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Is sarcopenia a predictor of overall survival in primary IDH-wildtype GBM patients with and without MGMT promoter hypermethylation?

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Abstract

Background: In this study, we aimed to examine the success of temporal muscle thickness (TMT) and masseter muscle thickness (MMT) in predicting overall survival (OS) in primary IDH-wild glioblastoma (GBM) patients with and without MGMT promoter hypermethylation through publicly available datasets. *Methods:* We included 345 primary IDH-wild GBM patients with known MGMT promoter hypermethylation status who underwent gross-total resection and standard treatment, whose data were obtained from the open datasets. TMT was evaluated on axial thin section postcontrast T1-weighted images, and MMT was evaluated on axial T2-weighted images. The median TMT and MMT were used to determine the cut-off point. *Results:* The findings showed that median TMT 9.5 mm and median MMT 12.7 mm determined the cut-off value in predicting survival. Both TMT and MMT values less than the median muscle thickness were negatively associated with OS (TMT<9.5: HR 3.63 CI 2.34–4.23, p <0.001, MMT<12.7: HR 3.53 CI 2.27–4.07, p <0.001). When patients were classified according to MGMT positivity, the findings showed MGMT-negative patients (TMT<9.5: HR 2.54 CI 1.89–3.56, p <0.001, MMT<12.7: HR 2.65 CI 2.07–3.62, p <0.001) and MGMT-positive patients (TMT<9.5: HR 3.84 CI 2.48–4.28, p <0.001, MMT<12.7: HR 3.73 CI 2.98–4.71, p <0.001). *Conclusion:* Both TMT and MMT successfully predict survival in primary GBM patients. In addition, it can successfully predict survival in patients with and without MGMT promoter hypermethylation.

Keywords: Sarcopenia, GBM, TMT, MMT

INTRODUCTION

Glioblastoma (GBM) is adults' most common primary malignant brain tumor.[1] GBM still represents the most common and fatal glioma subtype, with less than 10% of newly diagnosed patients surviving five years despite maximally safe surgical resection followed by an aggressive multimodality treatment approach based on radiotherapy (RT) and temozolomide (TMZ). Individualized treatment planning in oncology involves considering several parameters, including age, molecular and histological tumor characteristics, tumor location and size, and the patient's general physical condition. Most of these parameters can be evaluated objectively; however, the determination of the clinical status of patients, in particular, is affected by the subjective judgment of the attending physician, resulting in high interobserver variability and failure to predict survival.[2]

Sarcopenia is a progressive and generalized skeletal muscle loss associated with the increased probability of adverse events, including fractures, physical disability, and mortality.[3] Sarcopenia has significant clinical consequences regarding surgical oncology. The presence of sarcopenia indicates that patients have limited reserves to cope with the surgical stress response, making them more susceptible to complications, prolonged hospital stays, and mortality.[4,5] Sarcopenia is known to be a poor prognostic factor in various solid cancers.[6] Skeletal muscle mass is usually measured by the cross-sectional area of skeletal muscle at the level of the adjacent lumbar third vertebra on a computed tomography (CT) scan. Because most neuro-oncology patients do not routinely perform abdominal CT scans,

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it is not possible to measure skeletal muscle mass with this established method. Therefore, the evidence supporting a relationship between clinical outcomes and sarcopenia in brain tumor patients has been relatively limited compared with other cancers. However, recently published studies have revealed a high correlation between temporal muscle thickness (TMT) obtained on routine diagnostic brain MRI images and lumbar skeletal muscle cross-sectional areas. This suggests that lumbar and craniofacial muscles can be useful predictor parameters for estimating skeletal muscle mass.[7] Studies examine the relationship between TMT and masseter muscle thickness (MMT) and survival in GBM patients.[8-11] The common features of these studies were heterogeneity regarding other prognostic factors, such as surgery (extent of resection) and MGMT promoter hypermethylation.

In our study, we aimed to examine the success of temporal muscle and masseter muscle thickness in predicting overall survival in primary IDH-wild GBM patients with and without MGMT promoter hypermethylation on publicly available datasets.

