zone volume (p=0.02).

Conclusion: Volumetric analysis of the edema zone in patients with MRI scans suggestive of glioblastoma could offer the possibility of predicting tumor aggressiveness through correlation with Ki-67 index.

Introduction

Glioblastoma multiforme (GBM) represents up to 81% of all primary malignant tumors of the central nervous system (CNS).[1] This aggressive brain tumor has an incidence of four thousand new cases per year in the United States and increasing rates in Australia, Finland, South America and Europe.[1-4] Despite all the progress with genetic mapping and multimodal treatment over the last decade, the prognosis of GBM remains poor, with median overall survival (OS) of only 12 to 15 months.[5,6]

Clinical variables used to predict patient prognosis include age, Karnofsky performance status (KPS), extent of contrast-enhancing zone resection, methylation status of O-6-methylguanine-DNA methyltransferase and chemo-radiotherapy protocol. [7-10] A recent meta-analysis showed association between the overexpression of proliferation index Ki-67 and worse outcome scores.[11]

On the other hand, a few investigators have assessed direct or indirect correlations between GBM compartment volume in magnetic resonance imaging (MRI) and prognosis. However, these findings have not been consistent so far.

To increase lifespan and improve quality of life in glioblastoma patients, it is essential to further investigate possible prognostic factors in order to identify high risk patients and start the treatment as soon as possible.

The purpose of the present study is to determine possible correlations between the volumetric analysis of glioblastoma compartments and the proliferation index represented by Ki-67.

Materials And Methods

We performed a retrospective analysis of MRI studies of 70 patients with glioblastoma multiforme. Two pathologists confirmed their diagnosis through histological and immunohistochemical studies. All patients underwent surgical resection or stereotactic biopsy performed by three senior neurosurgeons in a single institution between January 2014 and December 2018.

MRI scans were acquired up to one week before surgery with 1.5T or 3.0T machines. Two neurosurgeons performed volumetric measurements using the semi-automatic method in the Horos Project software and volumes were expressed in cubic centimeters (Fig1). All MRI scans were realized before patient corticoid introduction.

Glioblastoma compartments were defined as:

- Enhancing zone: Heterogeneous gadolinium-enhancing zone associated with necrosis zone measured by T1-contrast MRI sequence.
- Edema zone: Zone of hyperintensity in FLAIR MRI sequence which involves the enhancing zone.
- Total tumor zone: The sum of the volumes of enhancing and edema zones.

We carried out statistical analyses using Minitab 14 software and applied descriptive statistics for categorical and continuous variables. We used a linear regression model to assess correlations between continuous variables. A p-value of 0.05 or lower was regarded as statistically significant.

Ethics Approval

This study was approved by the Fundação Faculdade Regional de Medicina de São José do Rio Preto - FAMERP ethics committee and was performed according institution guidelines.

Informed Consent

The need for informed consent was waived by Fundação Faculdade Regional de Medicina de São José do Rio Preto - FAMERP ethics committee for the present study.

Results

Male/female ratio in our study was 1.7:1, at a mean age of 60.7 ± 14.6 years. Approximately 75% of patients were 60 years old or younger. Mean Karnofsky performance status was 83 ± 7.3% at patient admission.

The predominant tumor location was the temporal lobe with 25% of cases, followed by frontal and parietal lobes with 21% each, occipital lobe with 20%, central core with 11%, and posterior fossa with 2% of cases. As for hemisphere distribution, 50% of tumors were in the left hemisphere, 47% were in the right hemisphere, and 3% of patients presented bilateral tumor. Lesions with cystic morphology were 17%.

The median of Ki-67 was 40%, and it did not appear to be related to age or sex.

The average tumor compartment volume was 40.8 cm^3 for contrast-enhancing zone, 62.7 cm^3 for edema zone and 103.5 cm^3 for total tumor volume.

There was significant association between Ki-67 index and edema zone volume (p=0.02), which was not the case for enhancing zone volume (p=0.10) and total tumor volume (p=0.33),(Fig2).

