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Correlation of Temporal Muscle Thickness and Prognostic Nutritional Index with High-Grade Brain Tumor Progression

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ABSTRACT Objective: This study aimed to evaluate the correlation between temporal muscle thickness (TMT) and Prognostic Nutritional Index (PNI) with disease progression in patients with high-grade brain tumors. **Material and Methods:** TMT was measured from the magnetic resonance images of 70 patients at the time of diagnosis. The TMT difference value was calculated by subtracting the post-treatment TMT value from the pre-treatment TMT value. The PNI value was determined by analyzing the complete blood count and biochemical parameter values at the time of diagnosis. Kaplan-Meier analyses and stepwise multivariate Cox regression analyses were used to assess the correlation of TMT and PNI with overall survival (OS) and progression-free survival (PFS). **Results:** Low PNI and high TMT difference values were correlated with the OS. OS analysis revealed that the mortality risk of patients with PNI<48.2 and TMT difference ≥0.9 was 3.4-fold higher than that of patients with PNI≥48.2 and TMT difference <0.9. Similarly, PFS analysis revealed that the mortality risk of patients with PNI<48.2 and TMT difference ≥0.9 was 2.3-fold higher than that in patients with PNI≥48.2 and TMT difference <0.9. **Conclusion:** This study demonstrated the prognostic value of TMT and PNI in high-grade brain tumors and revealed the enhanced power of the combination of TMT and PNI in predicting mortality. Thus, regular monitoring of TMT and PNI during the treatment can provide valuable insights into patient prognosis and aid in developing effective, individualized treatment strategies and consequently improving the OS outcomes and quality of life of patients.

Keywords: Brain neoplasms; temporal muscle; nutrition assessment

High-grade gliomas, which are the most common type of primary intracranial tumors, are associated with high mortality rates.[1] Tumor resection, followed by temozolomide-based chemoradiotherapy and adjuvant temozolomide treatment, does not prevent tumor progression within one year in almost all patients with high-grade tumors.[2] Thus, there is a need to identify predictive prognostic biomarkers for high-grade gliomas.

Objective parameters, such as the stage, location, grade of the tumor, and age, are used in treatment planning for patients with cancers. Molecular markers are also objective parameters, but their applications are not clinically practical and are associated with high costs. Specific therapeutic agents are not available to target several known mutated molecules. Thus, tests for evaluating molecular markers do not markedly contribute to developing treatment strategies for patients. Cost-effective diagnostic methods must be developed for patients with high-grade brain tumors who are associated with short survival.

In addition to objective parameters, the performance status of patients must be assessed. However, this assessment is a subjective evaluation and can vary depending on the observers, leading to differential survival predictions. The measurement of skeletal muscle mass objectively determines the physical condition of patients. Sarcopenia, a major cause of

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cancer-related cachexia, is associated with decreased skeletal muscle mass.[3] Previous studies have demonstrated that temporal muscle thickness (TMT) can aid in diagnosing sarcopenia and serve as a prognostic marker in patients with high-grade brain tumors. TMT can be easily measured from the cranial magnetic resonance (MR) images captured at the time of diagnosis.

The Prognostic Nutritional Index (PNI) is also a practical marker that indirectly shows the nutritional and immunological status of patients. Previous studies have demonstrated the value of PNI in assessing the nutritional status of patients and predicting the clinical prognosis of many cancer types. However, a limited number of studies have evaluated the value of PNI in predicting the prognosis of patients with high-grade brain tumors.[4] The findings of previous studies indicate that PNI is an effective, practical, and inexpensive prognostic indicator.

These studies have not evaluated the prognostic predictive value of the combination of PNI and radiological parameters in glioblastoma multiforme (GBM). This study aimed to evaluate the prognostic predictive value of the combination of TMT and PNI in high-grade gliomas. The findings of this study will enable the identification of indices that can effectively predict prognosis alone or in combination.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT SELECTION

This study was approved by the Clinical Research Ethics Committee (date: December 12, 2023, no: 984). Patients diagnosed with high-grade (Grade 3 and 4) brain tumors who were treated or followed up at the Medical Oncology Clinic and Radiation Oncology Clinic between January 2020 and September 2023 were included in the study. The patients were classified according to the World Health Organization 2016 classification system.

In total, 150 patient files were reviewed. The following cases were excluded: patients aged <40 years (n=40); patients whose diagnostic and/or post-treatment MR images were not available (n=20); patients whose follow-up period was less than 3 months (n=12); patients with a history of infection or inflammatory disease in the last three months (n=8). The data of patients were retrospectively analyzed. Data collection and analysis were conducted according to the ethical standards and the Declaration of Helsinki principles.

Clinical, pathological, and demographic data, such as age at diagnosis, gender, pathological diagnosis, tumor volume, tumor grade, tumor location, and type of surgery were recorded. The PNI value was calculated by examining the complete blood count and biochemical parameter values before surgery as follows: PNI=albumin (g/L)+[0.005×lymphocyte count (per microliter)].

ASSESSMENT OF TMT

T1-weighted MR images (1 mm isotropic resolution) captured using the contrast agent gadolinium and perpendicular to the temporal muscle axis were used to assess TMT. An experienced neuroradiologist, who was blinded to the patient data, measured the TMT. The level of measurement was determined to be at the level of the Sylvian fissure. The average TMT values of the right and left sides were calculated for each patient. In cases where the measurement of TMT on one side could affect the objectivity (those with temporal mass, temporal cranial edema, temporal surgical defect, and muscle atrophy), the contralateral TMT was used as a reference (Figure 1).

