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Influence of temporal muscle thickness on the outcome of radiosurgically treated patients with brain metastases from non–small cell lung cancer

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OBJECTIVE The purpose of this study was to assess the impact of temporal muscle thickness (TMT), a surrogate marker for sarcopenia, in radiosurgically treated patients with brain metastases (BMs) from non–small cell lung cancer (NSCLC).

METHODS For 566 patients with BMs from NSCLC in the period between June 2012 and December 2019, TMT values were retrospectively measured on the planning brain magnetic resonance imaging (MRI) studies that had been obtained before their first Gamma Knife radiosurgery treatment (GKRS1). Predefined sex-specific TMT cutoff values were used to stratify the study cohort into patients at risk for sarcopenia and patients with normal muscle status. Cox regression models adjusted for other prognostic parameters were used to evaluate sarcopenia as an independent prognostic factor.

RESULTS In sarcopenia patients with a TMT below the sex-specific cutoff values, the risk of death was significantly increased (HR 1.908, 95% CI 1.550–2.349, $p < 0.001$). In addition, sarcopenia was revealed as an independent prognostic factor even after adjusting for age groups, sex, number of BMs, presence of extracranial metastases, NSCLC subtypes, Karnofsky Performance Status groups, recursive partitioning analysis classes, and concomitant immunotherapy or targeted therapy (HR 1.680, 95% CI 1.347–2.095, $p < 0.001$). However, patients at risk for sarcopenia showed no significant differences in the estimated mean time until local BM progression after GKRS1, compared to patients with normal muscle status ($p = 0.639$).

CONCLUSIONS TMT obtained from planning MRI studies is an independent prognostic marker in radiosurgically treated patients with BMs from NSCLC and may aid patient stratification in future clinical trials.

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KEYWORDS sarcopenia; temporal muscle thickness; Gamma Knife radiosurgery; brain metastases; non–small cell lung cancer; stereotactic radiosurgery; oncology

Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, as well as the most common primary tumor for developing brain metastases (BMs).[1,2] Given an increasing number of diagnostic imaging methods and improved imaging quality, the incidence of BMs is constantly rising.[2,3] Local treatment options include microsurgical resection, whole-brain radiation therapy (WBRT), fractionated radiotherapy, and stereotactic radiosurgery. The local BM treatment should be tailored according to each patient's clinical condition, histopathological and molecular tumor characteristics, and number, volume, and localization of BMs.[2,4] Gamma

ABBREVIATIONS BM = brain metastasis; CT = computed tomography; DS-GPA = diagnosis-specific GPA; ECM = extracranial metastasis; GKRS = Gamma Knife radiosurgery; GKRS1 = first GKRS treatment; GPA = graded prognostic assessment; IT = immunotherapy; KPS = Karnofsky Performance Status; lung-molGPA = lung-specific molecular marker GPA; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; RPA = recursive partitioning analysis; SIR = score index for radiosurgery; TMT = temporal muscle thickness; TT = targeted therapy; WBRT = whole-brain radiation therapy.

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Knife radiosurgery (GKRS) is generally performed in patients with a good clinical condition but may even be used in a palliative setting. GKRS involves the application of a high dose of radiation precisely targeted to a lesion, thus enabling high tumor control rates and a rapid radiation falloff to surrounding brain parenchyma.[5,6] In contrast to microsurgical resection, GKRS allows the treatment of 10 and more BMs in one session.[7] In addition, neurocognitive risks have been shown to be significantly reduced compared to those with WBRT.[6]

In general, patients suffering from NSCLC with BMs are known to have poor overall survival; however, the individual survival duration can vary widely.[8,9] In clinical settings, a variety of prognostic measures, such as the general or diagnosis-specific graded prognostic assessment (DS-GPA), lung-specific molecular marker (lung-mol)GPA, recursive partitioning analysis (RPA), and score index for radiosurgery (SIR), are used to estimate the outcome of BM patients. Those scales all include the Karnofsky Performance Status (KPS). Consequently, subjective judgment of the patient's condition by the attending physician has been reported to show high observer variability and thus seemingly provides little accuracy.[9–13]

Sarcopenia is the progressive loss of skeletal muscle mass and strength, primarily found in elderly people or secondarily due to systemic disease.[14] In 2018, the European Working Group on Sarcopenia in Older People (EWGOP) defined sarcopenia by three diagnostic features: muscle strength, muscle quantity, and physical performance.[15] Sarcopenia highly impacts patient prognosis in various cancer types and is associated with cancer-related cachexia.[16–22]

