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The prognostic utility of temporalis muscle thickness measured on magnetic resonance scans in patients with intra-axial malignant brain tumours: A systematic review and meta-analysis

Olatomiwa Olukoya [a,b,*,#], Temidayo Osunronbi [a,c,#], Damilola A. Jesuyajolu [a], Blossom C. Uwaga [a], Ayomide Vaughan [a], Oluwabusayo Aluko [a], Temitayo O. Ayantayo [a], Jeremiah O. I. Daniel [a], Samuel O. David [a], Habiblah A. Jagunmolu [a], Alieu Kanu [a], Ayomide T. Kayode [a], Tobi N. Olajide [a], Lewis Thorne [b]

[a] Neurosurgery Department, Surgery Interest Group of Africa, Lagos, Nigeria
[b] The National Hospital for Neurology and Neurosurgery, London, United Kingdom
[c] Department of Neurosurgery, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

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ABSTRACT

Introduction: Sarcopenia is associated with worsened outcomes in solid cancers. Temporalis muscle thickness (TMT) has emerged as a measure of sarcopenia. Hence, this study aims to evaluate the relationship between TMT and outcome measures in patients with malignant intra-axial neoplasms.

Method: We searched Medline, Embase, Scopus and Cochrane databases for relevant studies. Event ratios with 95% confidence intervals (CI) were analysed using the RevMan 5.4 software. Where meta-analysis was impossible, vote counting was used to determine the effect of TMT on outcomes. The GRADE framework was used to determine the certainty of the evidence.

Results: Four outcomes were reported for three conditions across 17 studies involving 4430 patients. Glioblastoma: thicker TMT was protective for overall survival (OS) (HR 0.59; 95% CI 0.46–0.76) (GRADE low), progression free survival (PFS) (HR 0.40; 95% CI 0.26–0.62) (GRADE high), and early discontinuation of treatment (OR 0.408; 95% CI 0.168–0.989) (GRADE high); no association with complications (HR 0.82; 95% CI 0.60–1.10) (GRADE low). Brain Metastases: thicker TMT was protective for OS (HR 0.73; 95% CI 0.67–0.78) (GRADE moderate); no association with PFS (GRADE low). Primary CNS Lymphoma: TMT was protective for overall survival (HR 0.34; 95% CI 0.19–0.60) (GRADE moderate) and progression free survival (HR 0.23; 95% CI 0.09–0.56) (GRADE high).

Conclusion: TMT has significant prognostic potential in intra-axial malignant neoplasms, showing a moderate to high certainty for its association with outcomes following GRADE evaluation. This will enable shared decision making between patients and clinicians.

1. Introduction

Intra-axial tumours account for more than 75% of intracranial tumours, representing a significant burden of disease.[1] The most common primary central nervous system (CNS) tumour in adults is glioblastoma which is an aggressive tumour with a median survival time of 15-months and a 5-year survival of <5% following diagnosis, with outcomes that are influenced by the patient's age and performance status.[2] Brain metastases are in fact the most common central nervous system neoplasms seen in 10–40% of patients with systemic cancer. Despite advances in the treatment of systemic cancers, the prognosis for patients with cerebral metastases is poor. Surgical resection improves survival but only in selected patients: those with a limited burden of surgically accessible intracranial disease, good performance status and overall prognosis.[3] Primary central nervous system (CNS) lymphoma (PCNSL), in contrast, only represents 3–4% of all brain tumours and despite advances in therapeutic options, prognosis remains poor.[4] Interestingly,

* Corresponding author. Neurosurgery department, Surgery Interest Group of Africa, Lagos, Nigeria.
E-mail address: olatomiwa.olukoya1@nhs.net (O. Olukoya).
# Joint first authors: contributed equally.

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Abbreviations

AUC	Area-under-curve
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
GRADE	Grading of recommendations assessment, development and evaluation
HR	Hazard ratio
IQR	Interquartile range
MR	Magnetic resonance
OR	Odds ratio
OS	Overall survival
PCNSL	Primary central nervous system lymphoma
PFS	Progression free survival
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QUIPS	Quality in prognosis studies
RevMan	Review manager
RoB	Risk of bias
SWiM	Synthesis without meta-analysis
TMT	Temporalis muscle thickness

studies have shown that outcomes in PCNSL are attributable more to prognostic factors (such as patient age and performance status) than to treatment efficacy.[4,5] Given the apparent link between patient factors, particularly performance status, and outcome in patients with intracranial tumours, the need for an accurate, objective, and reliable prognostic marker in intra-axial tumours is evident. This is especially the case given the subjective way in which performance status is measured and the resulting high interobserver variability and inaccuracy when it is used to predict survival.[6,7] Additionally, such an objective surrogate marker would serve as an effective prognostic tool which would be useful for risk-benefit considerations and to enable shared decision making in the management of patients with intra-axial malignant tumours.