COMBINED NUTRITIONAL INDEX ASSESSMENT

A Combined Nutritional Index (CNI) variable was established using PNI and TMT values. The TMT difference variable was assessed as follows: TMT difference=pre-treatment TMT-post-treatment TMT. TMT measurement after radiotherapy (RT) was performed at 12 weeks, which is the most appropriate measurement time, considering the possibility of edema in early measurements and atrophy in late measurements.[5] The following four CNI groups were established according to the cut-off values:

Group 1: PNI≥48.2 and TMT difference <0.9 mm

Group 2: PNI<48.2 and TMT difference <0.9 mm

Group 3: PNI≥48.2 and TMT difference ≥0.9 mm

Group 4: PNI<48.2 and TMT difference ≥0.9 mm

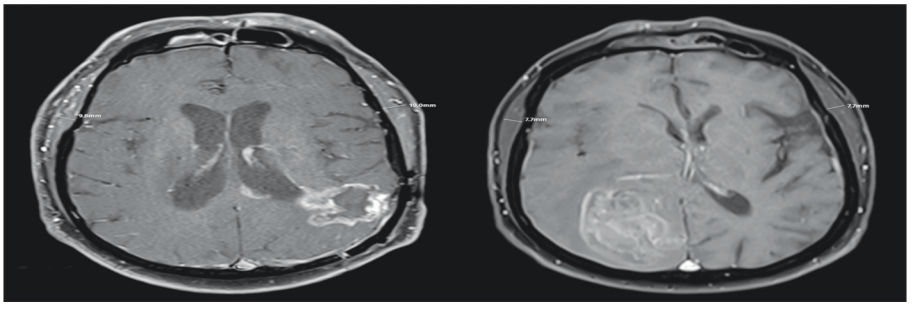

FIGURE 1: Axial T1-weighted contrast-enhanced cranial magnetic resonance images representing TMT assessment in a 71-year-old male patient (**A;** right TMT 9.8 mm left TMT 10 mm and mean TMT 9.9 mm) with a PFS of 12 months and an OS of 16 months in comparison to a 67-year-old male patient (**B;** bilateral TMT 7.7 mm and mean TMT value 7.7 mm) with a PFS of 1 months and an OS of 4 months.
TMT: Temporal muscle thickness; OS: Overall survival; PFS: Progression-free survival.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) were used to assess the normal distribution of continuous variables. Categorical data are expressed as frequency and percentage (%). Kaplan-Meier analysis of normally distributed data was performed using mean values, while that of non-normally distributed data was performed using median values. Two different models were used for survival analysis. Univariate analysis was performed using the Kaplan-Meier log-rank test, and hazard ratios were calculated using the Cox proportional hazards regression models. Multivariate analyses were performed with conditional backward selection Cox regression analysis to determine independent predictors of survival rates in high-grade brain tumors. Differences were considered significant at $p<0.05$.

RESULTS

PATIENT DISTRIBUTION

The study analyzed the data of 70 patients [30 females (42.9%) and 40 males (57.1%)] aged 18-79 years. The mean age of patients was 55.48 years. The types of tumors in the patients were as follows: GBM [n=55 (78.6%)], anaplastic astrocytoma [n=3 (4.3%)], anaplastic oligodendroglioma [n=2 (2.9%)], Grade 3 meningioma [n=5 (7.1%)], and other tumors-(pineoblastoma, gliosarcoma, adult-type medulloblastoma, pons glioma, and atypical teratoid rhabdoid tumor) [n=5 (7.1%)]. Based on the tumor grade, 60 and 10 patients had Grade 4 (85.7%) and Grade 3 (14.3%) tumors, respectively. The tumor location characteristics were as follows: temporal lobe [n=16 (22.9%)], parietal lobe [n=34 (48.6%)], frontal lobe [n=12 (17.1%)], occipital lobe [n=2 (2.9%)], cerebellum [n=4 (5.7%)], and brainstem [n=2 (2.9%)]. Based on the type of excision, 31 patients (44.3%) underwent gross total resection (GTR), 26 patients (37.1%) underwent subtotal resection (STR), 2 patients (2.9%) underwent biopsy, and 11 patients (15.7%) were not eligible for resection. Patients who were ineligible for resection were diagnosed based on radiological and clinical characteristics. Patient characteristics are shown in Table 1.

The mean tumor volume was 104.27 cm^3 (7.48-330.3 cm^3). The mean initial TMT at diagnosis (before surgery or RT) was 7.13 mm (3.5-11.8 mm). Meanwhile, the mean post-RT TMT was 6.2 mm (3.4-11.2 mm). Furthermore, the mean TMT difference value was 0.93 mm (0.6-1 mm).

At diagnosis, the mean values of albumin and lymphocyte count were 39.42 g/dL (23-48 g/dL) and 1.74×10^3 µL ($0.46\text{-}3.9\times10^3$ µL), respectively. The mean PNI value at diagnosis was 48.2 (29.3-59.5).

Among the study patients, 66 (94.3%) underwent RT, whereas 4 (5.7%) did not undergo RT.

To examine the correlation of overall survival (OS) with clinical and demographic characteristics, the data of patients who underwent biopsy and those

TABLE 1: Clinical, radiologic and demographic characteristics of the patients.

