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Research

Can Temporal Muscle Thickness Be a New Prognostic Factor for *De Novo* Glioblastoma?

Temporal Kas Kalınlığı Yeni Tanı Glioblastoma için Prognostik Faktör Olabilir mi?

Elif Eda Özer[1], Meltem Kırlı Bölükbaş[1], Mustafa Orhan Nalbant[2], Gülşen Pınar Soydemir[1], Metin Figen[1], Esengül Koçak Uzel[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey

ABSTRACT

Objective: Glioblastoma multiforme (GBM) is the most aggressive and commonly seen primary malignant brain tumor in adults. In addition to clinical, molecular and histopathological prognostic factors, sarcopenia, defined as low skeletal muscle mass, has become one of the important parameters. The relationship between skeletal muscle mass and temporal muscle thickness (TMT) has been demonstrated. We evaluated the prognostic value of TMT in patients with newly diagnosed GBM.

Methods: A total of 66 GBM patients were included in this retrospective study. Left and right TMT's from pre-operative magnetic resonance images were measured separately by an experienced radiologist, and the mean TMT value for each patient was calculated. The survival times and rates were examined with the Kaplan-Meier method. Overall survival (OS) was calculated from the day of diagnosis. The correlation coefficients and their significance were calculated using the Spearman test.

Results: The median right TMT was 4.4 (1.7-9.5) mm, the left TMT was 4.1 (1.5-9.6) mm. The median TMT was 4.38 (1.66-9.45) mm. Spearman correlation test revealed a slight correlation between the mean TMT value and the age at the diagnosis (p=0.044). Spearman correlation test for gender also showed a slight correlation between the mean TMT value and gender (p=0.024). In the multivariate analysis using the Cox regression model showed that increased TMT was a positive prognostic marker for OS in GBM patients (p=0.030).

Conclusion: TMT greater than 4.38 mm was found to be an independent prognostic factor in *de novo* glioblastoma. However, studies with larger series are needed to generalize this result to the Turkish population.

Keywords: Glioblastoma, sarcopenia, prognosis, temporal muscle

ÖZ

Amaç: Glioblastoma multiforme (GBM), yetişkinlerde görülen en agresif primer malign beyin tümörüdür. Klinik, moleküler ve histopatolojik faktörlerin yanı sıra düşük iskelet kası kütlesi olarak tanımlanan sarkopeni önemli prognostik faktörlerden biri haline gelmiştir. İskelet kası kütlesi ile temporal kas kalınlığı (TMT) arasındaki ilişki ortaya konmuştur. Çalışmamızda yeni tanı konmuş GBM'li hastalarda TMT'nin prognostik değerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya GBM tanısı olan 66 hasta dahil edildi. Ameliyat öncesi manyetik rezonans görüntülerinden sol ve sağ TMT'ler deneyimli bir radyolog tarafından ayrı ayrı ölçüldü ve her hasta için ortalama TMT değeri hesaplandı. Yaşam süreleri ve oranları Kaplan-Meier yöntemi ile incelendi. Genel sağkalım (OS) tanı gününden itibaren hesaplandı. Korelasyon katsayıları ve anlamlılıkları Spearman testi kullanılarak hesaplandı.

Bulgular: Medyan sağ TMT 4,4 (1,7-9,5) mm, sol TMT 4,1 (1,5-9,6) mm idi. Medyan TMT 4,38 (1,66-9,45) mm idi. Spearman korelasyon testi, ortalama TMT değeri ile tanı yaşı arasında hafif bir korelasyon olduğunu ortaya koydu (r=-0,248, p=0,044). Cinsiyete göre Spearman korelasyon testi de ortalama TMT değeri ile cinsiyet arasında hafif bir korelasyon gösterdi (r=-0,277, p=0,024). Cox regresyon analizi kullanılarak yapılan multivaryant analizde TMT'nin toplam OS için pozitif prognostik bir marker olduğu gösterildi (p=0,030).