Discussion

Ki-67 is a protein associated with cell proliferation which increases during the mitotic process, mainly in the S phase of the cycle. The expression of Ki-67 in tumor cells, quantified in percentage, is called the Ki-67 index, which could be associated with prognosis in tumors such as melanomas, and breast and bladder carcinomas.[12-15]

In 2000, Shimizu, et al[16] showed a relevant correlation between the Ki-67 index and choline levels on MR spectroscopy images. However, their research had limitations, such as a small number of patients, image artifacts and errors in spectral evaluation.[16,17]

Our study revealed a positive association between the Ki-67 index and edema zone volume in GBM. To the best of our knowledge, this is the first study to find this statistical correlation. Volume of necrosis zone and total tumor volume showed no association with a high proliferation index as shown by other authors.[17-19]

The method for volumetric calculations in this study was quantitative, semi-automatic, which offers the advantage of manually demarcating the contours of each type of volume selected in each of the regions of interest (ROI) of an image. This allowed us to avoid deviations in lesion volume that commonly occur when a completely automatic methodology is applied.[19,20]

According to Odland et al[20] the disadvantage of the semi-automatic method is an interobserver variation when quantifying volume. Thus, in order to avoid divergences in volume quantification, two neurosurgeons performed the volumetric analysis in the present work.

We chose Horos Project because it is an open source, easy-to-handle software and it is accurate to delimit tumor compartments.[21]

In 2019, Henker, et al[17] tried to show associations between tumor compartment volume and Ki-67 index in a study with 150 glioblastoma patients, using a 3D neuronavigation software. The authors, however, did not succeed, possibly due to a variation of volume measurement methodologies and the software used. Nevertheless, this same study found associations between elevated Ki-67 index and glioblastoma outcome.

Armocida, et al[22] presented an association between high Ki-67 index and large total volumes (>45 cm^3) but not edema volumes, unlike our study. In this case, despite the use of similar measurement methods and software, compartment definition, which is not clearly stated, could differ from ours.

Another divergence between findings of different studies is the proliferative index variation according to the site of extraction for biopsy, as proposed by Jakovlevs, et al.[23]

An interesting finding from Armocida, et al[22] was a negative association between Ki-67 index and patient progression-free survival.

Other authors support the idea of an association between the Ki-67 index and prognosis. Liang, et al[24] showed a correlation between the Ki-67 index and first-year mortality in 335 glioma patients and Chen, et al[11] revealed in their meta-analysis that elevated levels of Ki-67 can be a predictive factor for poor prognosis in glioblastoma.

Therefore, we could propose a negative association between edema volume and prognosis in patients with glioblastoma. Based on this, patients with large volumes of edema should undergo not only urgent surgery, but oncological evaluation during hospitalization and adjuvant treatment as soon as possible. This could contribute to better outcomes.

Despite these findings, a limitation of our research is the retrospective format and, therefore, prospective studies are necessary to clarify the relation between glioblastoma compartment volume and clinical variables such as prognosis.

Conclusion

Volumetric analysis of the edema zone in patients with MRI scans suggestive of glioblastoma could offer the possibility of predicting tumor aggressiveness through correlation with Ki-67 index. Patients presenting large zones of edema should be treated quickly to improve prognosis.

Declarations

Funding Source

No funding was obtained for this study.

Conflict of Interest

The authors have no financial disclosures to declare.

Submission Statement

The contents of this work have not been copyrighted or published previously.

Consent for publication

The authors consent the publication in this journal.

Data Availability

The datasets analyzed during the current study are available from corresponding author on reasonable request.