Sarcopenia, the loss of skeletal muscle and function, is the main manifestation of cancer-related cachexia. Sarcopenia serves as a surrogate marker of performance status and is strongly associated with long term outcomes in solid cancers such as hepatocellular carcinoma, pancreaticobiliary cancer, and oesophageal cancer.[8–12] Sarcopenia has typically been determined by sex-adjusted skeletal muscle mass index values derived from computed tomography (CT) images at the level of L3.[8–10,13] However, recent studies have demonstrated a correlation between skeletal muscle mass and temporalis muscle thickness (TMT).[8,14] TMT is typically measured on T1-weighted magnetic resonance (MR) images perpendicular to the long axis of the temporal muscle using the orbital roof (cranio-caudal) and the Sylvian fissure (anterior-posterior) as landmarks.[4,8,12] Furthermore, as TMT is readily quantifiable on MR scans,[8] it would be easily translatable and advantageous in patients with intracranial neoplastic lesions who are routinely assessed using this imaging modality. Consequently, this systematic review aims to analyse existing evidence and evaluate the relationship between TMT measured on MR scans and outcome measures in patients with malignant intra-axial neoplasms, with a view to improving risk-benefit considerations and shared decision making in the management of these patients.

2. Methods

2.1. Study design and registration

This systematic review and meta-analysis evaluated study level data and was reported in compliance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA)[15] and the Synthesis without meta-analysis (SWiM) in systematic reviews reporting guidelines.[16] The protocol for this review was published on PROSPERO (an international prospective register of systematic reviews) on 24 June 2022 (CRD42022341107).

2.2. Eligibility criteria

We included full-text original articles that reported the prognostic performance of TMT in predicting outcomes in patients with any malignant intracranial intra-axial neoplasms. We excluded review articles, expert opinions, letters, conference abstracts, case reports and case series, editorials, non-human studies, articles that used TMT for diagnostic purposes/assessment of disease severity or frailty only, and studies that reported neither an event ratio nor area-under-curve (AUC) nor provided raw data with which to calculate these parameters in the evaluation of the prognostic utility of TMT.

2.3. Search strategy

A systematic search of the Ovid Embase, Ovid Medline, Scopus and Cochrane databases was performed from inception till June 17, 2022. The abstracts/titles/keywords on these databases were searched using the following terms ((Temporalis Muscle Thickness) OR (temporal muscle) OR (temporalis) OR (TMT) OR (sarcopenia)) AND ((glioma) OR (glioblastoma) OR (GBM) or (brain tumour) or (brain tumor) or (lymphoma) or (metastases) OR (metastatic) OR (metastasis) OR (malignant) OR (malignancy) OR (astrocytoma) OR (ependymoma) OR (oligodendroglioma) OR (anaplastic) OR (medulloblastoma) OR (sarcoma) OR (gliosarcoma) OR (chondrosarcoma) OR (rhabdomyosarcoma) OR (gliomatosis cerebri) OR (Oligoastrocytoma) OR (gangliocytoma) OR (neurocytoma)). No additional search limits were applied. The full search strategy is described in the Supplementary Material.

2.4. Study selection

Duplicates were excluded in Zotero. The abstracts were screened independently by thirteen authors using the Rayyan software. The abstracts were divided into seven sets, and each set of abstracts was reviewed by a pair of authors, with a third author (OO or TO) adjudicating any discrepancies. Full texts of potentially relevant studies were assessed independently for eligibility by two authors (OO and TO). Disagreements were resolved by discussion among the reviewers until mutual agreement was reached. The reference list of the included studies was searched for additional potentially relevant articles.

2.5. Data extraction and quality assessment

Data extraction was conducted independently by thirteen of the authors using a predesigned data extraction proforma (Supplementary Material). The eligible full texts were divided into six groups, and data extraction from each group of full texts was performed by a pair of authors, with a third author (OO or TO) adjudicating any discrepancies.

The following data was extracted: outcome measure, country of study, study design, intracranial condition, sample size, mean age ± SD, median age and range, sex, length of follow-up, number of patients that had the outcome event, event ratio (hazard ratio (HR), odds ratio (OR)), TMT threshold, how the threshold was determined, and direction of effect. For the event ratio, adjusted estimates were preferred to crude estimates if both were provided. However, a crude estimate was deemed acceptable if the adjusted estimate was not reported.

Quality assessment of each full text article for inclusion was performed using the Quality in Prognosis Studies (QUIPS) tool in an identical way to data extraction.[17–19] The papers were categorised into high, moderate or low risk of bias based on the following criteria, modified from Grooten et al[20]: If all six of the QUIPS domains are classified as

having low risk of bias (RoB), or up to one domain is classified as moderate risk of bias, then that paper will be classified as low RoB. If one or more domains are classified as having high RoB, or ≥3 domains are classified as moderate RoB, then that paper will be classified as high RoB. All papers in between will be classified as having moderate RoB.[20] The QUIPS rating for each study (Fig. 1) is detailed in the Supplementary Material.