METHOD

Patient selection

Three hundred seventy-four GBM patients of The University of California San Francisco Preoperative Diffuse Glioma MRI (UCSF-PDGM) dataset[12] and 546 GBM patients Multi-parametric magnetic resonance imaging (mpMRI) scans for de novo Glioblastoma (GBM) patients from the University of Pennsylvania Health System (UPENN-GBM) dataset[13] were retrieved from the Cancer Imaging Archive (TCIA).[14] Patients' characteristics were obtained from TCIA, including age, gender, pathologic grade, genomic profile. Informed consent was not required since TCIA data contained no personal identifying information.

Inclusion criteria were determined as follows: (a) patients with a pathological diagnosis of primary (de novo) IDH wild-type GBM, and (b) patients with pre-operative imaging contrast-enhanced and non-contrast T1-weighted MR imaging data. Exclusion criteria were determined as (a) patients without MGMT and 1p19q co-deletion mutation data; (b) patients who could not undergo gross total resection (GTR) (c) cranial MR images of poor quality (iv) were determined as patients whose survival data could not be reached.

We included 345 patients who met the criteria in this study. The detailed flowchart of the patients excluded from the present study is shown in Figure 1 in detail.

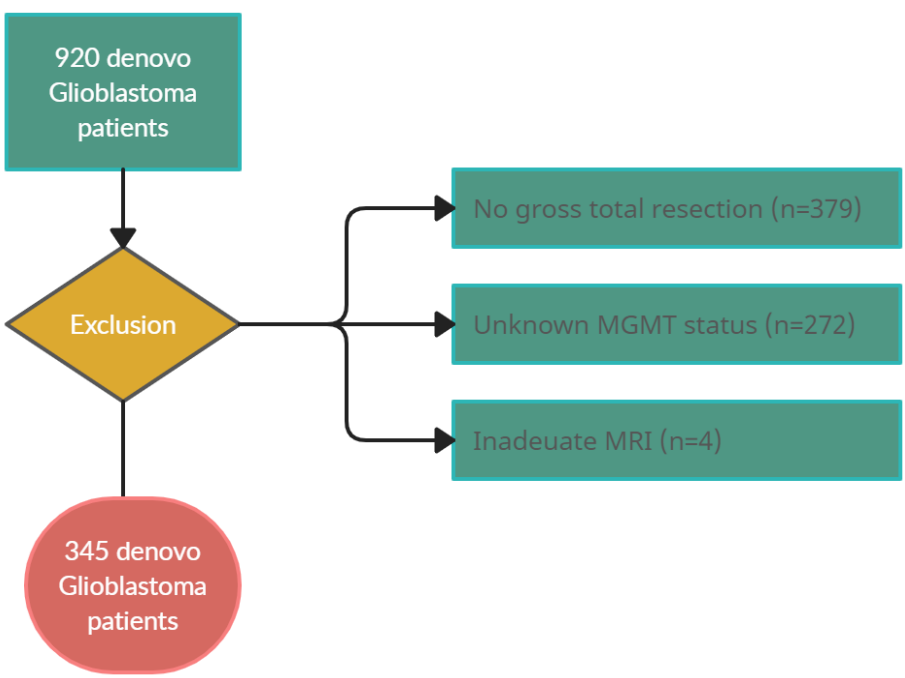

Figure 1. Patient selection flowchart

Measurement of muscle thickness

Measurements were made by a radiologist with five years of experience in MR reading and a neurosurgeon with 18 years of experience trained by another independent radiologist. The measurement was taken on patients who were anonymized before all statistical evaluations.

A series of applications were made to the images of all patients before measuring their muscle thickness. Advanced Normalization tools for Python and the Intensity-Normalization package were used for bias-field correction and Z-score normalization.[15,16] Resampling of images to 1 × 1 voxel spacing and resizing to 256 × 256 pixels was performed. Axial images were re-orientated to the anterior-posterior commissure line Slicer v.13 (http://www.slicer.org) was used in the process.