Despite knowledge of the individual and socioeconomic importance of preventing the loss of skeletal muscle mass and function, diagnostic procedures to establish an overview of skeletal muscle status are not yet routinely integrated into the clinical workflow.[23] For patients with extracranial tumors, muscle mass at the level of the third lumbar vertebra in cross-sectional areas on computed tomography (CT) scans can be measured.[22,24,25] Not only lumbar muscle mass but also craniofacial muscles can be used as surrogate parameters to determine skeletal muscle mass. Previous studies have shown a significant correlation between temporal muscle thickness (TMT) and lumbar skeletal muscle mass as well as arm muscle circumference and calf circumference.[26,27] TMT has also been shown to be highly correlated to grip strength of the dominant hand in healthy volunteers, as well as in patients with different types of neurological illnesses, and to the results of the SARC-F questionnaire for stroke patients.[28–30] Furthermore, TMT has been shown to be an independent survival predictor in patients with glioblastoma, primary central nervous system lymphoma, and newly diagnosed BMs.[17–19,31]

Although TMT measurements have recently been described as highly predictive of outcome in oncological patients, the clinical relevance in radiosurgically treated BM patients has not yet been evaluated. Thus, the purpose of the current study was to assess the impact of TMT on the outcome of radiosurgically treated patients with BMs from NSCLC.

Methods

Study Population

For this retrospective analysis, we considered all 573 patients with BMs from NSCLC who had undergone radiosurgical treatment at the Department of Neurosurgery of the Medical University of Vienna between June 2012 and December 2019. As standard practice, planning magnetic resonance imaging (MRI) sequences were obtained before the first GKRS treatment (GKRS1). However, in 7 patients (1%), MRI examinations could not be performed because of patients' contraindications. For these patients, CT with contrast was performed for treatment planning; therefore, these patients were excluded from our study. In the remaining 566 patients, the thickness of the temporal muscle could be measured on cranial contrast-enhanced T1-weighted GKRS planning MRI sequences. All radiosurgically treated patients with BMs had been routinely monitored at a 3-month interval with clinical and radiological follow-up in outpatient care. Clinical data, including current status of the primary tumor, extracranial metastases (ECMs), as well as oncological treatments and patient conditions, were collected via retrospective chart review. In addition, the general or DS-GPA, lung-molGPA, RPA, and SIR were assessed and compared between sarcopenia groups.[9–12] These scores all include the KPS. Patients who had been lost to follow-up were included in the study but excluded from the outcome analysis. Furthermore, a death register comparison for all study patients was performed.

The study was approved by the local ethics committee of the Medical University of Vienna and complied with the Declaration of Helsinki.

Analysis of TMT

TMT was retrospectively analyzed on the radiosurgical planning MRI studies that had been routinely performed at the time of GKRS treatment in the NSCLC patients. The measurements were taken on isovoxel contrast-enhanced T1-weighted MR images without fat saturation, perpendicular to the long axis of the temporal muscle. Predefined anatomical landmarks consisted of a parallel orientation to the anterior commissure–posterior commissure line, the sylvian fissure (anteroposterior landmark), and the level of the orbital roof (craniocaudal landmark). For further statistical analysis, mean TMT values were included with separate measurements of right and left TMT. If previous interventions had had an impact on the TMT on one side (e.g., muscle edema or atrophy from earlier craniotomy or radiation therapy), those measurements were excluded from further analysis. Examples of TMT measurements on contrast-enhanced T1-weighted MR images are presented in Fig. 1.

Previously, sex-specific TMT cutoff values were defined as 2.5 SDs below the mean TMT values of a normative reference, comprising a healthy volunteer cohort between 18 and 40 years of age, to identify patients at risk for sarcopenia.[15,29] Those cutoff values were set as ≤ 6.3 mm in male patients and ≤ 5.2 mm in female patients and were used in the current study to classify patients into two groups (normal muscle status > TMT cutoff value, at risk for sarcopenia ≤ TMT cutoff value).[29]

