Original Article

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Low temporal muscle thickness is an independent poor prognostic factor in patients with brain metastases treated with radiosurgery

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Objective: The aim of this Bulgarian study was to determine the impact of temporal muscle thickness (TMT), a prognostic factor for sarcopenia, in patients with brain metastases (BMs) treated with radiosurgery.

Methods: A retrospective analysis was conducted using TMT values from planning brain magnetic resonance imaging (MRI) studies for 232 patients diagnosed with brain metastases originating from various histological solid tumors. These measurements were taken prior to their initial radiosurgery procedure, conducted between January 2021 and December 2022. The total TMT for both the left and right sides was calculated by summing them and then dividing by two to determine the average TMT. The cut-off value was determined for TMT based on the median of the measured values among all participants. Additionally, sarcopenia was assessed as an independent prognostic factor through Cox regression models that accounted for other relevant prognostic variables.

Results: In sarcopenia patients with a TMT below the cut-off values, specifically the median TMT (5.42 mm), the risk of death was significantly increased (HR = 6.310, 95% CI: 4.161–9.568, $p < 0.001$). In addition, sarcopenia was revealed to be an independent prognostic factor even after adjusting for gender, number of BMs, cancer type, and ECOG Performance Status (HR = 5.757, 95% CI: 3.717–8.915, $p < 0.001$). Patients with sarcopenia had a significantly shorter mean OS (5.46 months, 95% CI = 5.00–5.91) compared to those without sarcopenia (23.40 months, 95% CI = 20.62–26.18) (log-rank test $P < 0.001$).

Conclusions: In patients with BMs treated with radiosurgery, TMT from planning MRI studies serves as an independent prognostic marker and may help with patient stratification in future clinical trials.

Keywords: *sarcopenia; temporal muscle thickness; radiosurgery; brain metastases*

Introduction

Primary brain tumors and metastatic brain lesions from various extracranial malignancies are both classified as types of brain cancer [1]. Despite the implementation of comprehensive treatment strategies—including surgery, radiation therapy, and systemic chemotherapy, the rate of morbidity and mortality remains high. The median overall survival (OS) for these patients is about 12 months [2]. Various factors—such as age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor location and size, along with molecular and histological features—can serve as prognostic indicators [3]. In individuals diagnosed with brain tumors, evaluations related to sarcopenia and skeletal muscle mass may enhance prognostic predictions and help refine treatment plans.

Sarcopenia is a progressive and generalized loss of skeletal muscle mass and strength [4], and it has been identified as a prognostic factor in several extracranial cancer types [5-7]. Assessing skeletal muscle mass and function requires additional examinations, which may result in increased radiation exposure, healthcare costs, and/or a prolonged hospital stay.

Skeletal muscle mass is most often calculated from the volume of the third lumbar vertebrae musculature on cross-sectional abdominal computed tomography (CT) imaging [8-9]. In the case of brain tumors, radiologic images of the abdomen are not routinely available. To address this limitation, researchers have introduced the temporal muscle thickness (TMT), measured on magnetic resonance imaging (MRI), as a novel surrogate biomarker of muscle mass [10-11]. In clinical settings cranial MRI is routinely performed on patients with brain tumors. Researchers have proposed measuring TMT as an alternative method to evaluate muscle mass and identify sarcopenia in patients with brain tumors. There is no universally used threshold for determining low muscle mass.

The aim of this Bulgarian study was to ascertain whether TMT is an independent prognostic factor for overall survival (OS) in patients with brain metastases.

Materials and Methods

Patient selection

In this retrospective study conducted in Bulgaria, we evaluated 232 patients diagnosed with brain metastases who received radiosurgery between January 2021 to December 2022. Institutional records were reviewed to obtain demographic, pathological, radiological, and treatment-related information. The procedure was approved by the scientific research ethics committee of the hospital.

The eligibility criteria were established as follows:

1) A primary tumor diagnosis confirmed by pathology.

2) Confirmation of brain metastasis through magnetic resonance imaging (MRI) by blinded neuroradiologists.

3) Patients who are inoperable.

4) No prior history of brain radiotherapy or surgery.

5) Individuals must be over 18 years old.

6) An Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranging from 0 to 2.

The TMT measurements were performed by blinded specialists (neuroradiologists). However, patients lacking survival data or those with a history of primary brain tumors before the onset of brain metastasis were excluded from the analysis.