2.5.1. Data analysis

We conducted meta-analyses using the Review Manager (RevMan) software (Version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Where meta-analysis was possible, for each outcome measure stratified by the intracranial condition, extracted event ratio and corresponding 95% confidence interval (CI) were pooled using the generic inverse-variance methods to evaluate the association between thicker TMT and the dichotomous outcome measure. A random-effects model was used to account for study heterogeneity. We evaluated heterogeneity among the studies using the Cochrane Q-statistic and I^2 statistic tests. To identify and minimise heterogeneity, we conducted subgroup analyses of the studies that investigated similar outcome measures in patients with similar intracranial conditions.

For some outcome measures, only a few articles reported event ratios meaning meta-analysis was not possible. Consequently, a narrative synthesis using the Synthesis without meta-analysis (SWiM) reporting guideline was conducted for each of these outcome measures.[16] Based on difference measures between outcome event and non-event groups (event ratio, mean/median difference, *p*-values), we summarised the direction of the effect of thicker TMT on the outcome (worsened outcome/no effect/improved outcome) and synthesised harvest plots by vote-counting the direction of effects.

The certainty of evidence for the association between TMT and each outcome measure, stratified according to intracranial condition, was evaluated independently by two authors (OO and TO) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for prognostic factor research.[21] Disagreements in the certainty evidence ratings were resolved through discussion between the two reviewers until mutual agreement was reached.

3. Results

3.1. Study selection

The search generated 5835 results. A total of 1778 duplicates were removed using Zotero, resulting in 4057 unique studies. Following the abstract/title screening, 20 articles were found to meet our selection criteria. On full-text screening, three studies were excluded for measuring TMT on CT scans with inconsistent markings[12]; measuring the temporalis muscle cross-sectional area rather than the TMT thickness[22]; and including benign intracranial conditions in the analysis.[23] The summary of findings of these excluded articles is presented in the Supplementary Material. In total, 17 studies consisting of 4430 patients were included (Fig. 2).

3.2. Description of included studies

Most of the studies were conducted in Austria (6 studies).[4,8,24–27] There were two studies from Turkey,[28,29] two from USA,[30,31] two from Germany,[32,33] two from Italy,[34,35] one from South Korea,[36] one from the Netherlands[37] and one from China.[38] Our review includes 17 retrospective cohort studies.[4,8,24–38] There were three intracranial conditions, and the association between TMT and four outcome measures investigated across the 17 studies.

In glioblastoma patients, ten studies investigated overall survival (OS)[26–28,30,31,33,34,36–38]; four studies investigated progression free survival (PFS)[26,27,36,37]; one study investigated early discontinuation of treatment due to toxicity and/or disease progression[37]; and two studies