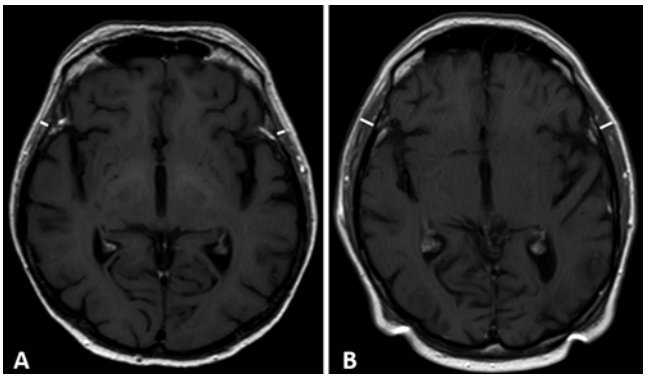

FIG. 1. TMT measurements on axial contrast-enhanced T1-weighted MR images from 2 female NSCLC patients with BMs. **A:** Image obtained in a 72-year-old female patient with a mean TMT of 2.9 mm (below the sex-specific cutoff value) and a survival duration of 23.0 months after GKRS1. **B:** Image obtained in a 70-year-old female patient with a TMT of 5.4 mm and a survival duration of 43.0 months after GKRS1. To avoid any potentially influencing factors, 2 patients with similar baseline characteristics (adenocarcinomas, age > 65 years, KPS > 80%, multiple BMs, no ECMs, negative oncological markers, GPA/RPA/SIR classifications, and no previous oncological treatments before or at GKRS1) were chosen.

Statistical Analyses

Continuous variables were presented as their median and range, and categorical variables were shown as frequencies and percentages. To compare differences between the two groups, chi-square and Mann-Whitney U-tests were performed as appropriate. The Kaplan-Meier method was used to estimate survival in patients below and above the sex-specific TMT cutoff values. To compare differences in overall survival or progression-free survival after the GKRS1 between the TMT groups, the generalized Wilcoxon-Breslow test or log-rank test was applied as appropriate. Univariate Cox proportional hazards regression analyses were applied to estimate the effect of sarcopenia on overall survival after GKRS. In a next step, multivariate Cox regression models with an automated stepwise forward selection and a threshold p value of 15% were performed, including age groups (≤ 65 vs > 65 years), sex, number of BMs (single vs multiple), presence of ECMs, NSCLC subtypes, KPS groups (< 80% vs ≥ 80%), RPA classes, concomitant immunotherapy (IT) or targeted therapy (TT), and TMT/sarcopenia groups. Statistical analyses were performed with IBM SPSS Statistics for Windows (version 24, IBM Corp.). A two-sided p value < 0.05 was considered statistically significant.

Results

Study Population

Patient baseline characteristics are listed in Table 1. The median TMT value for the whole study population of NSCLC patients with BMs at GKRS1 was 5.3 mm (range 1.7–9.4 mm). TMT values were shown to be significantly higher in male patients (5.6 mm, range 1.8–9.4 mm) than in female patients (4.9 mm, range 1.7–8.4 mm; p < 0.001). Based on the sex-specific TMT cutoff values, the study population consisted of 357/566 (63%) patients at risk for sarcopenia (TMT value ≤ sex-specific cutoff value; female: 176/357; male: 181/357) and 209/566 (37%) patients with a normal skeletal muscle status (TMT value > sex-specific cutoff value; female: 121/209; male: 88/209). Furthermore, patients at risk for sarcopenia were significantly older (p = 0.001), had significantly lower KPS scores (p = 0.001), and had significantly shorter survival as predicted by all prognostic scores. Patients at risk for sarcopenia also tended to be male (p = 0.048). Moreover, among patients with no risk for sarcopenia (190/209, 91%) a higher percentage of adenocarcinomas was diagnosed compared to patients at risk for sarcopenia (285/357, 80%; p < 0.001).

Association of TMT With Survival After GKRS1

Of the 566 study-eligible patients, 8 (1%) were lost to follow-up. Therefore, 558/566 patients (99%) could be included in the survival analyses. Kaplan-Meier survival estimates showed that after GKRS1, patients at risk for sarcopenia (351/558 [63%]) showed a significant shorter survival with an estimated median survival time of 7.5 months (95% CI 6.2–8.8 months), in comparison to patients with a normal muscle status (207/558 [37%]) whose estimated median survival time was 18.6 months (95% CI 16.2–21.0 months, p < 0.001; Fig. 2A) In a subanalysis, the influence of sarcopenia on the estimated median survival duration after GKRS1 was separately evaluated for female and male patients. The patients at risk for sarcopenia had significantly shorter median survival durations after GKRS1, regardless of their sex (female, p < 0.001; male, p < 0.001).