	Overall survival		Progression-free survival		
	Survived	Ex	No	Yes	Total
Gender					
Female	8 (34.8)	22 (46.8)	9 (50)	21 (41.2)	30 (42.9)
Male	15 (65.2)	25 (53.2)	9 (50)	30 (58.8)	40 (57.1)
Age					
<60	13 (56.5)	22 (46.8)	10 (55.6)	24 (47.1)	35 (50)
≥60	10 (43.5)	25 (53.2)	8 (44.4)	27 (52.9)	35 (50)
CNI					
PNI≥48.2 & TMT difference <0.9	10 (45.5)	14 (29.8)	6 (35.3)	18 (35.3)	24 (34.8)
PNI<48.2 & TMT difference <0.9	3 (13.6)	13 (27.7)	3 (17.6)	13 (25.5)	16 (23.2)
PNI≥48.2 & TMT difference ≥0.9	6 (27.3)	9 (19.1)	5 (29.4)	9 (17.6)	15 (21.7)
PNI<48.2 & TMT difference ≥0.9	3 (13.6)	11 (23.4)	3 (17.6)	11 (21.6)	14 (20.3)
Tumor grade					
Grade 4	16 (69.6)	44 (93.6)	10 (55.6)	49 (96.1)	60 (85.7)
Grade 3	7 (30.4)	3 (6.4)	8 (44.4)	2 (3.9)	10 (14.3)
Excision type					
Gros total resection	15 (65.2)	16 (34)	14 (77.8)	16 (31.4)	31 (44.3)
Subtotal resection	6 (26.1)	20 (42.6)	3 (16.7)	23 (45.1)	26 (37.1)
Biopsy	---	2 (4.3)	---	2 (3.9)	2 (2.9)
Inoperable	2 (8.7)	9 (19.1)	1 (5.6)	10 (19.6)	11 (15.7)
Tumor lateralite					
Right	15 (65.2)	25 (53.2)	9 (50)	30 (58.8)	40 (57.1)
Left	8 (34.8)	17 (36.2)	9 (50)	16 (31.4)	25 (35.7)
Bilateral	---	3 (6.4)	---	3 (5.9)	3 (4.3)
Midline	---	2 (4.3)	---	2 (3.9)	2 (2.9)
Tumor area					
Temporal	6 (26.1)	10 (21.3)	4 (22.2)	12 (23.5)	16 (22.9)
Pariatel	9 (39.1)	25 (53.2)	6 (33.3)	27 (52.9)	34 (48.6)
Frontal	6 (26.1)	6 (12.8)	5 (27.8)	7 (13.7)	12 (17.1)
Oksipital	---	2 (4.3)	---	2 (3.9)	2 (2.9)
Cerebellar	2 (8.7)	2 (4.3)	3 (16.7)	1 (2)	4 (5.7)
Brainstem	---	2 (4.3)	---	2 (3.9)	2 (2.9)
ITV					
<104.3	15 (65.2)	26 (55.3)	12 (66.7)	28 (54.9)	41 (58.6)
≥104.3	8 (34.8)	21 (44.7)	6 (33.3)	23 (45.1)	29 (41.4)
Post-RT TMT					
<6.2	11 (47.8)	29 (61.7)	9 (50)	30 (58.8)	40 (57.1)
≥6.2	12 (52.2)	18 (38.3)	9 (50)	21 (41.2)	30 (42.9)
TMT					
<7.1	13 (59.1)	27 (57.4)	10 (58.8)	29 (56.9)	40 (58)
≥7.1	9 (40.9)	20 (42.6)	7 (41.2)	22 (43.1)	29 (42)
Initial albumin					
<39.4	11 (47.8)	25 (53.2)	10 (55.6)	26 (51)	36 (51.4)
≥39.4	12 (52.2)	22 (46.8)	8 (44.4)	25 (49)	34 (48.6)
Initial lymphocytes					
<1.8	9 (39.1)	28 (59.6)	9 (50)	28 (54.9)	37 (52.9)
≥1.8	14 (60.9)	19 (40.4)	9 (50)	23 (45.1)	33 (47.1)
Pathologic diagnosis					
Glioblastoma multiforme	14 (60.9)	41 (87.2)	8 (44.4)	46 (90.2)	55 (78.6)
Anaplastic astrositoma	3 (13)	---	3 (16.7)	---	3 (4.3)
Anaplastic oligodendroglioma	1 (4.3)	1 (2.1)	1 (5.6)	1 (2)	2 (2.9)
Anaplastic menengioma	3 (13)	2 (4.3)	4 (22.2)	1 (2)	5 (7.1)
Others	2 (8.7)	3 (6.4)	2 (11.1)	3 (5.9)	5 (7.1)
Diagnosis type					
Pathologic	22 (95.7)	37 (78.7)	18 (100)	40 (78.4)	59 (84.3)
Radiologic	1 (4.3)	10 (21.3)	---	11 (21.6)	11 (15.7)

CNI: Combined Nutritional Index; PNI: Prognostic Nutritional Index; TMT: Temporal muscle thickness; ITV: Initial tumor volume; RT: Radiotherapy.

who were ineligible for surgery were combined in the excision type variable as the number of samples was insufficient for the analyses. Additionally, bilateral and midline categories in the tumor laterality variable and occipital and brainstem categories in the tumor area variable were not included in the analyses due to an insufficient number of observations. To examine the correlation of progression-free survival (PFS) with clinical and demographic characteristics, the data of patients undergoing biopsy and those who were ineligible for surgery in the excision type variable, patients with bilateral and midline tumors in the tumor laterality variable, and occipital, cerebellar, and brainstem categories in the tumor area variable were not included in the analyses.