Address for Correspondence: Esengül Koçak Uzel, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 536 417 39 25 E-mail: dresengulkocakuzel@gmail.com ORCID ID: orcid.org/0000-0001-6953-6805

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Sonuç: TMT'nin 4,38 mm'den büyük olmasının *de novo* glioblastomda bağımsız bir prognostik faktör olduğu bulundu. Ancak bu sonucun Türk toplumuna genellenmesi için daha geniş serili çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Glioblastoma, sarkopeni, prognoz, temporal kas

INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and commonly seen primary malignant brain tumor in adults (1). GBM accounts for 52% of all primary brain tumors and 60%-70% of gliomas (2). Glioblastomas are more common in men than in women. The median age of patients at the time of diagnosis is 64 years (3). Median survival in GBM is usually 14,6 months after diagnosis, and long-term survival is rare (4). Surgical resection within safe limits followed by adjuvant radiotherapy (RT) and chemotherapy is the standard treatment approach for GBM. Concurrent and adjuvant temozolomide (TMZ) improves the median 2- and five-year survival of patients with glioblastoma (4). Prognostic factors are age at diagnosis, performance status (PS), the extent of resection, duration of symptoms, O-6-methylguanine-DNA methyltransferase (MGMT) status, and neurological functional/mental status (3).

In addition to all these clinical, molecular, and histopathological data, sarcopenia, defined as low skeletal muscle mass, has become one of the important parameters to be considered, particularly in cancer patients recently. However, objective measurement of sarcopenia is required. It is a parameter that indicates the prognosis and survival in various types of extracranial cancers (5-8). Previously, skeletal muscle mass measurement was performed on abdominal computed tomography (CT) at the third lumbar vertebra level (L3) (5,9,10). However, it was impossible to measure skeletal muscle mass, whereas routine abdominal CT scans are not performed, such as in head and neck or nervous system cancers. Therefore, muscle mass measurement from the third cervical vertebra (C3) level was presented as an alternative to the L3 vertebra level in head and neck cancer studies (11,12). Studies supporting sarcopenia regarding the prediction of clinical outcomes of brain tumor patients in the literature are limited compared with other cancers. After demonstrating a relationship between skeletal muscle mass and temporal muscle thickness (TMT), (13) studies were published reporting TMT as an independent prognostic parameters in patients with newly diagnosed brain metastases (14,15). Subsequently, based on these studies, researches have conducted that report TMT's prognostic value in patients with recurrent GBM. There have also been studies on its use as a marker (15-18).

Our study aimed to evaluate the prognostic value of TMT for overall survival (OS) rate and to investigate the importance of TMT as a marker of muscle loss in patients with newly diagnosed GBM. Also, it is to retrospectively analyze the prognostic relationship of TMT with known factors such as age, resection type, and PS of GBM patients.

METHODS

Patients Selection and Treatment

The study included 66 patients with GBM diagnosis and pre-operative magnetic resonance (MR) images who received simultaneous/adjuvant TMZ and postoperative RT. Additionally, patients' age, gender, The European Cooperative Oncology Group (ECOG) performance score, tumor diameter, Ki-67 index, tumor location, mean TMT, date of diagnosis, treatment details, last follow-up, and death information were recorded. Approval was obtained from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital for our study (decision no: 2021-11-14, date: 07.06.2021).

According to the planning target volume (PTV), all patients received a median dose of 60 Gy (59.4-64 Gy) of RT once a day, 2.0 Gy per fraction, according to the PTV, using the volumetric arc therapy treatment method with a 6 million volt linear accelerator. TMZ chemotherapy was planned for all patients. Concurrent 75 mg/m^2/day TMZ RT was initiated from the first day of RT and continued throughout RT. Adjuvant TMZ was started four weeks after the end of RT. While the adjuvant TMZ dose was 150 mg/m^2 for the first cycle, it was increased to 200 mg/m^2 per day for five days every 28 days after the second cycle in patients without hematological toxicity.