We also assessed the potential influence of NSCLC subtypes on survival. Patients with adenocarcinoma (467/558 [84%]) had a significantly longer median survival after GKRS1 (11.5 months, 95% CI 9.9–13.1 months) than the patients with non-adenocarcinomas (91/558 [16%], 3.5 months, 95% CI 2.3–4.8 months; p < 0.001). This significant difference was further evaluated in terms of the presence or absence of the risk for sarcopenia. Among patients at risk for sarcopenia, those with adenocarcinoma revealed a significantly longer median survival after GKRS1 (279/351 [79%], 8.8 months, 95% CI 7.4–10.1 months) than the patients with non-adenocarcinoma (72/351 [21%], 3.5 months, 95% CI 2.2–4.9 months; p < 0.001). Similarly, among patients with a normal muscle status, those with adenocarcinoma also showed a significantly longer median survival (188/207 [91%], 19.4 months, 95% CI 16.5–22.2 months) than the patients with non-adenocarcinoma (19/207 [9%], 3.0 months, 95% CI 0.5–5.5; p < 0.001).

Of note, patients with a single BM at the GKRS1 had a significantly longer estimated median survival after GKRS1 (12.0 months, 95% CI 9.7–14.4 months) than the patients with multiple BMs (9.1 months, 95% CI 7.5–10.7 months; p = 0.025). In a next step, the influence of sarcopenia on the estimated median survival duration after GKRS1 was separately evaluated for patients with multiple BMs and those with a single BM. In this subanalysis, patients at risk for sarcopenia had a significantly shorter median survival after GKRS1, regardless of their BM status (single BM, p < 0.001; multiple BMs, p = 0.001).

TABLE 1. Overview of baseline characteristics at GKRS1

	Total Sample	Patients w/ No Risk for Sarcopenia	Patients at Risk for Sarcopenia	p Value
No. of patients	566	209 (37)	357 (63)	
Median age in yrs	63 (27–87)	62 (28–82)	65 (27–87)	**0.001**
Male	269 (48)	88 (42)	181 (51)	**0.048**
Median KPS in %	80 (40–100)	80 (40–100)	80 (40–100)	**0.001**
KPS group				**<0.001**
≥80%	391 (69)	164 (78)	227 (64)	
<80%	175 (31)	45 (22)	130 (36)	
NSCLC subtype				**0.001**
Adenocarcinoma	475 (84)	190 (91)	285 (80)	
Non-adenocarcinoma	91 (16)	19 (9)	72 (20)	
ECM status at time of BM diagnosis				0.508
Yes	378 (67)	136 (65)	242 (68)	
No	188 (33)	73 (35)	115 (32)	
No. of BMs at GKRS1				0.172
Single	231 (41)	93 (44)	138 (39)	
Multiple	335 (59)	116 (56)	219 (61)	
CNS treatment before GKRS1				0.142
Yes	89 (16)	39 (19)	50 (14)	
No	477 (84)	170 (81)	307 (86)	
Neurological symptoms				0.059
Yes	403 (71)	139 (67)	264 (74)	
No	163 (29)	70 (33)	93 (26)	
Median predicted survival after prognostic scores in mos				
DS-GPA	5.5 (3.0–14.8)	5.5 (3.0–14.8)	5.5 (3.0–14.8)	**0.005**
General GPA	3.8 (2.6–11.0)	3.8 (2.6–11.0)	3.8 (2.6–11.0)	**0.019**
Lung-molGPA	13.7 (5.3–46.8)	13.7 (5.3–46.8)	13.7 (5.3–46.8)	**<0.001**
RPA	4.5 (2.3–7.7)	4.5 (2.3–7.7)	4.5 (2.3–7.7)	**0.001**
SIR	6.0 (2.1–8.8)	6.0 (2.1–8.8)	6.0 (2.1–8.8)	**<0.001**
RPA class				**0.011**
1	75 (13)	35 (17)	40 (11)	
2	431 (76)	161 (77)	270 (76)	
3	60 (11)	13 (6)	47 (13)	
Median TMT in mm	5.3 (1.7–9.4)	6.4 (5.3–9.4)	4.6 (1.7–6.3)	**<0.001**
IT or TT				0.318
Yes	277 (49)	109 (52)	168 (47)	
No	267 (47)	94 (45)	173 (48)	
Unknown	22 (4)	6 (3)	16 (4)	

Values are expressed as number (%) or median (range), unless indicated otherwise. Boldface type indicates statistical significance.