FACTORS AFFECTING THE OS

The OS duration significantly varied according to the age of the patients (p=0.001). The median OS durations of patients aged <60 years and those aged ≥60 years were 27 and 10 months, respectively. The OS duration significantly varied between CNI groups (p=0.018). In particular, the OS durations of patients in Group 1 (PNI≥48.2 and TMT difference <0.9) and Group 2 (PNI<48.2 and TMT difference <0.9) were significantly different from those of patients in Group 4 (PNI<48.2 & TMT difference ≥0.9) with patients in groups 1 and 2 exhibiting enhanced survival duration. The median OS durations of patients in groups 1, 2, and 4 were 21, 12, and 5 months, respectively. The OS durations significantly varied according to the tumor grades (p<0.001). The median OS durations of patients with Grade 4 and Grade 3 tumors were 19.63 and 82.7 months, respectively. Additionally, the OS durations significantly varied according to the excision types (p<0.001). This significant difference was observed in all excision types with patients undergoing GTR exhibiting the highest survival duration. The median OS durations of patients undergoing GTR and STR were 40 and 11 months, respectively, while those of patients ineligible for surgery were 4 months. The OS durations significantly varied according to the post-RT TMT values (p=0.030). The median OS durations of patients with post-RT TMT values <6.2 and those with post-RT TMT values ≥6.2 were 11 and 21 months, respectively. Other demographic and clinical characteristics did not significantly affect the OS (p>0.050) (Table 2).

Table 3 shows the factors affecting the OS analyzed using the Cox regression models. Univariate analysis revealed that the age, CNI group, tumor class, excision types, and post-RT TMT values significantly affected the OS (p<0.05). The risk of mortality in patients aged ≥60 years was approximately 2.8 times higher than that in patients aged <60 years. Meanwhile, the risk of mortality in patients in Group 4 (PNI<48.2 and TMT difference ≥0.9) was approximately 3.4 times higher than that in patients in Group 1 (PNI≥48.2 and TMT difference <0.9). Compared with that in patients with Grade 4 tumors, the risk of mortality was approximately 0.1 times lower in patients with Grade 3 tumors. The mortality risk in patients undergoing STR was approximately 2.8 times higher than that in patients undergoing GTR. Compared with that in patients undergoing GTR, the mortality risk was approximately 6 times higher in patients ineligible for surgery. The risk of mortality in patients with post-RT TMT values ≥6.2 was approximately 0.5 times lower than that in patients with post-RT TMT values <6.2. Multivariate analysis revealed that gender, age, tumor class, tumor laterality, and tumor area significantly affected the OS (p<0.05). The mortality risk in male patients was approximately 0.3 times lower than that in females. Compared with that in patients aged <60 years, the mortality risk was approximately 2.9 times higher in patients aged ≥60 years. The mortality risk in patients with Grade 3 tumors was approximately 0.1 times lower than that in patients with Grade 4 tumors. Compared with that in patients with right-sided tumors, the mortality risk was approximately 6.4 times higher in patients with left-sided tumors. The mortality risk in patients with parietal lobe tumors was approximately 2.9 times higher than that in patients with temporal lobe tumors. Other variables did not significantly affect the OS (p>0.05) (Figure 2).

FACTORS AFFECTING THE PFS

The PFS durations significantly varied according to the age of the patients (p=0.039). The mean PFS durations of patients aged <60 years and those aged ≥60

TABLE 2: Kaplan-Meier analysis for overall survival (months).

	Mean (95% CI)	Median (95% CI)	Chi-squaremc	p value
Gender				
Female	16.38 (10.46-22.31)	12 (8.05-15.95)	2.648	0.104
Male	34.65 (21.85-47.45)	13 (7.89-18.11)		
Age				
<60	39.51 (26.05-52.97)	27 (0-55.54)	11.067	**0.001**
≥60	11.02 (7.3-14.75)	10 (7.17-12.83)		
CNI				
PNI≥48.2 & TMT difference <0.9	40.4 (21.66-59.15)	21 (0-52.03)[b]	10.031	**0.018**
PNI<48.2 & TMT difference <0.9	23.14 (10.84-35.44)	12 (8.3-15.7)[b]		
PNI≥48.2 & TMT difference ≥0.9	22.57 (12.45-32.69)	12 (3.01-20.99)[ab]		
PNI<48.2 & TMT difference ≥0.9	9.25 (4.35-14.15)	5 (0-13)[a]		
PNI				
<48.2	17.52 (9.45-25.58)	12 (9.01-14.99)	4.118	**0.042**
≥48.2	38.31 (22.98-53.63)	16 (5.96-26.04)		
TMT difference				
<0.9	32.46 (20.64-44.28)	16 (11.48-20.52)	2.867	0.090
≥0.9	16.85 (10.09-23.61)	11 (5.74-16.26)		
Tumor grade				
Grade 4	19.63 (13.18-26.08)	11 (9.71-12.29)	12.357	**<0.001**
Grade 3	82.7 (56.31-109.09)	---		
Excision type				
Gros total resection	45.29 (28.37-62.21)	40 (13.33-66.68)[c]	22.085	**<0.001**
Subtotal resection	16.6 (7.79-25.42)	11 (7.55-14.45)[b]		
Inoperable	7.44 (0.96-13.92)	4 (2.17-5.83)[a]		
Tumor lateralite				
Right	34.37 (20.05-48.69)	12 (9.67-14.33)	0.005	0.942
Left	26.75 (16.15-37.36)	16 (10.52-21.48)		
Tumor area				
Temporal	33.12 (15.83-50.41)	16 (8.17-23.83)	1.581	0.664
Pariatel	26.95 (13.35-40.55)	12 (10.32-13.68)		
Frontal	23.7 (13.04-34.36)	16 (10.98-21.03)		
Cerebellar	22.25 (4.82-39.68)	---		
ITV				
<104.3	36.41 (21.95-50.88)	12 (0.66-23.34)	1.745	0.187
≥104.3	17.94 (9.54-26.35)	12 (8.38-15.62)		
Post-RT TMI				
<6.2	21.29 (12.48-30.11)	11 (8.64-13.36)	4.690	**0.030**
≥6.2	37.72 (21.99-53.46)	21 (0-45.25)		
Initial TMT				
<7.1	29.15 (15.97-42.34)	12 (10.94-13.06)	0.083	0.774
≥7.1	27.42 (17.33-37.51)	14 (9.78-18.22)		
Initial albumin				
<39.4	21.36 (12.5-30.23)	12 (9.14-14.87)	1.713	0.191
≥39.4	37.06 (21.4-52.72)	12 (5.58-18.42)		
Initial lymphosyte				
<1.8	26.77 (14.49-39.06)	11 (9.18-12.82)	0.591	0.442
≥1.8	29.33 (18.75-39.9)	16 (9.94-22.06)		