Before surgery, all patients underwent 1.5 Tesla (Siemens Amira) contrast-enhanced MR imaging. TMT at diagnosis of GBM was measured on T1-weighted contrast-enhanced axial brain MR images, at the level of the orbital roof perpendicularly to the long axis of the temporal muscle on an axial plane, which was oriented parallel to the anterior-posterior commissure line. Left and right TMT's were measured separately by an experienced radiologist, and the mean TMT value for each patient was calculated. The orbital roof and Sylvian fissure are used as anatomical landmarks for more accurate assessments. The radiologist was blinded to the patients' results, clinical features, and survival data. Patients with post-therapeutic changes that affected TMT were excluded from further evaluation. The measurements also included the diameter of the mass before surgery and the cavity diameter in post-op patients (Figure 1).

Survival status and/or death dates were obtained by searching each patient' file data. OS was defined as the number of days between the initial surgery and death. Patients who were confirmed as alive on December 31, 2021 were entered into the database.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) v.22 (SPSS, Chicago, IL, USA) was used for the statistical analysis. The mean TMT was calculated by taking the arithmetic mean of the right and left TMTs. Based on the median value of the mean TMT, the patients were divided into thin and thick temporal muscle groups. The descriptive and frequency statistics were calculated, and the chi-square test was conducted to evaluate the differences in categorical variables. The survival times and rates were examined with the Kaplan-Meier method. OS was calculated from the day of diagnosis. The correlation coefficients and their significance were calculated using the Spearman test. The factors affecting the OS were evaluated using Log-rank and Cox regression tests. A p-value <0.05 is considered statistically significant.

RESULTS

Sixty-six patients were included in the study, and their descriptive characteristics are listed in Table 1. The median age of the patients was 57 (24-83) years. Twenty-eight patients were female, and 38 patients were male. According to PS, 15 patients (54.9%) had an ECOG score of 0-1, while 52 patients had an ECOG score of ≥2. The most common tumor localizations were temporal lobe (23/66, 34.8%), frontal lobe (21/66, 31.8%), and parietal lobe (14/66, 18.2%), and less frequently other regions. Gross total resection was performed in approximately half of the patients (n=32, 48.5%). There were 19 (28.8%) patients who had an isocitrate dehydrogenase (IDH)1 mutation. The median PTV 60 volume was 265 (126.5-829.2) cc. The median right TMT was 4.4 (1.7-9.5) mm, the left TMT was 4.1 (1.5-9.6) mm. The median TMT was 4.38 (1.66-9.45) mm. Concomitant TMZ was applied to all patients. With adjuvant therapy, 50% of the patients received six cycles or less of TMZ, while the other half received more than six cycles of TMZ. The mean follow-up period was 14.0 months (1-123 months). Up to the last follow-up visit, 36 (54.5 %) patients died, and the median OS was 11.3 (1.2-49.4) months.

The patients were divided into two groups according to the median TMT (4.38 mm). The characteristics of the two groups according to the median TMT are shown in Table 2.

The strength of the association between the two variables was calculated using the Spearman correlation coefficient. Spearman correlation test revealed a slight correlation between the mean TMT value and the age at the diagnosis (r =-0.248, p=0.044). It was shown that TMT thickness decreased with increasing age. A slight correlation was not reflected in the log-rank test at the level of statistical significance (p=0.581). Spearman correlation test for gender also showed a slight correlation between the mean TMT value and gender (r =-0.277, p=0.024). The mean TMT in men [median 4.5 mm (2.3-9.4 mm)] was higher than in women [median 3.9 mm (1.6-8.8 mm)]. However, thicker TMT in men did not have a positive effect on survival (p=0.53).

A log-rank test was used to identify the factors on OS. The gender, age, tumor or cavity volume, PTV 60 volume, ECOG-PS, operation type, IDH 1 mutation, Ki-67 index, number of adjuvant TMZ cycles, and TMT were examined for univariate analysis. ECOG-PS ≤2 (p=0.036), IDH mutant type (p=0.05), >6 cycles of adjuvant TMZ treatment (p=0.006), and younger age (p=0.002) were found significant factors for OS.