As expected, survival after GKRS1 differed significantly among patients of the different RPA classes. The longest survival was observed among patients in RPA class 1 (25.2 months, 95% CI 12.3–38.1 months), followed by patients in RPA class 2 (9.3 months, 95% CI 7.9–10.7 months) and RPA class 3 (2.2 months, 95% CI 1.0–3.4 months; $p < 0.001$). Next, the influence of sarcopenia on estimated median survival duration after GKRS1 was separately evaluated for patients in each RPA class. In this subanalysis, patients at risk for sarcopenia in each RPA class had significantly shorter median survival after GKRS1 (RPA class 1, $p = 0.006$; RPA class 2, $p < 0.001$; RPA class 3, $p = 0.013$).

Data on concomitant IT or TT at or after GKRS1 were available for 541/558 patients (97%). Of note, patients with concomitant IT or TT at or after GKRS (16.0 months, 95% CI 12.5–19.5 months) had a significantly longer survival after GKRS1 than the patients without IT or TT (5.1 months, 95% CI 4.1–6.2 months; $p < 0.001$). Next, the influence of sarcopenia on estimated median survival duration after GKRS1 was separately evaluated for patients with and without concomitant IT or TT. In this subanalysis, patients at risk for sarcopenia had significantly shorter median survival after GKRS1, regardless of their concomitant IT or TT status (patients with concomitant IT or TT, $p < 0.001$; patients without, $p < 0.001$).

As a next step, we performed univariate followed by multivariate Cox regression analyses to validate sarcope-

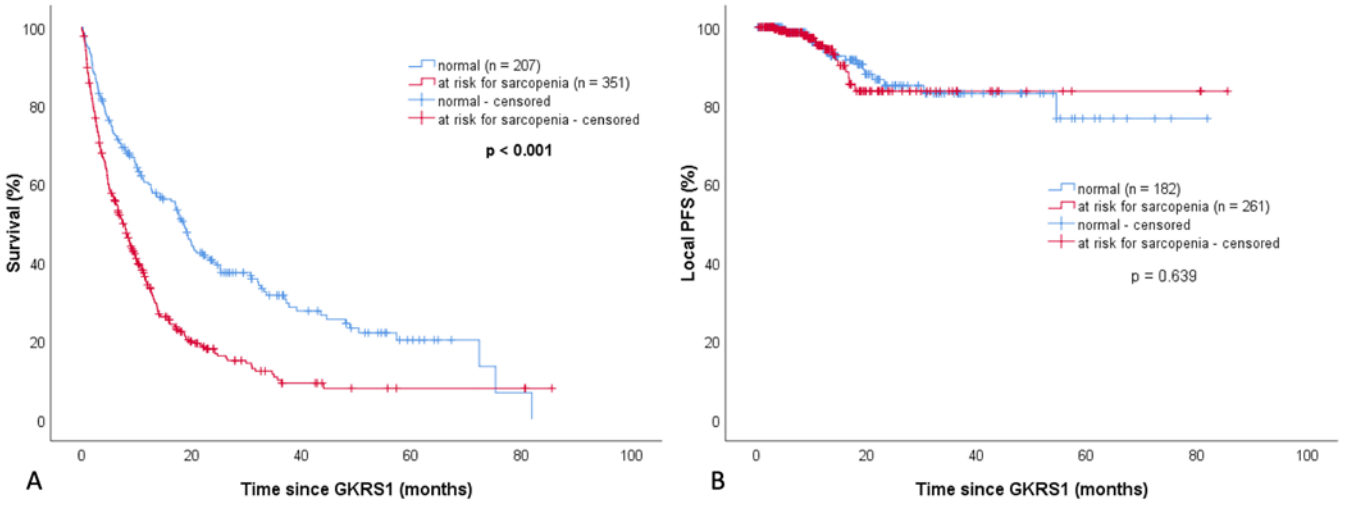

FIG. 2. A: Kaplan-Meier curve for survival after GKRS1, in relation to sarcopenia. Sex-specific TMT cutoff values dividing patients into those at risk for sarcopenia (≤ sex-specific TMT cutoff values indicated by *red lines*) and those with normal muscle status (> sex-specific TMT cutoff values indicated by *blue lines*). **B:** Kaplan-Meier curve for local progression after GKRS1, in relation to sex-specific TMT cutoff values. PFS = progression-free survival.