Temporal muscle thickness (TMT) was calculated on the axial thin slice contrast-enhanced T1-weighted MR images, which was routinely performed on pre-operative imaging. The measurements were performed perpendicular to the long axis of the temporal muscle using the orbital roof and the Sylvian fissure as anatomical landmarks, according to the previously reported method[10] (Figure 2 A).

Masseter muscle thickness (MMT) was assessed by measuring this musculature from medially to laterally, perpendicular to the mandible on axial T2-weighted MRI views at the level of the mandibular notch.[11] (Figure 2 B).

Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA). The intraclass correlation coefficient (ICC) was used to assess the reliability of the two observers. Student's t-test or Mann–Whitney U test was utilized to determine whether there were significant differences in the TMT-MMT and OS between male and female patients. The Pearson correlation analysis was adopted to evaluate the correlation between the age at GBM diagnosis and TMT, MMT. All patients were divided into groups based on their median TMT and MMT. The Kaplan–Meier curve was used to calculate the OS curve, and the log-rank test was applied to investigate differences in OS between the two groups. The association between TMT-MMT and OS of GBM patients was investigated. Univariate and multivariate analyses were conducted using a Cox proportional regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Multivariate analysis was performed on the variables; p-values <0.05 were considered to indicate statistical significance.

RESULT

Descriptive analyses were performed for the patient group. The group consisted of 205 men and 140 women. MGMT was positive in 201 (58.3%) of the patients. The mean day of survival was calculated as 526.90±378.09. The mean age of the patients at the time of diagnosis was calculated as 61.92 ± 12.01.

The ICC of left- and right-sided TMT calculated was 0.908 and 0.918 (p <0.001). The ICC of left- and right-sided MMT calculated was 0.923 and 0.915 (p <0.001). Mean TMT was calculated as 9.62±1.52 mm in the male gender and 9.31±1.23 mm in the female gender. Mean MMT was calculated as 13.05±2.52 mm in males and 12.45±1.32 mm in females.

There was no significant difference in the mean survival time between the sexes (p:0.119). A negative correlation was found between age at diagnosis and survival time (r =–0.307, p<0.001). Therefore, in addition to the standard statistical analysis, propensity score matching was applied with covariable values of age and gender at the time of diagnosis to prevent potential bias.

To carry out the evaluation more accurate according to MGMT promoter hypermethylation, the group was divided into two, and evaluations were made.

Median TMT (9.5 mm) and MMT (12.7 mm) values determined the cut-off value in predicting survival. Median OS was higher in the group with greater muscle thickness for both TMT value (TMT<9.5 mm: 292 days TMT> 9.5: 624 days) and MMT value (MMT<12.7 mm: 302 days MMT> 12.7: 677 days). A strong correlation was found between muscle thickness and OS when patients were grouped according to MGMT promoter hypermethylation, an essential marker in predicting survival. In patients without MGMT promoter hypermethylation, median overall survival was calculated as TMT<9.5 mm: 275 days, TMT> 9.5: 565 days, MMT<12.7 mm: 271 days, MMT> 12.7: 610 days. In patients with MGMT promoter hypermethylation, median OS was calculated as TMT<9.5 mm: 324 days, TMT> 9.5: 743 days, MMT<12.7 mm: 335 days, MMT> 12.7: 753 days. A statistically significant difference was found between all groups according to the log-rank test (p<0.001) (Figure 2).