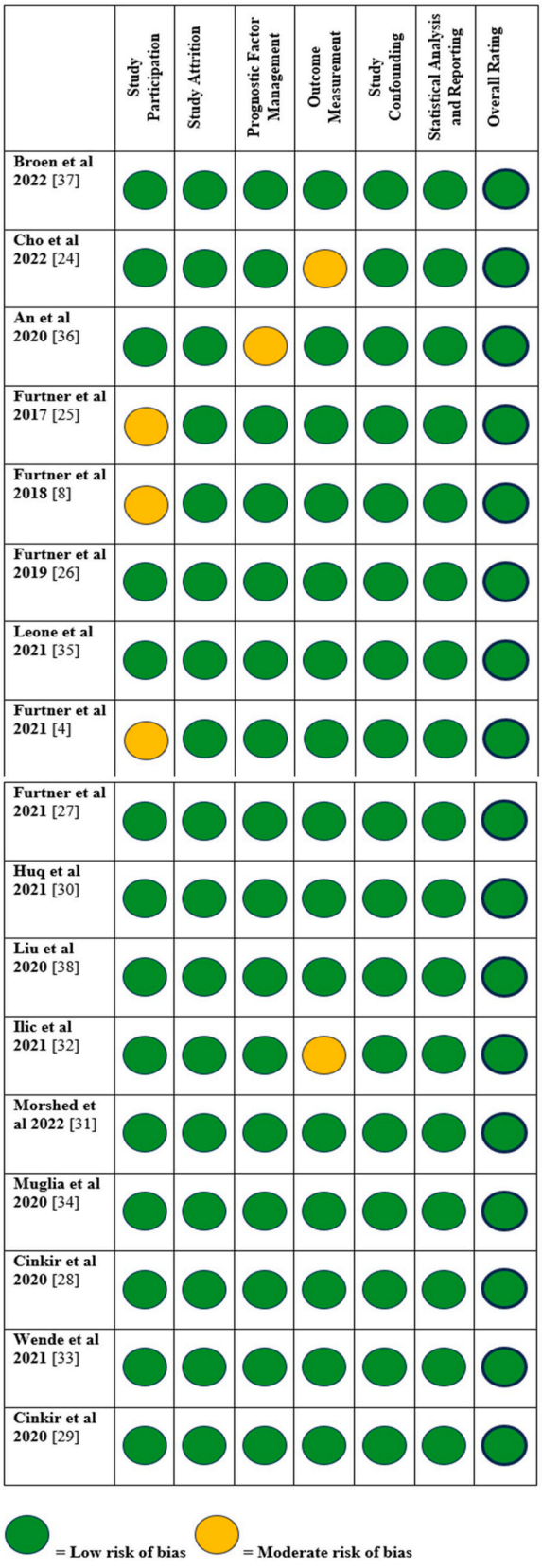

Fig. 1. Quality assessment of each full text article for inclusion using the Quality in Prognosis Studies (QUIPS) tool. Orange circle = moderate risk of bias, green circle = low risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

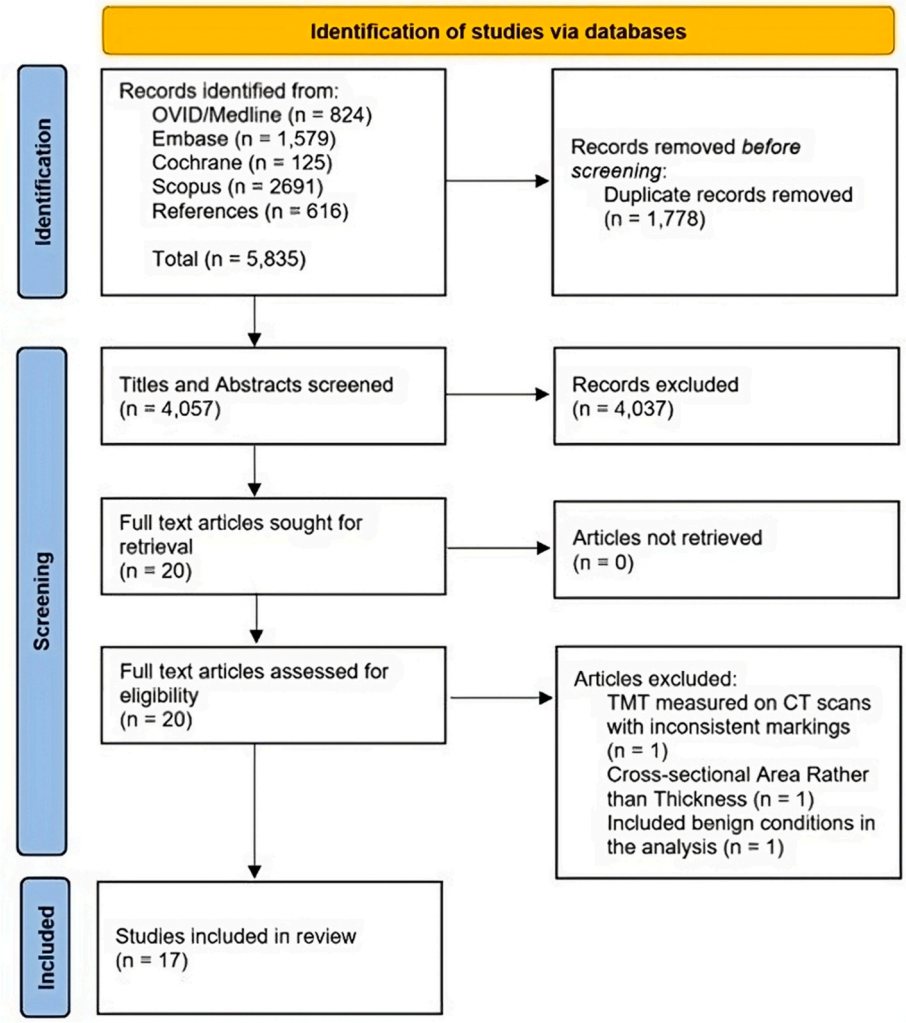

Fig. 2. The flowchart of the selection process of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

investigated treatment-related complications.[31,37] For patients with brain metastases, five studies investigated OS[8,24,25,29,32] and one study investigated PFS.[24] Two studies investigated OS in PCNSL patients[4,35] while only one study investigated PFS in the same condition.[35]

The outcomes explored, study design, sample size, patient demographics, intracranial condition, details of TMT threshold and threshold selection, length of follow-up, and event ratio, are detailed in the Supplementary Material. Using the QUIPS tool for risk of bias assessment, all 17 studies were deemed to have a low risk of bias. The rating for each study is detailed in the Supplementary Material.