nia as an independent outcome predictor. The univariate Cox regression analysis revealed that the patients at risk for sarcopenia at GKRS1 were significantly associated with an increased risk of death after GKRS (HR 1.908, 95% CI 1.550–2.349, $p < 0.001$). Next, a multivariate forward stepwise Cox regression analysis including sarcopenia groups, age groups, sex, number of BMs, presence of ECMs, NSCLC subtypes, KPS groups, RPA classes, and concomitant IT or TT was performed. The multivariate Cox regression revealed sarcopenia (HR 1.680, 95% CI 1.347–2.095, $p < 0.001$), male sex (HR 1.360, 95% CI 1.112–1.664, $p = 0.003$), multiple BMs (HR 1.400, 95% CI 1.135–1.729, $p = 0.002$), presence of ECMs (HR 1.734, 95% CI 1.368–2.199, $p < 0.001$), non-adenocarcinomas (HR 1.678, 95% CI 1.288–2.186, $p < 0.001$), KPS < 80% (HR 1.934, 95% CI 1.536–2.436, $p < 0.001$), higher RPA classes (HR 1.557, 95% CI 1.241–1.952, $p < 0.001$), and no concomitant IT or TT (HR 2.537, 95% CI 2.039–3.156, $p < 0.001$) as independent prognostic factors for an increased risk of death.

Association of TMT and Risk for Sarcopenia With Local BM Progression

In 443/558 (79%) patients, clinical and radiological follow-up data were available. Among those patients, 261/443 (59%) patients showed TMT values below the sex-specific cutoff values.

As suspected, no significant differences in the mean time until local progression after GKRS1 were observed between patients with a normal muscle status (182/443 [41%], 69.1 months, 95% CI 63.2–75.1 months) and patients at risk for sarcopenia (261/443 [59%], 73.8 months, 95% CI 67.9–79.7 months; $p = 0.639$; Fig. 2B). Even after separating the study cohort according to sex, no significant differences could be observed for male and female patients.

Discussion

In this study, the prognostic role of TMT measurements in radiosurgically treated NSCLC BM patients was investigated. To evaluate the measurement's clinical relevance, a clearly defined cohort of NSCLC BM patients at the time of their first radiosurgical treatment was selected. We separated the cohort into patients at risk for sarcopenia and patients with a normal muscle status, depending on predefined sex-specific TMT cutoff values.[29] After the GKRS1, patients at risk for sarcopenia had a significantly shorter median overall survival with a 90.8% increase in the risk of death, compared to patients with a normal muscle status. The influence of the presence or absence of sarcopenia at the GKRS1 on survival after radiosurgical treatment was shown to be independent of established prognostic factors such as age, sex, KPS, presence of ECMs or multiple BMs, NSCLC subtypes, RPA class, and concomitant IT or TT. Our findings are in accordance with the published literature. Muscle loss, represented by the reduction of temporal muscle diameter, has been shown to be an adverse prognostic parameter in patients with primary and secondary brain tumors.[17–20,29,31]

Although sarcopenia was revealed to be an independent prognostic factor for survival after GKRS1, several significant differences in patient characteristics were observed between those at risk and those not at risk for sarcopenia. The patients at risk for sarcopenia were significantly older than those with a normal muscle status. This finding may be explained by the fact that sarcopenia can be attributable to age (primary sarcopenia); to systemic disease, physical inactivity, or malnutrition (secondary sarcopenia); or to a combination of the two types.[15]

Moreover, patients at risk for sarcopenia had a significantly lower KPS score, which is accompanied by the fact that both KPS and TMT represent the physical condition of patients.[32] In contrast, the majority of patients at risk for sarcopenia were classified among the RPA class 1 or

2. As previously described, RPA includes 3 classes that are defined by patient age, KPS, ECMs, and status of primary tumor.[10] Still, we could show that among each RPA class, the patients at risk for sarcopenia had a significantly shorter survival after the GKRS1. Moreover, as previously shown, TMT values were significantly lower in female patients than in male patients, which is in line with the overall sex-related body composition; therefore, sex-specific TMT cutoff values are highly important.[22,29,33]