CI: Confidence interval; mc: Mantel-Cox log rank statistic; CNI: Combined Nutritional Index; PNI: Prognostic Nutritional Index; TMT: Temporal muscle thickness; ITV: Initial tumor volume; RT: Radiotherapy. a-c: There is no difference between groups with the same letter.

TABLE 3: Univariate and multivariate Cox regression for factors affecting overall survival.

	Univariate		MultivariateCB	
	HR (95% CI)	p value	HR (95% CI)	p value
Gender (Ref.: Female)				
Male	0.62 (0.341-1.127)	0.117	0.311 (0.144-0.671)	**0.003**
Age (Ref.: <60)				
≥60	2.791 (1.465-5.318)	**0.002**	2.875 (1.216-6.798)	**0.016**
CNI (Ref.: PNI≥48.2 & TMT difference <0.9)				
PNI<48.2 & TMT difference <0.9	1.509 (0.698-3.26)	0.296	0.524 (0.197-1.394)	0.195
PNI≥48.2 & TMT difference ≥0.9	1.333 (0.564-3.151)	0.513	0.633 (0.202-1.983)	0.433
PNI<48.2 & TMT difference ≥0.9	3.395 (1.477-7.805)	**0.004**	2.395 (0.85-6.75)	0.099
PNI (Ref.: <48.2)	0.56 (0.313-1.003)	0.051		
TMT difference (Ref.: <0.9)	1.646 (0.904-2.997)	0.103		
Tumor grade (Ref.: Grade 4)	0.122 (0.029-0.507)	**0.004**	0.13 (0.024-0.702)	**0.018**
Grade 3				
Excision type (Ref.: Gros total resection)				
Subtotal resection	2.791 (1.418-5.493)	**0.003**	2.289 (0.949-5.517)	0.065
Inoperable	6.04 (2.56-14.251)	**<0.001**		
Tumor lateralite (Ref.: Right)				
Left	1.023 (0.545-1.919)	0.943	6.357 (1.989-20.32)	**0.002**
Tumor area (Ref.: Temporal)				
Pariatel	1.316 (0.624-2.775)	0.470	2.87 (1.062-7.755)	**0.038**
Frontal	0.821 (0.294-2.289)	0.706	0.996 (0.292-3.398)	0.995
Cerebellar	0.849 (0.184-3.922)	0.834	1.353 (0.117-15.603)	0.809
ITV (Ref.: <104.3)				
≥104.3	1.467 (0.815-2.641)	0.201		
Post-RT TMT (Ref.: <6.2)				
≥6.2	0.528 (0.288-0.965)	**0.038**		
Initial TMT (Ref.: <7.1)				
≥7.1	0.919 (0.509-1.659)	0.780		
Initial albumin (Ref.: <39.4)				
≥39.4	0.686 (0.384-1.228)	0.205		
Initial lymphosyte (Ref.: 1.8)				
≥1.8	0.797 (0.44-1.445)	0.455		

HR: Hazard ratio; CI: Confidence interval; CB: Conditional bacward stepwise method; CNI: Combined Nutritional Index; PNI: Prognostic Nutritional Index; TMT: Temporal muscle thickness; ITV: Initial tumor volume; RT: Radiotherapy.