In the Cox regression analysis, both TMT and

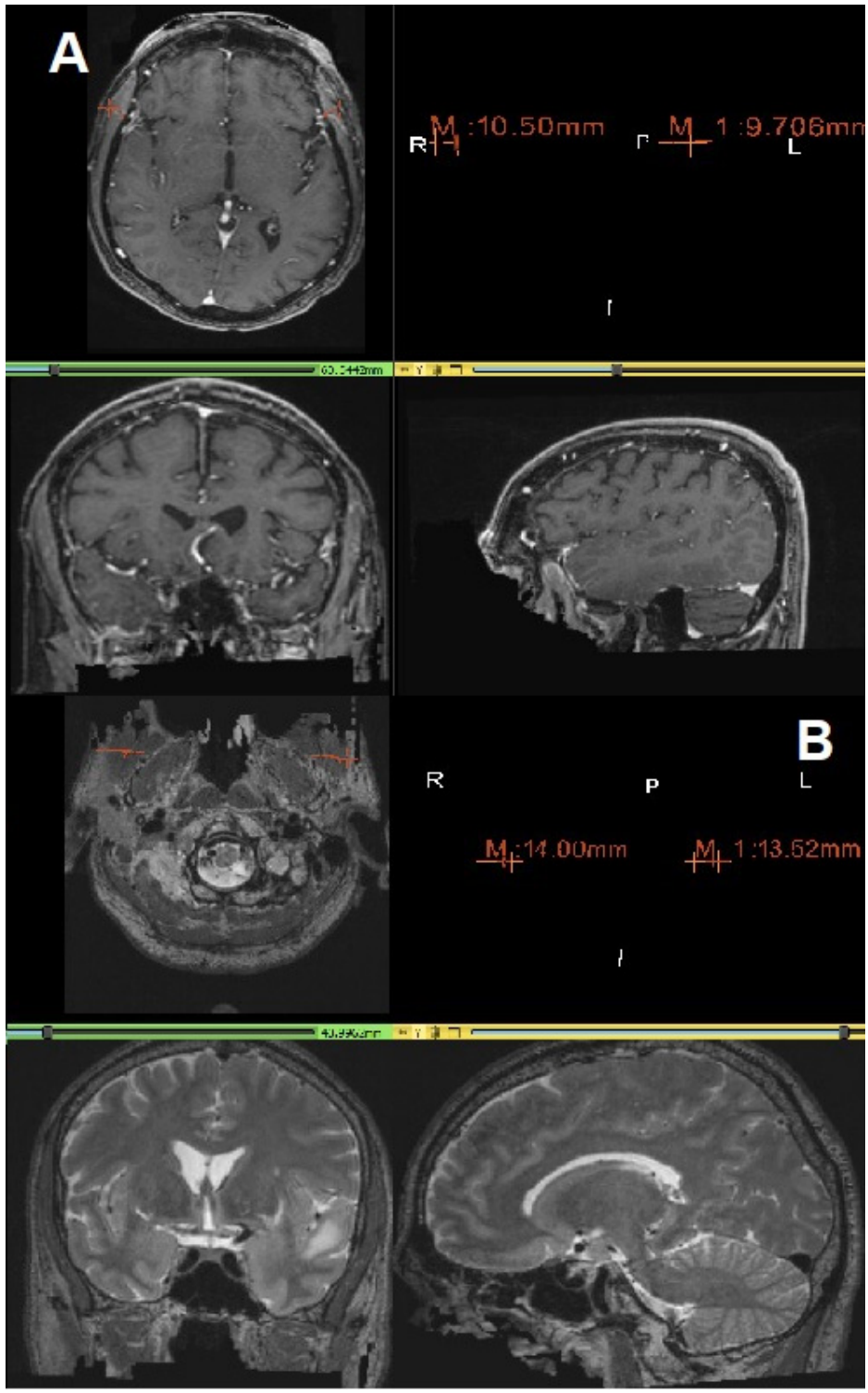

Figure 2. A) Contrast enhanced axial T1- weighted magnetic resonance images showing temporal muscle thickness (TMT) measurement. B) T2- weighted magnetic resonance images showing masseter muscle thickness (TMT) measurement.