In the multivariate survival analysis using a Cox regression model showed that ECOG ≤2 [hazard ratio (HR) 8.292; 95% confidence interval (CI) 1.684-40.834; p=0.009], gross total resection (HR 3.906; 95% CI 1.087-14.033; p=0.037),

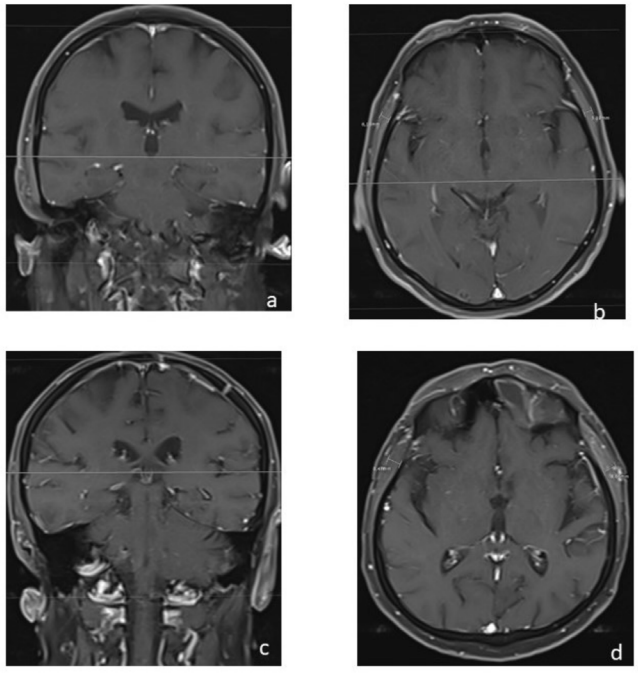

Figure 1. Representative TMT assessment on contrast-enhanced cranial T1-weighted MR images. Coronal (a), axial (b) images of a female patient (mean TMT =5.68 mm) and coronal (c) and axial (d) views of a male patient (mean TMT =8.56 mm) TMT was measured at the level of the orbital roof perpendicularly to the long axis of the temporal muscle on an axial plane, which was oriented parallel to the anterior-posterior commissure line

TMT: Temporal muscle thickness, MR: Magnetic resonance

Table 1. The descriptive analysis of the entire study group

Gender	
Female	28 (42.4%)
Male	38 (57.6%)
Age (min-max)	57 (24-83)
ECOG performance score	
<2	52 (78.8%)
≥2	14 (21.2%)
The side of the tumor	
Right	38 (57.6%)
Left	28 (42.4%)
The location of the tumor	
Frontal	21 (31.8%)
Temporal	23 (34.8%)
Parietal	12 (18.2%)
Occipital	4 (6.1%)
Temporoparietal	2 (3.0%)
Parietoccipital	4 (6.1%)
The form of the surgery	
Total resection	32 (48.5%)
Subtotal resection	19 (28.8%)
Biopsy	15 (22.7%)
IDH mutation	
Wild	47 (71.2%)
Mutant	19 (28.8%)
Ki-67	
≤20	40 (60.6%)
>20	26 (39.4%)
The diameter of the tumor (mm)	12.9 (1.0-65.0)
The diameter of the operation cavity (mm)	20.6 (2.0-68.0)
PTV 60 (cc)	265.0 (126.5-829.2)
The thickness of the right temporal muscle (mm)	4.4 (1.7-9.5)
The thickness of the left temporal muscle (mm)	4.1 (1.5-9.6)
The median of the mean temporal muscle thickness (mm)	4.38 (1.66-9.45)

Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group, IDH: Isocitrate dehydrogenase, PTV: Planning target volume, *Chi-square test

presence of IDH mutation (HR 4.656; 95% CI 1.332-16.273; p=0.016) and, >6 courses of adjuvant TMZ (HR 0.005; 95% CI 0.000-0.0.061; p=0.000) were significantly associated with the OS time of GBM patients. Additionally, TMT was a prognostic marker for OS in GBM patients (HR 10.786; 95% CI 1.257-92.544; p=0.030) (Figure 2). There was no significant association between the survival of GBM patients and gender, age at diagnosis, tumor or cavity volume, PTV 60 volume, and Ki-67 index (p>0.05).