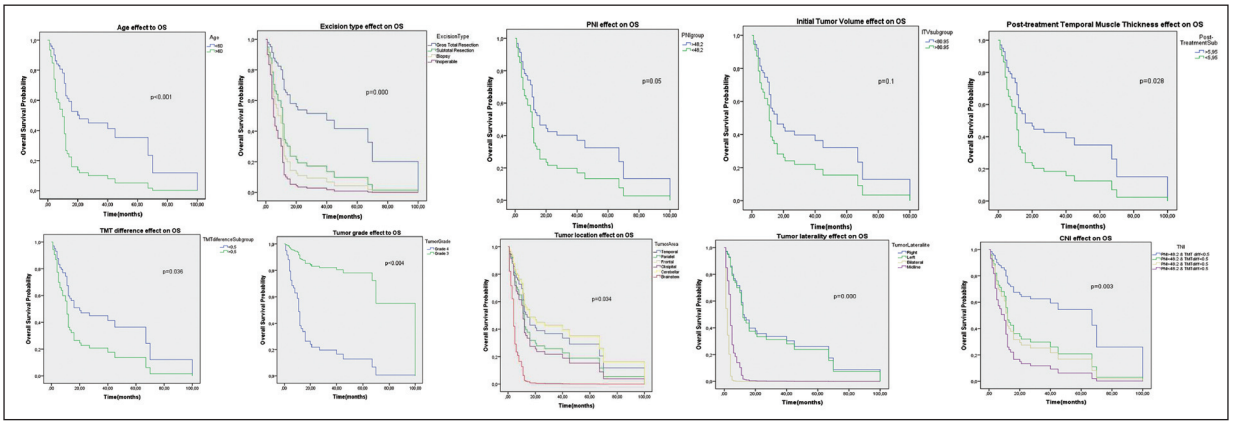

FIGURE 2: Kaplan-Meier analyzes in terms of OS.

OS: Overall survival; ITV: Initial tumor volume; post-RT TMT: After radiation therapy temporal muscle thickness; PNI: Prognostic Nutritional Index; TMT-difference: Temporal muscle thickness difference (initial TMT-post-RT TMT); CNI: Combined Nutritional Index.

years were 32.4 and 7.8 months, respectively. The PFS durations varied according to the tumor grades (p<0.001). The mean PFS durations of patients with Grade 4 tumors and those with Grade 3 tumors were 10.55 and 88.6 months, respectively. The PFS survival durations varied according to the excision types (p=0.003). The median survival durations of patients undergoing GTR and STR were 44 and 6 months, respectively. Other demographic and clinical characteristics of the patients did not significantly affect the PFS durations (p>0.050) (Table 4).

Table 5 shows the factors affecting the PFS analyzed using the Cox regression models. Univariate analysis revealed that the CNI group, tumor class, and

TABLE 4: Kaplan-Meier analysis for progression-free survival (months).

	Mean (95% CI)	Median (95% CI)	Chi-squaremc	p value
Gender				
Female	14.13 (7.2-21.06)	6 (3.64-8.36)	0.066	0.798
Male	23.44 (11.21-35.66)	8 (3.83-12.17)		
Age				
<60	32.4 (17.17-47.62)	7 (0-14.4)	4.259	**0.039**
≥60	7.82 (4.5-11.14)	7 (4.05-9.95)		
PNI				
<48.2	13.82 (5.05-22.6)	6 (3.13-8.87)	1.944	0.163
≥48.2	26.23 (12.69-39.77)	8 (1.79-14.21)		
TMT difference				
<0.9	24.81 (12.73-36.88)	9 (4.8-13.2)	1.333	0.248
≥ 0.9	11.92 (4.83-19)	5 (1.59-8.41)		
CNI				
PNI≥48.2 & TMT difference <0.9	27.07 (10.85-43.3)	11 (4.39-17.61)	5.555	0.135
PNI<48.2 & TMT difference <0.9	18.31 (5.99-30.64)	7 (3.08-10.92)		
PNI≥48.2 & TMT difference ≥0.9	16.96 (6.15-27.76)	8 (1-15)		
PNI<48.2 & TMT difference ≥0.9	4.48 (1.75-7.2)	2 (0-9.33)		
Tumor grade				
Grade 4	10.55 (5.8-15.29)	6 (4.07-7.93)	17.453	**<0.001**
Grade 3	88.6 (63.88-113.32)	---		
Excision type				
Gros total resection	39.78 (20.52-59.05)	44 (0.41-87.59)	8.630	**0.003**
Subtotal resection	9.49 (3.9-15.08)	6 (3.21-8.79)		
Tumor lateralite				
Right	24.53 (11.9-37.15)	6 (3.81-8.19)	0.795	0.373
Left	21.63 (10.96-32.3)	12 (7.37-16.63)		
Tumor area				
Temporal	22.62 (9-36.23)	8 (0-17.15)	4.447	0.108
Pariatel	15.71 (3.75-27.67)	4 (2.52-5.48)		
Frontal	18.32 (7.75-28.9)	11 (6.78-15.22)		
ITV				
<104.3	27.11 (13.37-40.85)	9 (2.53-15.47)	2.302	0.129
≥104.3	11.67 (3.95-19.4)	6 (3.25-8.76)		
Post-RT TMT				
<6.2	12.98 (5.64-20.32)	6 (3.26-8.74)	2.990	0.084
≥6.2	29.51 (13.21-45.81)	9 (3.16-14.84)		
Initial TMT				
<7.1	21.7 (8.9-34.49)	6 (1.02-10.98)	0.005	0.941
≥7.1	17.97 (8.9-27.04)	7 (3.86-10.14)		
Initial albumin				
<39.4	16.49 (6.65-26.33)	5 (1.75-8.25)	1.407	0.236
≥39.4	24.08 (11.37-36.8)	8 (3.77-12.23)		
Initial lymphosyte				
<1.8	24.31 (11.07-37.55)	6 (3.35-8.65)	0.010	0.919
≥1.8	18.34 (9.43-27.26)	9 (3.33-14.67)		

CI: Confidance interval; mc: Mantel-Cox log rank statistic; CNI: Combined Nutritional Index; PNI: Prognostic Nutritional Index; TMT: Temporal muscle thickness; ITV: Initial tumor volume; RT: Radiotherapy.