4. Association between TMT and patient outcomes

4.1. Glioblastoma

1. Overall survival:

10 studies (13 sub-cohorts) involving 2885 patients, investigated the association between baseline TMT and OS in glioblastoma patients.[26–28,30,31,33,34,36–38] Three of the studies each had two sub-cohorts.[26,27,30] One study assessed TMT as a continuous variable,[33] while nine studies dichotomised TMT values as 'thick' vs 'sarcopenic'. Three studies reported sex-specific TMT threshold values.[27,36,37] Two studies determined the threshold according to existing literature[27,37]; five studies determined the threshold based on the median TMT of their cohorts[28,31,34,36,38]; one study determined the threshold using ROC and Youden's index[26]; while one study determined the threshold based on postoperative survival prediction via maximally selected log rank statistics.[30] The median (IQR) sarcopenia cut-off values amongst the patients was: 7.125 mm (6.3–7.5 mm) for male patients and 7.125 mm (5.2–7.5 mm) for female patients.

On vote-counting the direction of effect, thicker TMT was associated with improved OS in nine cohorts while there was no association in four cohorts (Fig. 3a). The median OS was 14.34 months in the thicker TMT group, and 10.93 months in the sarcopenic group. After pooling the HRs, thicker TMT was protective for OS (HR: 0.59, 95% CI: 0.46–0.76) (Fig. 4a). There was substantial study heterogeneity ($\tau^2 = 0.15$; $I^2 = 88\%$; $p = <0.00001$).

Four studies investigated the association between thicker TMT and OS in primary glioblastoma[28,30,36,38] whilst two studies (three sub-cohorts) looked at the same outcome in progressive glioblastoma.[27,30] Subgroup analysis was performed for both and found no association between thicker TMT and OS in primary glioblastoma (HR: 0.71, 95% CI: 0.50–1.03), but a protective association of thicker TMT on OS in progressive glioblastoma (HR: 0.49, 95% CI: 0.40–0.60) (Supplementary Material). There was moderate study heterogeneity ($\tau^2 = 0.08$; $I^2 = 62\%$; $p = 0.05$) in the primary glioblastoma group, but no appreciable heterogeneity in the progressive glioblastoma cohorts ($\tau^2 = 0.00$; $I^2 = 0\%$; $p = 0.57$).