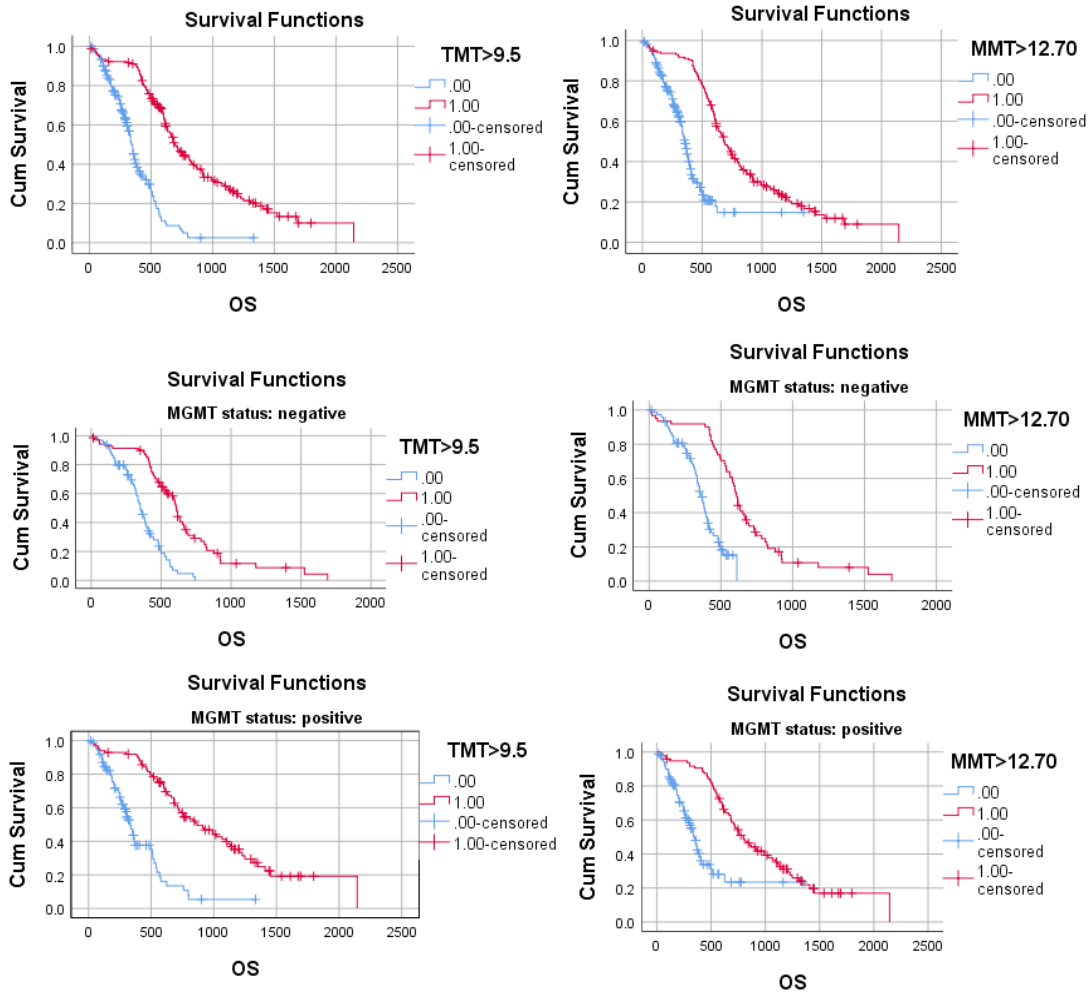

Figure 3. Kaplan-Meier analysisiof overall survival according to median temporal muscle thickness (TMT) and masseter muscle thickness (MMT).

MMT values were less than the median muscle thickness was negatively associated with OS (TMT<9.5: HR 3.63 CI 2.34–4.23, p <0.001, MMT<12.7: HR 3.53 CI 2.27–4.07, p <0.001). In the univariate regression analysis performed according to the age at the diagnosis, HR was 1.08 CI 0.89–1.26, p:0.048. Although there was a weak relationship between age and survival, in the subgroup analysis of 94 people created according to the propensity matching analysis performed according to age, gender, and MGMT status, both TMT and MMT values were less than the median muscle thickness, which was associated with poor survival (TMT<9.5: HR 2.93). CI 2.21–4.07, p <0.001, MMT <12.7: HR 3.01 CI 2.17–4.11, p <0.001).

When patients were classified according to MGMT positivity, the findings showed MGMT-negative patients (TMT<9.5: HR 2.54 CI 1.89–3.56, p <0.001, MMT<12.7: HR 2.65 CI 2.07–3.62, p <0.001) and MGMT-positive patients (TMT<9.5: HR 3.84 CI 2.48–4.28, p <0.001, MMT<12.7: HR 3.73 CI 2.98–4.71, p <0.001).