DISCUSSION

Sarcopenia is defined as the loss of skeletal muscle mass. It is used as an important and independent biomarker in cancer prognosis. Sarcopenia has recently started to be used in neuro-oncological patients. In the study of Ranganathan et al. (13) on trauma patients in 2014, TMT was reported as an ideal marker of sarcopenia. TMT measurement studies in neuro-oncological patients were frequently conducted for brain metastases (14). Leitner et al. (14) suggested the use of TMT for sarcopenia in brain metastases, stating that L3 and TMT were correlated with brain metastases. In current studies, studies on TMT are performed on patients with progressive and newly diagnosed GBM (16,18-22).

In our study, 66 patients with de-novo GBM were examined with pre-operative MR images. When the mean TMT was calculated, the mean TMT of our study group was found to be lower than all other groups (16,20-22). Many factors affect TMT, such as tumor type, trauma, surgery, infection, nutrition, and age (21,23,24). However, the fact that the mean TMT value determined in our study was consistent with the value in the study of Yesil Cinkir and Colakoglu Er (18), which

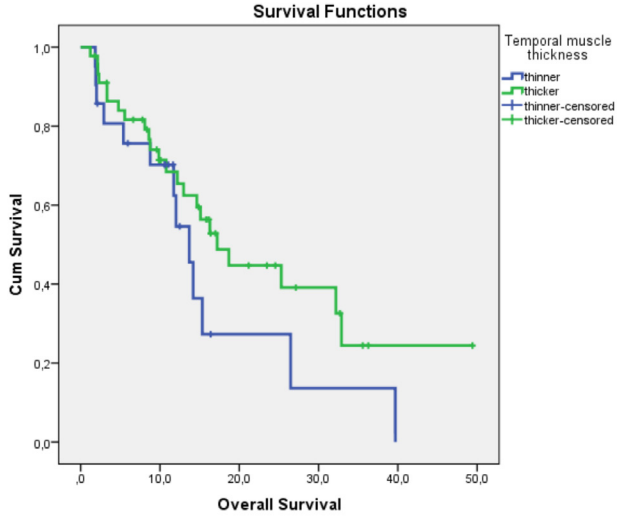

Figure 2. The effect of temporal muscle thickness on overall survival (p=0.03)

is also a Turkish study, showed that geographic and ethnic origin might also affect TMT. When the characteristics were examined, although the gender difference was not significant according to our study in contrast with other studies, TMT was higher in the male gender than in the female gender. However, this difference was not reflected in OS.

The median age of the patients included in the study was 57, which is consistent with the literature. The probability of developing sarcopenia increases with advancing age (8,25). In our study, we found a slight correlation between the TMT decrease and advancing age. In a report by The European Working Group on Sarcopenia in Older People, it was revealed that the cause of sarcopenia might be age-

Table 2. The descriptive analysis according to the temporal muscle thickness

	Thinner TM (n=33)	Thicker TM (n=33)	p*
	Median (min-max)	Median (min-max)	
Gender			0.046
Female	18 (54.4%)	10 (30.3%)	
Male	15 (45.5%)	23 (69.7%)	
Age (years)			0.218
<57 (median)	14 (42.4%)	19 (57.6%)	
≥57 (median)	19 (57.6%)	14 (42.4%)	
ECOG performance score			0.228
<2	24 (72.7%)	28 (84.8%)	
≥2	9 (27.3%)	5(15.2%)	
The side of the tumor			0.618
Right	18 (54.5%)	20 (60.6%)	
Left	15 (45.5%)	13 (39.4%)	
The form of the surgery			0.378
Total and subtotal resection	24 (72.7%)	27 (81.8%)	
Biopsy	9 (27.3%)	6 (18.2%)	
IDH mutation			0.786
Wild	24 (72.7%)	23 (69.7)	
Mutant	9 (27.3%)	10 (30.3)	
Ki-67 group			0.114
≤20	12 (50.0%)	12 (75.0%)	
>20	12 (50.0%)	4 (25.0%)	
The diameter of the tumor/operation cavity (mm)			0.453
35 mm and below	21 (63.6%)	18 (54.5%)	
Over 35 mm	12 (36.4%)	15 (44.5%)	
PTV 60 (cc)			0.026
265 and below	14 (42.4%)	23 (29.7%)	
265 and over	19 (57.6%)	10 (30.3%)	
Adjuvant temozolomide usage			0.460
≤6 cycles	15 (45.5%)	18 (54.5%)	
>6 cycles	18 (54.5%)	15 (45.5%)	