2. Progression Free survival

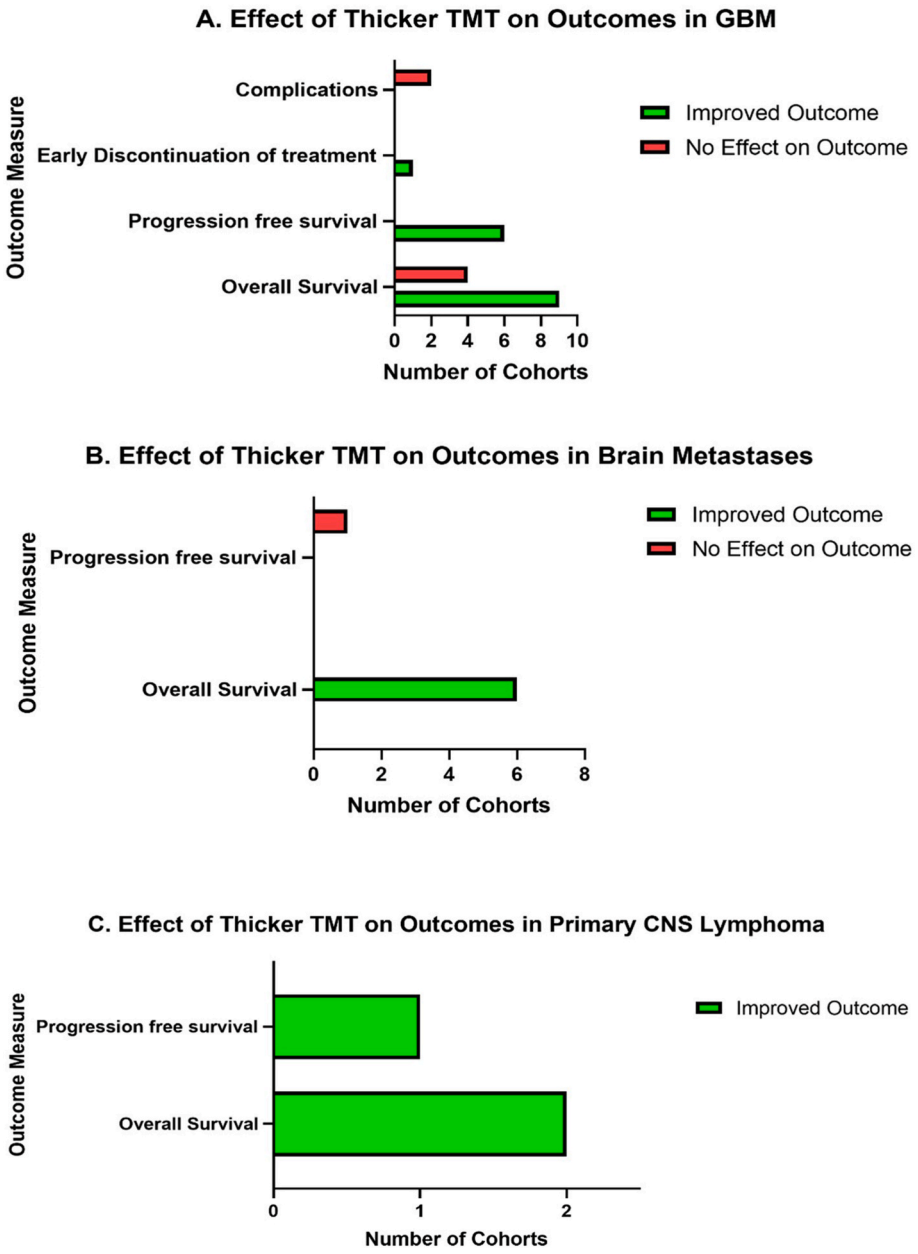

Fig. 3a. Harvest plot showing the association between thicker TMT and Outcomes in Glioblastoma. Fig. 3b: Harvest plot showing the association between thicker TMT and Outcomes in Brain Metastasis. Fig. 3c: Harvest plot showing the association between thicker TMT and Outcomes in Primary CNS Lymphoma.

Four studies (six sub-cohorts), involving 1828 patients, investigated the association between baseline TMT and PFS in glioblastoma.[26,27,36,37] Two studies reported two sub-cohorts.[26,27] Three studies reported sex-specific TMT thresholds.[27,36,37] Two studies determined the threshold according to existing literature[27,37]; one determined the threshold based on the median TMT of their cohorts[36]; while one study determined the threshold using ROC and Youden's index.[26] The median (IQR) sarcopenia cut-off amongst the patients was 6.7 mm (6.3–7.175 mm) for males and 5.37 mm (5.2–6.785 mm) for females. On vote-counting the direction of effect, thicker baseline TMT was associated with improved PFS in all six cohorts (Fig. 3a). After pooling the HRs, thicker TMT was protective for PFS (HR: 0.40, 95% CI: 0.26–0.62) (Fig. 4b). There was substantial study heterogeneity ($\tau^2 = 0.28$; $I^2 = 92\%$; $p = <0.00001$).

One study (two sub-cohorts) investigated the association between thicker TMT and PFS in progressive glioblastoma.[26] Subgroup analysis was performed and found a protective association between thicker TMT and overall survival in progressive glioblastoma (HR: 0.48, 95% CI: 0.40–0.59). There was no appreciable heterogeneity ($\tau^2 = 0.00$; $I^2 = 0\%$; $p = 0.76$) (Supplementary Material).

3. Early discontinuation of treatment

One study involving 328 patients investigated the association between thicker TMT and early discontinuation of treatment due to toxicity and/or disease progression in glioblastoma.[37] This study used different TMT thresholds for men and women derived from existing literature. The sarcopenia cut-off value was 6.3 mm in males and 5.2 mm in females. The authors found that a thicker TMT was significantly protective for early discontinuation of treatment (OR: 0.408, 95% CI: 0.168–0.989).