Temporal Muscle Thickness (TMT)

The day prior to radiosurgery, the TMT was assessed using a 1 mm axial slice from contrast-enhanced T1-weighted MRI. The axial plane of the MRI was aligned parallel to the line connecting the anterior and posterior commissures. Anatomical landmarks including the Sylvian fissure (in an anterior-posterior orientation) and the orbital roof (in a cranio-caudal direction), were used to create a perpendicular reference line relative to the long axis of the temporal muscle. The mean TMT value was calculated as the average of bilateral measurements. The cut-off value for TMT was established as the median measurement among all patients included in this study [12-14].

Statistical design and analysis

Data was processed and analyzed with IBM SPSS Statistics software version 23. The demographic details were presented as frequencies and percentages for categorical variables, while medians and means, accompanied by standard deviations, represented quantitative variables. To compare and assess the relationships between TMT and various clinicopathological characteristics of patients — including age, gender, tumor volume, and hematologic inflammation markers—the $\chi 2$ test was employed. The diagnostic performance of biomarkers was evaluated by calculating the maximum area under the curve (AUC) from receiver operating characteristic curve analysis. AUC values were classified as follows: ≥ 0.9 were considered excellent; ≥ 0.80 good; ≥ 0.7 fair, whereas values below 0.70 indicated poor accuracy. Survival curves based on treatment response were estimated using the Kaplan–Meier method, with differences tested through the log-rank test methodology. Additionally, multinomial logistic regression analyses were conducted to determine how TMT influenced treatment responses. Two-tailed p-values < 0.05 were considered statistically significant.

Ethical approval

All procedures conducted in studies involving human participants adhered to the ethical guidelines established by the relevant institutional and/or national research committees, as well as the 1964 Declaration of Helsinki, along with its subsequent amendments or equivalent ethical standards. Approval was secured from the local ethics committee.

Results

Baseline characteristics and their relationship with temporal muscle thickness (TMT)

This single-center retrospective study included 232 patients with brain metastases (133 males and 99 females) receiving radiosurgery treatment. At the time of diagnosis, the mean age of the patients was 63 ± 10.1 years. The primary tumors included 122 non-small cell lung cancers (NSCLC), 22 small cell lung cancers (SCLC), 30 breast cancers, 29 melanomas, 12 renal cancers, and 18 gastrointestinal (GI) cancers. The number of patients with brainstem metastases was 63, and those with brain edema were 129. After radiosurgery, 39 patients developed brain progression. The aforementioned cut-off value of TMT was used as the median TMT value (5.42 mm) for the included patients. Low TMT was observed in 56.5% of those patients, and high TMT was observed in 43.5%. Clinical characteristics of the patients and their relationship with TMT were summarized in ***Table 1***.

A Chi-squared analysis was performed to assess associations between the levels of TMT and the clinicopathological characteristics of the patients. The age of the patients at diagnosis ($p=0.148$) and the number of metastases ($p=0.147$) did not correlate with the TMT levels ***(Table 1)***. There were no significant differences between the values of PLR, SII, and TMT (***Table 1***). However, the levels of TMT were significantly related to gender ($p=0.008$), ECOG (PS) ($p<0.001$), cancer type ($p = 0.022$), tumor volume ($p<0.001$), brainstem metastases ($p=0.002$), brain edema ($p<0.001$), NLR ($p=0.024$), and brain progression ($p<0.001$) *(**Table 1**).*

Clinical outcomes and prognostic role of the TMT

The median duration of the follow-up was 32 months. Patients with sarcopenia had a significantly shorter mean OS than those without sarcopenia (log-rank test $p<0.001$). (***Fig. 1***).

In a univariate Cox regression analysis, high levels of TMT were associated with longer OS (HR = 6.310, 95% CI: 4.161–9.568, $p<0.001$; ***Table 2***). The multivariate analysis confirmed this association (HR = 5.757, 95% CI: 3.717–8.915, $p=0.001$; ***Table 2***).

TMT as a non-invasive biomarker for the discrimination between patients with or without sarcopenia

A receiver operating characteristic (ROC) curve analysis was conducted to investigate the predictive capacity of TMT as a non-invasive biomarker for distinguishing between responders and non-responders. At the established optimal cut-off value for TMT, this biomarker was able to effectively distinguish between these groups, achieving a sensitivity of 84.1% and a specificity of 73.6% (***Fig. 2***).