TM: Temporal muscle, Min: Minimum, Max: Maximum, ECOG: Eastern Cooperative Oncology Group, IDH: isocitrate dehydrogenase, PTV: Planning target volume, *Chi-square test

related primary sarcopenia, as well as decreased physical activity with a sedentary life, the patient's comorbidities (inflammatory, oncological, endocrinological) and secondary causes such as malabsorption and nutrition (25). The slight correlation detected between increasing age and decreasing TMT in our study was not reflected in the log-rank test at the level of statistical significance. Similarly, age was not found as a significant prognostic factor in the studies by Yesil Cinkir and Colakoglu Er (18) and An et al. (21). Huq et al.'s (20) study consisting of 381 patients with newly diagnosed and progressive GBM reported that TMT was associated with age, albumin, body mass index (BMI), and Karnofsky perfomance score (KPS). Albumin and BMI are directly related to nutrition and sarcopenia (26). However, because of the retrospective design of our study, patients' albumin and BMI levels were excluded from the analysis.

In the multivariate analysis of our study, ECOG ≤2, gross total resection (GTR), IDH mutation, TMZ more than six cycles, and thick TMT were found among the prognostic factors that positively affected OS. An et al. (21) reported low ECOG, GTR, and thick TMT, Liu et al. (22) reported thick TMT, age at diagnosis, and concomitant CRT, and Yesil Cinkir and Colakoglu Er (18) reported age and thick TMT to be good prognostic factors. Unlike these studies, which found a significant relationship between thick TMT and OS, Huq et al. (20) showed that TMT did not affect OS in newly diagnosed GBM but positively affected survival in progressive GBM. Muglia et al. (16) studied a small but homogeneous group of 51 patients diagnosed with methylated MGMT promoter, IDH1-2 wild-type glioblastoma, who underwent complete surgical resection followed by RT with concomitant and maintenance TMZ treatment. TMT of all patients was measured bilaterally from pre-operative MR images. The mean TMT was 8.43 mm. TMT was not associated with prognosis, age, or ECOG-PS. TMT has been argued to be an ineffective marker for predicting survival in GBM patients with newly diagnosed and untreated IDH1-2 wild-type, methylated-MGMT (16). However, the small number of patients and the fact that the patients are in the more aggressive group may be a reasons that suppress the effect of TMT.

Our study has some limitations. Initially, the patients included in the study caused a molecular and genetic heterogeneity pattern due to the retrospective design. Although our results were consistent with many studies in the literature, they differed from some studies examining a homogeneous patient group (16). Also, because of the retrospective study design, no additional research was conducted on other factors affecting TMT, such as patients' nutritional status and oral-dental health. Further studies with a larger sample size are needed to support our results and represent the Turkish population.

CONCLUSION

TMT greater than 4.38 mm was found to be an independent prognostic factor in de-novo glioblastoma. However, studies with larger series are needed to generalize this result to the Turkish population.

ETHICS

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital for our study (decision no: 2021-11-14, date: 07.06.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.E.Ö., M.O.N., E.K.U., Concept: E.E.Ö., M.K.B., G.P.S., E.K.U., Design: G.P.S., E.K.U., Data Collection or Processing: E.E.Ö., M.O.N., M.F., Analysis or Interpretation: M.K.B., E.K.U., Literature Search: E.E.Ö., M.O.N., M.F., E.K.U., Writing: E.E.Ö., G.P.S.

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