4. Complications

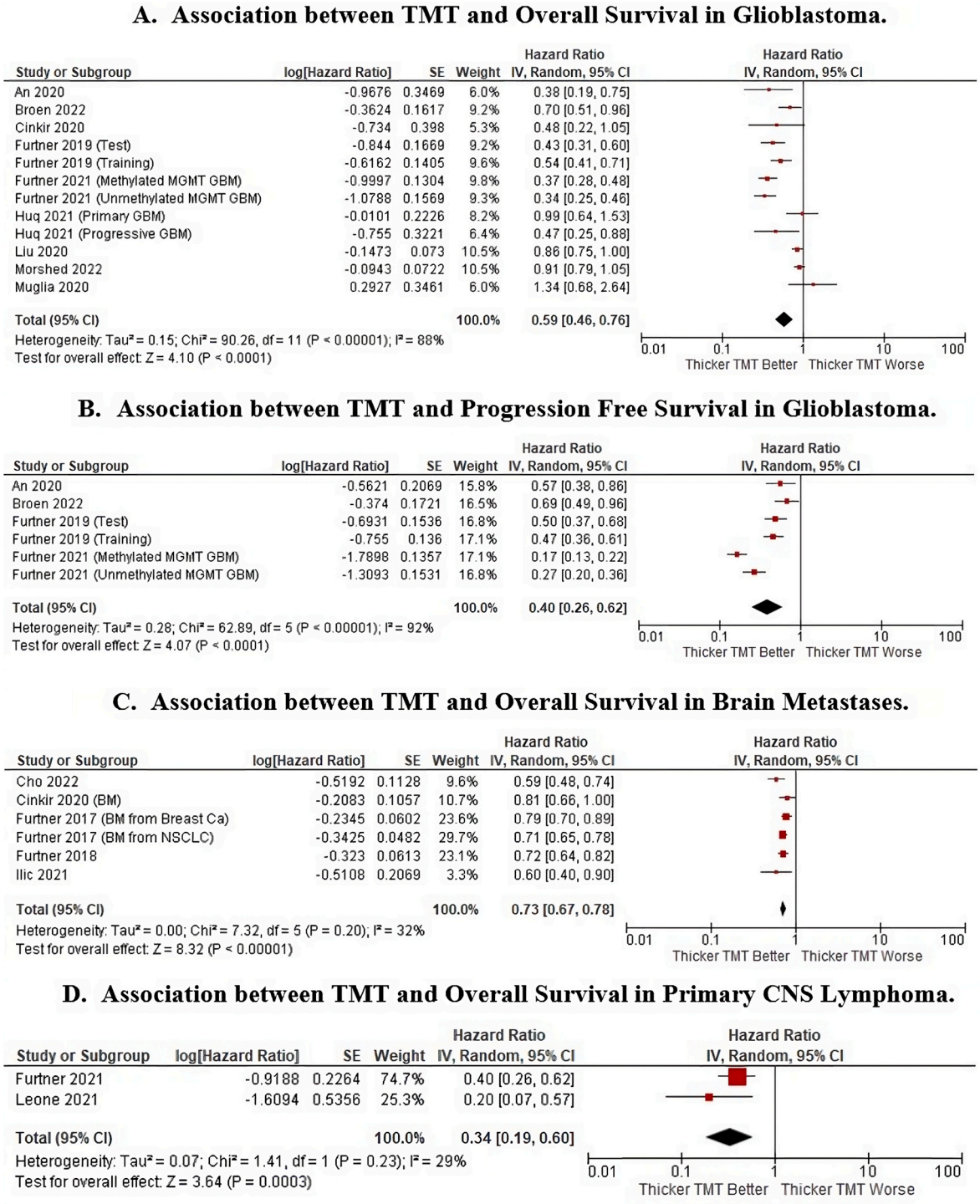

Fig. 4a. Forest plot of included studies evaluating the association between TMT and Overall Survival in Glioblastoma. Fig. 4b: Forest plot of included studies evaluating the association between TMT and Progression Free Survival in Glioblastoma. Fig. 4c: Forest plot of included studies evaluating the association between TMT and Overall Survival in Brain Metastases. Fig. 4d: Forest plot of included studies evaluating the association between TMT and Overall Survival in Primary CNS Lymphoma.

Two studies involving 438 patients investigated the association between thicker TMT and treatment-related complications in glioblastoma.[31,37] One study used different TMT thresholds for men and women derived from existing literature,[37] while the other used the median TMT of their cohort as the threshold.[31] The median (IQR) sarcopenia cut-off value was 7.7 mm (7–8.4 mm) for males and 7.25 mm (6.325–8.175 mm) for females. On vote-counting the direction of effect, there was no association between thicker TMT and complications (Fig. 3a). Only one study reported their event ratio (HR: 0.82, 95% CI: 0.60–1.10).[35]

4.2. Brain metastases

1. Overall survival:

Five studies (six sub-cohorts) including 1374 patients, investigated the association between TMT and OS in patients with brain

metastases.[8,24,25,29,32] One study used sex-specific TMT thresholds for men and women derived from existing literature[24]; whilst the four studies used the median TMT of their cohorts as the threshold. The median (IQR) sarcopenia cut-off value was 5.9 mm (5.4–6.3 mm) in males and 5.4 mm (5.2–5.9 mm) in females. On vote counting the direction of effect, all six cohorts showed that thicker TMT was associated with improved OS (Fig. 3b). The median OS was 16.5 months in the thicker TMT group and 5 months in the sarcopenic group. After pooling the HRs, thicker TMT was protective for OS (HR: 0.73, 95% CI: 0.67–0.78) (Fig. 4c). There was no appreciable heterogeneity ($\tau^2 = 0.00$; $I^2 = 32\%$; $p = 0.20$).

Four studies investigated the association between thicker TMT and overall survival in brain metastases from lung cancer[24,25,29,32] whilst three studies looked at the association specifically in non-small cell lung cancer.[24,25,32] Subgroup analysis was performed and found a protective association between thicker TMT and lung cancer (HR: 0.70, 95% CI 0.62–0.79), as well as non-small cell lung cancer (HR: 0.67, 95% CI 0.60–0.76) (Supplementary Material). There was no appreciable study heterogeneity in the lung cancer ($\tau^2 = 0.01$; $I^2 = 36\%$; $p = 0.20$) or non-small cell lung cancer ($\tau^2 = 0.00$; $I^2 = 21\%$; $p = 0.28$) subgroups.