Table 1. Relationship between the baseline clinicopathological characteristics of patients and temporalis muscle thickness (TMT)

Characteristics	TMT≤ median (n=131)	TMT>median n=101	p-value
Age			**0.148**
≤63y	64 (27.6%)	59 (25.4%)	
>63y	67 (28.9%)	42 (18.1%)	
Gender			**0.008**
Male	85 (36.6%)	48 (20.7%)	
Female	46 (19.8%)	53 (22.9%)	
ECOG (PS)			**<0.001**
0	36 (15.5%)	55 (23.7%)	
1	63 (27.2%)	39 (16.8%)	
2	32 (13.8%)	7 (3.0%)	
Cancer type			**0.022**
NSCLC	74 (31.8%)	47 (20.3%)	
SCLC	14 (6.0%)	8 (3.5%)	
Breast cancer	8 (3.4%)	22 (9.5%)	
Melanoma	16 (6.9%)	13 (5.6%)	
Renal cancer	7 (3.0%)	5 (2.2%)	
GI	12 (5.2%)	6 (2.6%)	
Tumor volume			**<0.001**
≤median	50 (21.5%)	66 (28.4%)	
>median	81 (35.0%)	35 (15.1%)	
Number metastasis			**0.147**
≤3	77 (33.2%)	69 (29.7%)	
4-9	35 (15.1%)	25 (10.8%)	
≥10	19 (8.2%)	7 (3.0%)	
Brainstem metastasis			**0.002**
Yes	46 (19.8%)	17 (7.4%)	
No	85 (36.6%)	84 (36.2%)	
Brain edema			**<0.001**
Yes	90 (38.8%)	39 (16.8%)	
No	41 (17.7%)	62 (26.7%)	
NLR			**0.024**
≤median	57 (24.7%)	59 (25.4%)	
>median	74 (31.8%)	42 (18.1%)	
PLR			**0.691**
≤median	67 (28.9%)	49 (21.1%)	
>median	64 (27.6%)	52 (22.4%)	
SII			**0.659**
≤600×109 cells/L	25 (10.8%)	17 (7.4%)	
>600×109 cells/L	106 (45.6%)	84 (36.2%)	
Brain progression			**<0.001**
Yes	11 (4.8%)	28 (12.1%)	
No	120 (51.7%)	73 (31.4%)	

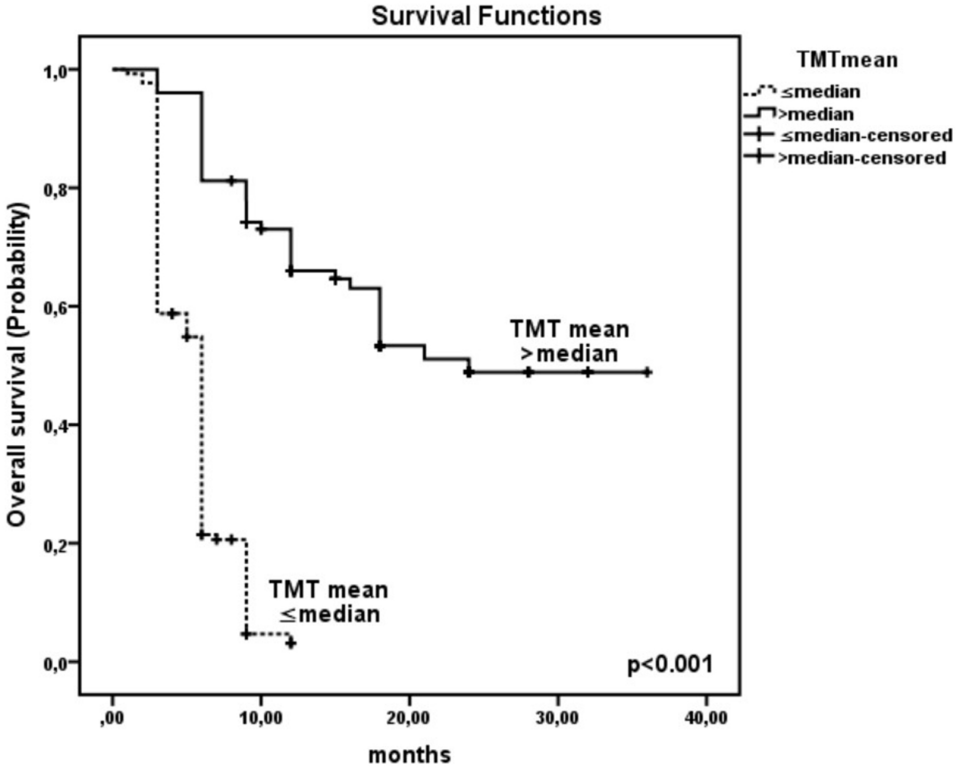

Fig. 1. Kaplan–Meier estimates of overall survival (OS) in patients with sarcopenia and non-sarcopenia. Patients with TMT ≤ median had a significantly shorter mean OS than patients with TMT > median