TABLE 5: Univariate and multivariate Cox regression for factors affecting progression-free survival.

	Univariate		Multivariatebc	
	HR (95% CI)	p value	HR (95% CI)	p value
Gender (Ref.: Female)				
Male	0.931 (0.525-1.652)	0.807		
Age (Ref.: <60)				
≥60	1.799 (0.993-3.26)	0.053		
CNI (Ref.: PNI≥48.2 & TMT difference <0.9)				
PNI<48.2 & TMT difference <0.9	1.204 (0.578-2.51)	0.620		
PNI≥48.2 & TMT difference ≥0.9	1.066 (0.468-2.425)	0.880		
PNI<48.2 & TMT difference ≥0.9	2.298 (1.038-5.088)	0.040		
PNI (Ref.: <48.2)	0.684 (0.389-1.203)	0.187		
TMT difference (Ref.: <0.9)	1.38 (0.774-2.462)	0.275		
Tumor grade (Ref.: Grade 4)				
Grade 3	0.053 (0.007-0.385)	0.004	0.054 (0.007-0.402)	0.004
Excision type (Ref.: Gros total resection)				
Subtotal resection	2.581 (1.312-5.077)	0.006		
Tumor lateralite (Ref.: Right)				
Left	0.762 (0.408-1.422)	0.393		
Tumor area (Ref.: Temporal)				
Pariatel	1.619 (0.806-3.251)	0.176	2.969 (1.243-7.091)	0.014
Frontal	0.76 (0.297-1.942)	0.566	1.321 (0.46-3.788)	0.605
ITV (Ref.: <104.3)				
≥104.3	1.513 (0.859-2.667)	0.152		
Post-RT TMT (Ref.: <6.2)				
≥6.2	0.616 (0.344-1.103)	0.103		
Initial TMT (Ref.: <7.1)				
≥7.1	0.98 (0.556-1.728)	0.944		
Initial albumin (Ref.: <39.4)				
≥39.4	0.723 (0.411-1.272)	0.261		
Initial lymphosyte (Ref.: 1.8)				
≥1.8	0.973 (0.553-1.711)	0.923		

HR: Hazard ratio; CI: Confidence interval; CNI: Combined Nutritional Index; PNI: Prognostic Nutritional Index; TMT: Temporal muscle thickness; ITV: Initial tumor volume; RT: Radiotherapy.

excision types significantly affected the PFS ($p<0.05$). The mortality risk in patients in Group 4 (PNI<48.2 and TMT difference ≥0.9) was approximately 2.3 times higher than that in patients in Group 1 (PNI≥48.2 and TMT difference <0.9). Compared with that in patients with Grade 4 tumors, the mortality risk was approximately 0.1 times lower in patients with Grade 3 tumors. The mortality risk in patients undergoing STR was approximately 2.6 times higher than that in patients undergoing GTR. Multivariate analysis revealed that the tumor grade and tumor area significantly affected the PFS ($p<0.05$). The mortality risk in patients with Grade 3 tumors was approximately 0.1 times lower than that in patients with Grade 4 tumors. Compared with that in patients with temporal lobe tumors, the mortality risk was approximately 3 times higher in patients with parietal lobe tumors. Other variables did not significantly affect the PFS ($p>0.05$) (Figure 3).

DISCUSSION

TMT, a parameter used to estimate skeletal muscle mass in patients, is reported to be a negative independent prognostic factor for OS and PFS in patients with high-grade brain tumors.[6] PNI, which is calculated using albumin and lymphocyte values, reflects both nutritional and inflammation status and can effectively predict the OS and PFS. This is the first

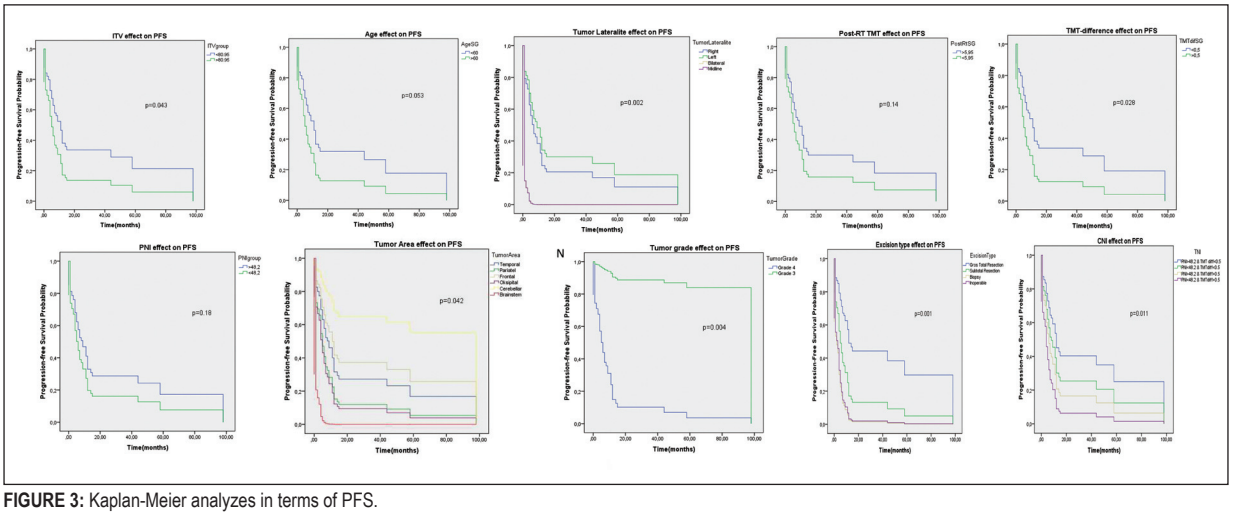

FIGURE 3: Kaplan-Meier analyzes in terms of PFS.