A significantly different distribution of histological NSCLC subtypes was seen between patients with a TMT below and above the sex-specific cutoff values. As previously reported, we could also show that our NSCLC BM patients with adenocarcinomas had a significantly longer survival than the patients with non-adenocarcinoma. This difference in survival between the NSCLC groups was observed among both sarcopenia groups and may be attributable to different age-specific incidences in each subtype.[12,34]

We used an algorithm of measuring TMT according to previously described, highly reproducible, defined anatomical landmarks in patients with available data on the temporal muscle on routine MR images.[17] TMT assessment has been shown to have excellent interrater and intrarater reliability.[17] In addition, in comparison to that with plane or volume muscle segmentation, TMT measurement on MR images takes approximately 30 seconds per patient.[17,28,29] Thus, we believe that the assessment of TMT, after validation of our results in a prospective setting, could be a suitable parameter to be integrated into the clinical workflow. However, we do not want to imply that patients at risk for sarcopenia should not be treated radiosurgically. Indeed, at our institution, patients in a palliative setting and even with multiple BMs are treated with GKRS, if any benefit for the patient can be anticipated. However, those decisions are always made according to patient wishes, along with the interdisciplinary agreement of the radiosurgeon and the oncologist.

Still, an awareness of the association between sarcopenia and cancer may induce further research and new therapeutic targets since not only nutrition, but also exercise training, nutritional supplements such as omega-3 fatty acids, or medication-based concepts such as myostatin inhibitors may help in the prevention of muscle loss.[17,35–37] It is, therefore, important to include muscle mass assessment in the routine clinical settings of cancer patients to confirm the loss of muscle mass close to its onset, so that steps to improve or delay the progression of muscle loss can be started as early as possible.

Study Limitations

Potential limitations of this study are its retrospective design and the fact that the thickness of the temporal muscle could be influenced by oral or dental disorders.[38] To minimize dental or oral muscle alterations, TMT values were measured on both sides, and a mean TMT value for each patient was determined. Since patients underwent GKRS, we used MR images obtained at the time of GKRS1. If the temporal muscle on one side showed any signs of alteration due to previous interventions, the measurement of that side was not taken into account.

Conclusions

In summary, our data showed that preradiosurgical TMT measurements are simple and easily accessible survival predictors for radiosurgically treated NSCLC patients with BMs. Integrating TMT measurements into clinical settings may help to predict the outcome of BM patients and may facilitate patient stratification for clinical trials. Further prospective studies may be needed to correlate TMT with other clinical parameters.

References

1. Preusser M, Capper D, Ilhan-Mutlu A, et al. Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol*. 2012;123(2):205-222.
2. Planchard D, Popat S, Kerr K, et al. Correction to: "Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Ann Oncol*. 2019;30(5):863-870.
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14(1):48-54.
4. Le Rhun E, Guckenberger M, Smits M, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. *Ann Oncol*. 2021;32(11):1332-1347.
5. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316(4):401-409.
6. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
7. Yamamoto M, Serizawa T, Higuchi Y, et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): irradiation-related complications and long-term maintenance of Mini-Mental State Examination scores. *Int J Radiat Oncol Biol Phys*. 2017;99(1):31-40.
8. Berghoff AS, Schur S, Füreder LM, et al. Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers. *ESMO Open*. 2016;1(2):e000024.
9. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419-425.
10. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745-751.
11. Weltman E, Salvajoli JV, Oliveira VC, et al. Score index for stereotactic radiosurgery of brain metastases. *J Radiosurg*. 1998;1(2):89-97.
12. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the Graded Prognostic Assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol*. 2017;3(6):827-831.
13. Kondziolka D, Parry PV, Lunsford LD, et al. The accuracy of predicting survival in individual patients with cancer. *J Neurosurg*. 2014;120(1):24-30.
14. Dhillon RJ, Hasni S. Pathogenesis and management of sarcopenia. *Clin Geriatr Med*. 2017;33(1):17-26.
15. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16-31.
16. Fearon K, Strasser F, Anker SD, et al. Definition and classifi-