Table 2. Results of the Cox regression analysis for predicting overall survival

	Univariate Analysis			Multivariate Analysis		
Variable	**Hazard ratio**	**95%CI**	***p*-value**	**Hazard ratio**	**9%CI**	***p*-value**
TMT ≤median vs. >median	6.310	4.161-9.568	<0.001	5.757	3.717-8.915	<0.001
Age ≤63y. vs >63y.	0.793	0.582-1.079	0.140			
Gender Male vs Female	1.387	1.009-1.906	0.044	1.030	0.743-1.427	0.861
ECOG 0 vs 1 and 2	0.538	0.386-750	<0.001	0.833	0.524-1.324	0.439
Number metastasis ≤3 vs > 4	0.700	0.512-0.957	0.025	0.778	0.544-1.112	0.168
Brainstem metastasis Yes vs. No	1.703	1.220-2.378	0.002	1.237	0.856-1.789	0.258
Tumor volume ≤median vs >median	1.569	1.149-2.143	0.005	1.096	0.738-1.628	0.649
Brain edema Yes vs. No	1.926	1.395-2.660	<0.001	1.247	0.863-1.801	0.240
NLR ≤median vs >median	0.678	0.497-0.924	0.014	0.822	0.599-1.126	0.222
PLR ≤median vs >median	0.987	0.725-1.342	0.932			
SII ≤600×109 cells/L vs >600×109 cells/L	1.038	0.686-1.571	0.860			
Cancer type NSCLC vs other type	1.211	0.889-1.650	0.225			

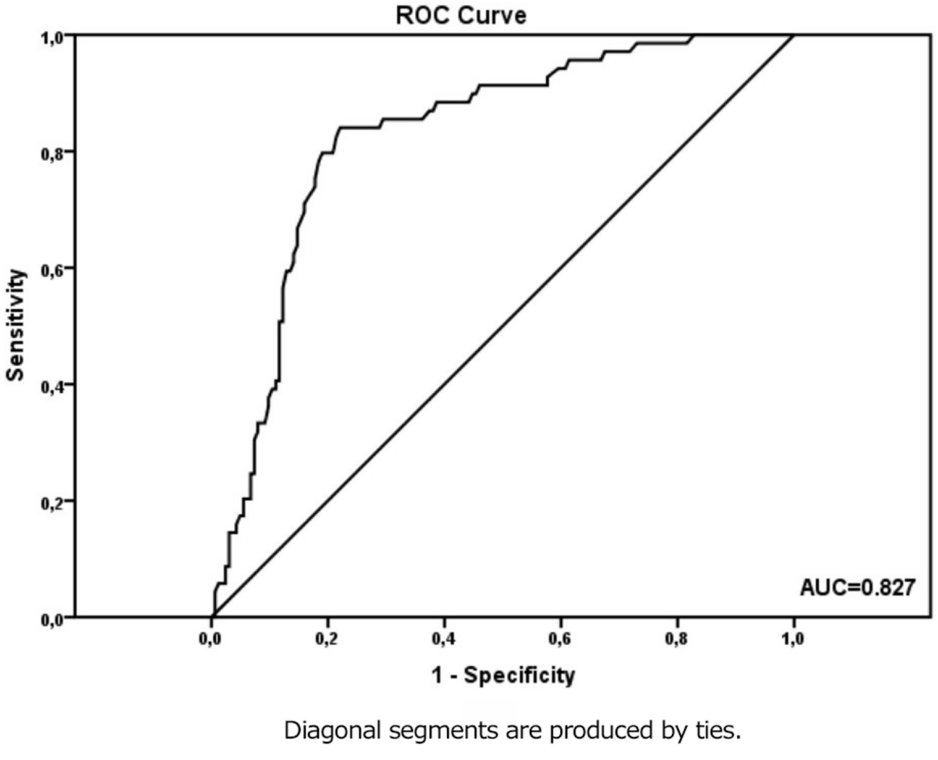

Fig. 2. ROC analysis demonstrates the predictive capacity of TMT as a non-invasive biomarker in responders and non-responders (AUC = 0.827, 95% CI: 0.770–0.884; $p < 0.001$), achieving a sensitivity of 84.1% and a specificity of 73.6%.