PFS: Progression-free survival; ITV: Initial tumor volume; post-RT TMT: After radiation therapy temporal muscle thickness; PNI: Prognostic Nutritional Index; TMT-difference: Temporal muscle thickness difference (initial TMT-post-RT TMT); CNI: Combined Nutritional Index.

study to evaluate the prognostic value of the combination of TMT and PNI in patients with high-grade brain cancer. The findings of this study indicate that both TMT and PNI are significant prognostic markers in the study cohort and that the prognostic value of CNI derived from the combination of these parameters is higher than that of individual parameters alone.

In this study, low PNI and high TMT difference values were associated with mOS. OS analysis revealed that the mortality risk of patients with PNI<48.2 and TMT difference ≥0.9 was 3.4-fold higher than that of patients with PNI≥48.2 and TMT difference <0.9. Similarly, PFS analysis revealed that the mortality risk of patients with PNI<48.2 and TMT difference ≥0.9 was 2.3-fold higher than that in patients with PNI≥48.2 and TMT difference <0.9.

Tumor location, degree of resection, and grade are known factors affecting the prognosis in patients with brain cancer.[7] Consistently, this study demonstrated that these factors affected the prognosis of patients with high-grade gliomas.

Previous studies have evaluated the correlation between TMT and prognosis in patients with brain tumors.[8-12] A meta-analysis published in 2022 reported that TMT was associated with the PFS and OS.[9] Consistent with this meta-analysis, this study demonstrated that low TMT was negatively associated with the mOS and PFS. Similarly, a retrospective multicenter study reported that TMT is an independent prognostic marker for OS in newly diagnosed glioblastoma.[13]

The negative correlation between decreased TMT and prognosis reported in this study is consistent with the findings of previous studies, which demonstrated that skeletal muscle mass reflected through TMT is a significant prognostic factor in patients with high-grade brain tumors. However, one study did not demonstrate the prognostic benefit of TMT in patients with high-grade glioma and did not recommend the use of TMT as the sole parameter for predicting OS in these patients.[14]

Various inflammatory markers are involved in tumor formation and development. The number of studies evaluating systemic inflammatory markers to predict prognosis in patients with malignant tumors has been increasing.[6] The inflammatory and nutritional status of patients is associated with prognosis.[15] Nutritional status affects the content of albumin (a negative acute phase reactant synthesized in the liver) and is associated with a chronic inflammatory response to malignancy. Inflammation downregulates the albumin levels.[15] Previous studies have reported that albumin downregulation is associated with poor survival in patients with cancer.[4] Tumor necrosis factor-alpha and interleukin-6 exert protective effects

against the cytotoxicity of immune cells in patients with GBM and inhibit albumin expression.[16,17] Lymphocytes are involved in immune regulation and are essential components of immune responses, suppressing cancer cell proliferation, invasion, and migration. Thus, lymphocytes determine the prognosis of patients with cancer.

The PNI score, which is calculated from serum albumin concentration and total lymphocyte count, is an independent prognostic marker for OS in various cancers.[18,19] However, consensus on the prognostic value of PNI in patients with brain tumors has not been reached.[20,21] A multicenter retrospective study revealed that PNI was not correlated with OS in patients with GBM.[22] In contrast, a meta-analysis revealed that the PNI score has a prognostic value in glioblastoma.[4] One study reported that the preoperative PNI level was an independent prognostic factor in patients with Grade 4 gliomas. In this study, PNI was not an independent prognostic factor in patients with Grade 3 gliomas, which can be attributed to the small sample size.[23] However, this study demonstrated that PNI affected the OS and PFS of patients with Grade 3 and Grade 4 gliomas.

This study has various limitations. First, this study performed retrospective analysis and involved patients from a single institution, which may limit the applicability of the results to broader populations with different demographic characteristics and under different healthcare settings. Moreover, the measurement of TMT and PNI, although practical, can vary depending on the techniques and protocols used. Thus, future studies must standardize TMT and PNI measurements.

Additionally, this study did not account for all possible confounding factors that could affect the outcomes, such as other comorbidities, treatments received outside the scope of the study, and lifestyle factors. Multicenter studies with a large sample size must be performed to address these limitations and further validate the findings of this study.

CONCLUSION

The findings of this study improved our understanding of the prognostic factors in patients with high-grade brain tumors. This study demonstrated the prognostic value of TMT and PNI in patients with high-grade brain tumors and suggested that the combination of TMT and PNI provides increased predictive power for disease mortality.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Şafak Yıldırım Dişli, Hatice Başaran Gökşen;* ***Design:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen;* ***Control/Supervision:*** *Şafak Yıldırım Dişli, Ahmet Kürşad Dişli;* ***Data Collection and/or Processing:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen, Hasan Erdoğan;* ***Analysis and/or Interpretation:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen, Hasan Erdoğan;* ***Literature Review:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen, Ahmet Kürşad Dişli;* ***Writing the Article:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen, Ahmet Kürşad Dişli;* ***Critical Review:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen;* ***References and Fundings:*** *Şafak Yıldırım Dişli;* ***Materials:*** *Şafak Yıldırım Dişli, Hatice Başaran Gökşen, Hasan Erdoğan.*

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