Authors' contributions

Ricardo Lourenço Caramanti – Study design, Literature search, Data acquisition, Statistical analysis, Manuscript editing

Feres Chaddad-Neto - Study design, Statistical analysis, Manuscript review

Dionei Freitas de Morais - Study design, Statistical analysis, Manuscript review

Carlos Eduardo Rocha - Literature search, Data acquisition, Statistical analysis, Manuscript editing

Lúcia Helena Neves Marques - Study design, Literature search, Data acquisition, Statistical analysis, Manuscript editing

Waldir Antônio Tognola - Study design, Statistical analysis, Manuscript review

Mário José Góes - Literature search, Manuscript review

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Figures

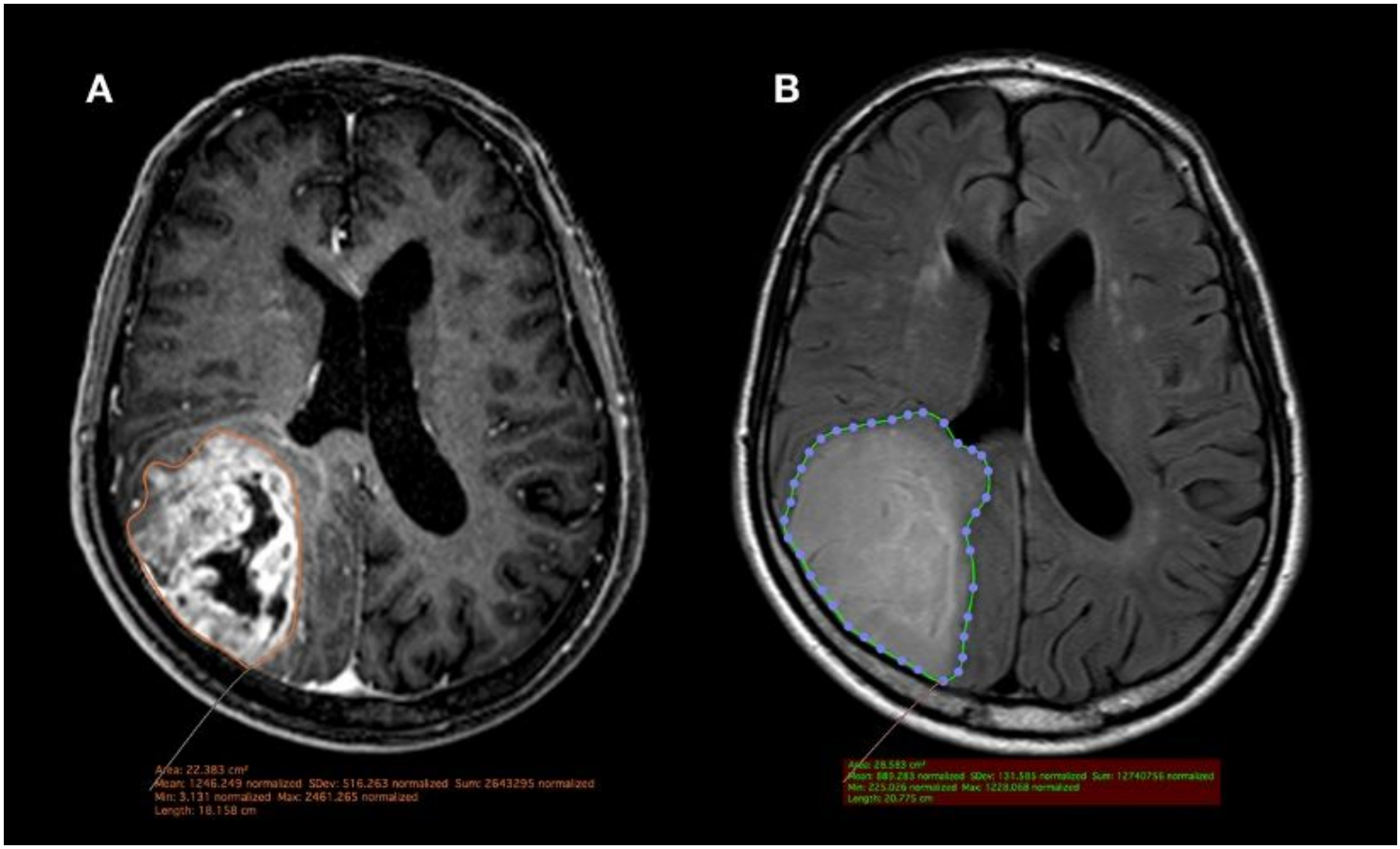

Figure 1

a - MRI in T1-weighted sequence with gadolinium showing the calculation of the lesion volume for the enhancing zone. b - MRI in FLAIR-weighted sequence showing the calculation of the lesion volume for tumor edema zone. Volumetric calculations were estimated with the manual tracer of the Horos Project software, by measuring the area of interest with a slice-by-slice semi-automatic method