cation of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495.
17. Furtner J, Berghoff AS, Albtoush OM, et al. Survival prediction using temporal muscle thickness measurements on cranial magnetic resonance images in patients with newly diagnosed brain metastases. *Eur Radiol*. 2017;27(8):3167-3173.
18. Furtner J, Berghoff AS, Schöpf V, et al. Temporal muscle thickness is an independent prognostic marker in melanoma patients with newly diagnosed brain metastases. *J Neurooncol*. 2018;140(1):173-178.
19. Furtner J, Genbrugge E, Gorlia T, et al. Temporal muscle thickness is an independent prognostic marker in patients with progressive glioblastoma: translational imaging analysis of the EORTC 26101 trial. *Neuro Oncol*. 2019;21(12):1587-1594.
20. An G, Ahn S, Park JS, Jeun SS, Hong YK. Association between temporal muscle thickness and clinical outcomes in patients with newly diagnosed glioblastoma. *J Cancer Res Clin Oncol*. 2021;147(3):901-909.
21. Tamandl D, Paireder M, Asari R, Baltzer PA, Schoppmann SF, Ba-Ssalamah A. Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer. *Eur Radiol*. 2016;26(5):1359-1367.
22. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629-635.
23. Mijnarends DM, Luiking YC, Halfens RJG, et al. Muscle, health and costs: a glance at their relationship. *J Nutr Health Aging*. 2018;22(7):766-773.
24. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539-1547.
25. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Dis*. 2015;17(1):O20-O26.
26. Ranganathan K, Terjimanian M, Lisiecki J, et al. Temporalis muscle morphomics: the psoas of the craniofacial skeleton. *J Surg Res*. 2014;186(1):246-252.
27. Hasegawa Y, Yoshida M, Sato A, et al. Temporal muscle thickness as a new indicator of nutritional status in older individuals. *Geriatr Gerontol Int*. 2019;19(2):135-140.
28. Leitner J, Pelster S, Schöpf V, et al. High correlation of temporal muscle thickness with lumbar skeletal muscle cross-sectional area in patients with brain metastases. *PLoS One*. 2018;13(11):e0207849.
29. Steindl A, Leitner J, Schwarz M, et al. Sarcopenia in neurological patients: standard values for temporal muscle thickness and muscle strength evaluation. *J Clin Med*. 2020;9(5):1272.
30. Nozoe M, Kubo H, Kanai M, et al. Reliability and validity of measuring temporal muscle thickness as the evaluation of sarcopenia risk and the relationship with functional outcome in older patients with acute stroke. *Clin Neurol Neurosurg*. 2021;201:106444.
31. Furtner J, Nenning KH, Roetzer T, et al. Evaluation of the temporal muscle thickness as an independent prognostic biomarker in patients with primary central nervous system lymphoma. *Cancers (Basel)*. 2021;13(3):566.
32. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak*. 2013;13:72.
33. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol (1985)*. 2000;89(1):81-88.
34. Yuan P, Cao JL, Rustam A, et al. Time-to-progression of NSCLC from early to advanced stages: an analysis of data from SEER registry and a single institute. *Sci Rep*. 2016;6:28477.
35. Argilés JM, Busquets S, López-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? *J Cachexia Sarcopenia Muscle*. 2012;3(2):73-76.
36. Di Girolamo FG, Situlin R, Mazzucco S, Valentini R, Toigo G, Biolo G. Omega-3 fatty acids and protein metabolism: enhancement of anabolic interventions for sarcopenia. *Curr Opin Clin Nutr Metab Care*. 2014;17(2):145-150.
37. Padhi D, Higano CS, Shore ND, Sieber P, Rasmussen E, Smith MR. Pharmacological inhibition of myostatin and changes in lean body mass and lower extremity muscle size in patients receiving androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2014;99(10):E1967-E1975.
38. Grünheid T, Langenbach GE, Korfage JA, Zentner A, van Eijden TM. The adaptive response of jaw muscles to varying functional demands. *Eur J Orthod*. 2009;31(6):596-612.

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Author Contributions

Conception and design: Frischer, Cho, Hennenberg, Preusser, Furtner. Acquisition of data: Frischer, Cho, Hennenberg, Untersteiner, Hirschmann, Gatterbauer, Furtner. Analysis and interpretation of data: Frischer, Cho, Hennenberg, Furtner. Drafting the article: Frischer, Cho, Hennenberg, Furtner. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Frischer. Statistical analysis: Frischer, Cho. Study supervision: Frischer, Furtner.

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