DISCUSSION

In this study, we aimed to investigate the relationship between TMT, MMT, and OS in IDH wild-type GBM patients treated with GTR and standard treatment and to examine the difference regarding MGMT promoter hypermethylation through dual-center retrospective open datasets. Our findings showed that muscle thicknesses below the median value were associated with poor survival in patients with and without MGMT promoter hypermethylation. Both TMT and MMT were associated with poor survival in the groups obtained after the propensity score matching

procedure based on age, gender, and MGMT status, which we applied to make the general evaluation of the patient group more accurate and to reduce potential bias.

Sarcopenia, defined as the loss of muscle mass, has been proposed as an important and independent biomarker for clinical outcomes, postoperative complications, and chemotherapy-induced toxicity in various patients with cancer.[17,18] Recently, a growing body of research has drawn attention to the correlation between TMT and the survival of patients with brain tumors.[8-10] Similarly, Morshed *et al*.[11] found a relationship between MMT and mortality in old GBM patients. The same study found no significant relationship between TMT value and 90-day mortality. The common feature of these studies is the heterogeneity in the study group and the small sample group, although they found a relationship between muscle mass and survival. In the study of An *et al*.[8], the group was not homogeneous regarding the extent of resection (EOR), which is one of the most critical parameters regarding survival. Liu *et al*.[9] could not be investigated MGMT promoter hypermethylation in the patient group. Similarly, in Morshed *et al*.'s study[11], MGMT promoter hypermethylation could not be evaluated in half of the patients. Contrary to these studies, Muglia *et al*.[19], in a relatively small and homogeneous patient group, in their single-center study on 51 patients with IDH wild-type with MGMT promoter hypermethylation, no correlation was found between survival and median TMT. To eliminate the contradiction between the results found when evaluated in the light of the literature, we were able to evaluate the effects of both MMT and TMT values on survival in a relatively large patient group with open datasets while maintaining homogeneity.

With increasing innovations, integrating artificial intelligence-based solutions into radiology opens new windows. While our study and most other studies in the literature manually evaluate only the thickness of the muscle tissue, Mi *et al*.[20], with the model they developed, found a negative relationship between muscle area and survival when the temporal muscle is automatically segmented. This study is promising for developing user-independent decision models in the future.

Personalized treatment is becoming an even hotter topic. Optimizing treatment selection and treatment plans according to the patient has been shown to improve treatment success. Determining patient frailty is very useful in predicting postoperative complications, in-hospital mortality and length of hospitalization.[21] Patient age, weight and performance status are already used to determine patient frailty. Sarcopenia has been defined as an objectively measurable parameter indicating patient frailty and unfavorable prognosis. We believe that TMT and MMT as indicators of sarcopenia are practical and usable for this purpose. In future studies, we think that these parameters can be used as markers for predicting preoperative and postoperative complications, can be used to individualize treatment according to the parameters, and even reduce patient frailty with physical exercises and pharmacological treatments such as myostatin inhibitors. In this way, perhaps radiology, oncology and surgery will gain a firm foothold in daily practice.[22,23]

There are some critical limitations in our study. This study was a planned retrospective because it was a study on open datasets. In most of the patients, we did not obtain information about the performance status of the patients at the time of diagnosis, such as ECOG and KPS. Since the patients were not separated according to their race, the differences between races could not be evaluated. Evaluations were carried out on median cut-off values, and detailed evaluation was not applied regarding quartiles or quantitative values. Since patients who underwent surgery other than GTR were excluded from this study, no evaluation could be made about these patients. Given that measurements are not made with automatic segmentation, this creates user dependence. The evaluation was made only on OS, and progression-free survival was not evaluated.

In conclusion, both TMT and MMT successfully predict survival in primary GBM patients. In addition, it can successfully predict survival in patients with and without MGMT promoter hypermethylation.

DISCLOSURE

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Conflict of interest: None

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