Discussion

This research aimed to explore the predictive significance of TMT assessed through standard MRI scans of the brain in individuals with brain metastases, conducted on the day prior to initiating radiosurgery. We focused on patient groups from prevalent tumor types known for central nervous system dissemination and included only those patients who had complete clinical follow-up data. Our findings revealed a robust association between initial TMT levels and patient outcomes within this cohort. Notably, this relationship remained significant regardless of established prognostic indicators. Therefore, we believe that measuring TMT can enhance survival predictions for patients with brain metastases in clinical practice and may facilitate better patient selection and stratification during clinical trials. Various factors such as age, heterogeneity of the different primary tumors, and exclusion of patients due to loss of follow-up were the main limitations of this retrospective single-center study.

The gold standard for evaluating sarcopenia includes not only the loss of skeletal muscle mass but also the decline in muscle function, such as gait speed and grip strength, according to the European Working Group on Sarcopenia in Older People (EWGSOP) [4], EWGSOP2 [15], and the Asian Working Group for Sarcopenia [16]. However, measuring muscle functions such as grip strength and gait speed sometimes cannot be accomplished because patients with brain tumors often have problems with motor proficiency or a decrease in muscle strength due to the neuromuscular dysfunction caused by the brain tumor itself [17].

MRI is the gold standard for the non-invasive assessment of muscle mass [18]. Patients with cancer commonly use CT images of the third lumbar vertebra (L3) to measure skeletal muscle mass, which significantly correlates with whole-body muscle and predicts prognosis [19]. A meta-analysis of 38 studies demonstrated that sarcopenia obtained from CT imaging is associated with worse survival in patients with extracranial solid tumors [9]. However, for brain tumors, using lumbar paravertebral muscles to calculate skeletal muscle is not feasible in clinical settings.

Routinely performed cranial imaging allows for full delineation of the temporal muscle, which is preferable for estimating muscle mass loss. Its thickness remains unaffected by muscular edema or radiation-related atrophy, only by oral disease or previous surgery. Regular cranial MRIs in patients with brain tumors allow for monitoring the TMT skeletal muscle status throughout the disease course. Therefore, we can use TMT to evaluate the musculoskeletal condition of these patients [20]. Several studies have demonstrated an excellent correlation between TMT and total skeletal muscle mass [16, 21].

In comparison to the plane or volume of muscle segmentation, TMT measurement on MRIs takes approximately 30 seconds per patient [10, 12, 22]. Therefore, we believe that TMT assessment, once validated in a prospective setting, could serve as a suitable parameter for integration into the clinical workflow.

Our research did not investigate the specific pathobiology associated with atrophy of the temporal

muscles; however, we believe this condition likely indicates a broader cancer-related sarcopenic syndrome. Supporting this idea, prior research [20] has shown a significant correlation between skeletal muscle mass and TMT measurements. While corticosteroids are known to lead to considerable muscle loss over time due to their side effects, they are often prescribed by physicians for managing symptomatic brain edema in patients diagnosed with brain metastases. In our investigation, baseline TMT was measured before commencing radiosurgery treatment, which minimizes the chance of extended corticosteroid exposure among participants.

Correlations with various patient characteristics were conducted, and the results of these analyses indicate that the TMT measurement offers insights not captured by other clinical parameters. Initially, we observed a weak inverse correlation between TMT and patient age. This suggests that assessing sarcopenia as an indicator of a patient's physical condition may provide more valuable information for clinical decision-making than relying solely on chronological age [23]. The variation in median TMT across different cancer types within the patient cohort could be attributed to differences in gender predominance.

Furthermore, recognizing the link between sarcopenia and cancer could encourage additional research and lead to new therapeutic targets. Interventions such as nutritional support, including omega-3 fatty acids, exercise training, or pharmacological strategies like myostatin inhibitors, could potentially aid in preventing muscle loss [12, 24-26]. Consequently, integrating muscle mass assessment into standard clinical practice for cancer patients is crucial; this allows for the early detection of muscle mass decline enabling prompt implementations to prevent or slow down its progression.

Disclosure

Conflict of interest

The authors declare no conflicts of interest.

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