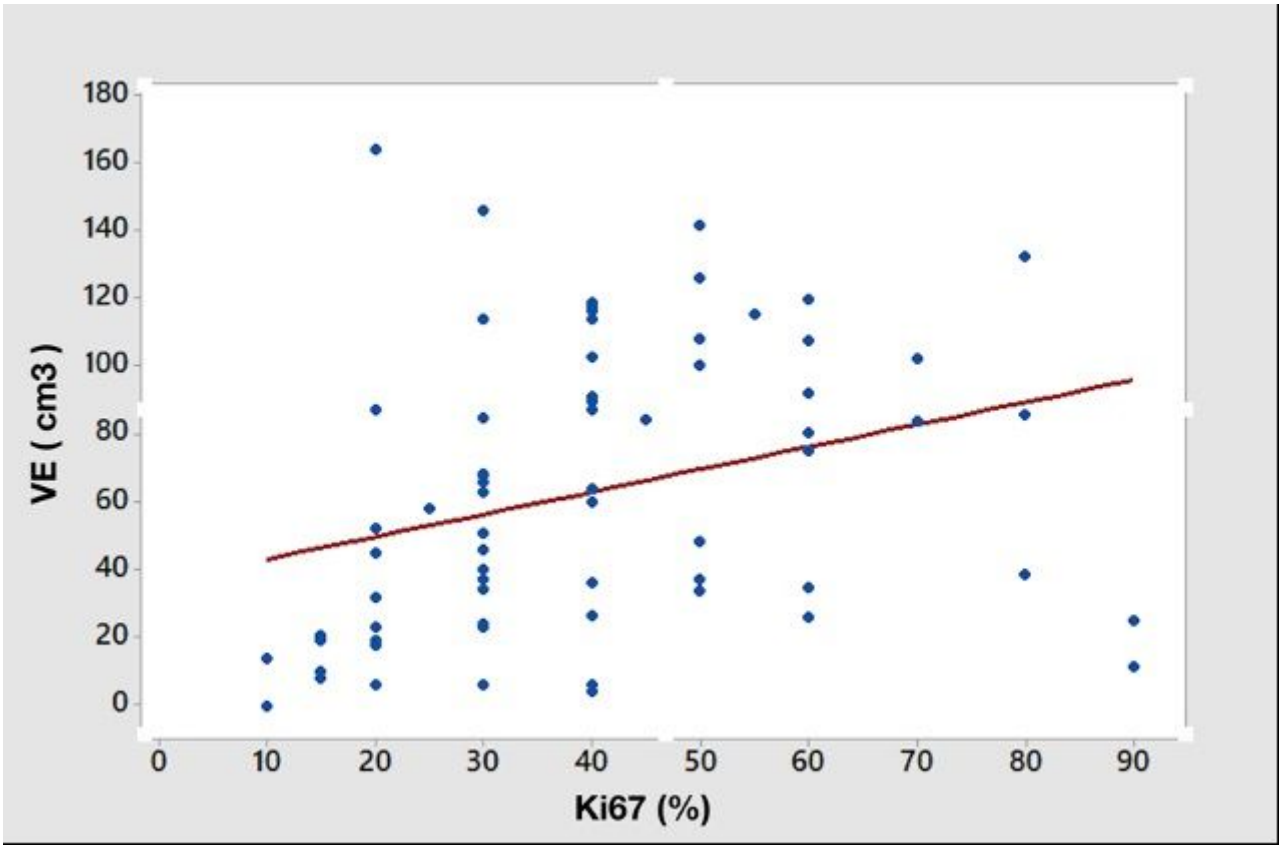

Figure 2

Scatter diagram showing positive correlation between Ki-67 index and volume of edema (p=0.02)