2. Progression free survival

One study involving 558 patients investigated the association between TMT and PFS in brain metastases.[24] This study used sex-specific TMT thresholds derived from existing literature: 6.3 mm in males and 5.2 mm in females. The authors found that there was no association between thicker TMT and progression free survival in brain metastases, however, they did not report their event ratio.

4.2.1. Primary CNS lymphoma

1. Overall survival

Two studies involving 171 patients investigated the association between TMT and OS in primary CNS lymphoma.[4,35] Both studies used different TMT thresholds for men and women derived from existing literature: 6.3 mm in males and 5.2 mm in females. On vote-counting the direction of effect, thicker TMT was associated with prolonged OS (Fig. 3c). The median OS was 54.2 months in the thicker TMT group, and 9.4 months in the sarcopenic group. After pooling the HRs, thicker TMT remained protective for overall survival (HR: 0.34, 95% CI: 0.19–0.60) (Fig. 4d). There was no appreciable heterogeneity ($\tau^2 = 0.07$; $I^2 = 29\%$; $p = 0.23$).

2. Progression free survival

Only one study involving 43 patients investigated the association between TMT and PFS in primary CNS lymphoma.[35] The authors used sex-specific TMT thresholds derived from existing literature: 6.3 mm in males and 5.2 mm in females. The authors found that a thicker TMT was significantly protective for PFS (HR: 0.23, 95% CI: 0.09–0.56).

5. Discussion

In this systematic review and meta-analysis, we evaluated the prognostic utility of TMT measured on MR scans on outcomes in intracranial, intra-axial malignant neoplasm. Our results suggest that glioblastoma patients with thicker TMT have a significantly prolonged overall survival, and on average, live four months longer than those with sarcopenia. Thicker TMT is also associated with prolonged PFS and is protective against the early discontinuation of treatment in glioblastoma patients. Although TMT was not associated with PFS in brain metastases patients, those with thicker TMT had significantly prolonged OS, and on average, live 11.5 months longer than those with sarcopenia. In primary CNS lymphoma, we found that thicker TMT resulted in longer PFS and OS, with thicker TMT patients living 3.7 years longer than sarcopenic patients. In this section, we discuss the potential mechanisms by which TMT influences patient outcomes. Furthermore, we utilised the GRADE framework for prognostic factor research[21] to evaluate the certainty of evidence for each outcome measure stratified by intracranial condition.

TMT can be quickly assessed through a standardised, resource-efficient method using existing MR images within established clinical practices. Neurosurgeons, neuro-oncologists, or neuroradiologists could perform TMT measurements, and this measurement could be incorporated in the radiology reports of patients with intra-axial malignant tumours.[12,30] The ease of acquisition and the conferred survival benefit would make personalised treatment plans based on TMT readily available. Several mechanisms have been postulated as to why sarcopenia, secondary to malignancy and/or other causes, has such a profound effect on patient outcomes. These mechanisms include systemic inflammation; insulin-dependent glucose handling; protein status; and pharmacokinetics.[39] Primary CNS tumours are not associated with systemic cachexia, and in this group, TMT may be functioning as a non-specific marker of frailty.

Skeletal muscle has a role in regulating the immune system through cytokines and myokines. Consequently, arcopenia results in a chronic low-grade inflammation which has been shown to increase the risk of mortality and poor treatment response.[39] Furthermore, skeletal muscles are the main site of insulin-mediated glucose uptake and metabolism. Sarcopenia results in the accumulation of lipids in muscle tissues which can induce insulin resistance and glucose intolerance. This increased insulin resistance has been shown to be associated with reduced overall and disease-free survival. The impaired glucose tolerance results in a greater availability of glucose for uptake by tumour cells, accelerating their growth and progression of the disease.[39–41] Sarcopenia represses protein synthesis and function, due to a reduction in the number of ribosomes. This results in a greater availability of amino acids within the bloodstream for uptake by cancer cells, promoting their growth. Finally, sarcopenia results in an alteration in the pharmacokinetics of chemotherapeutic agents. Dosing of chemotherapeutic agents has historically been based on body surface area, however, sarcopenia results in a reduced volume of distribution of drugs and consequently a relative overdosing of treatment.[39,42–44] In addition to this, given that skeletal muscles play an important role in the clearance of many chemotherapy agents, sarcopenia inevitably results in toxicity and early discontinuation of treatment.[39]

TMT is clinically relevant because it can provide information on the likelihood of a patient tolerating more aggressive treatments and consequently outcomes. This will enable personalised and earlier conversations about what treatment options are recommended and likely to be well tolerated whilst accounting for patients' preferences. Using TMT as a sarcopenia measure in clinical practice can help guide the management of patients with intra-axial malignant tumours before and after surgery. Patients with normal/thick TMT may proceed to surgery immediately, while those with thin TMT could undergo a short period of preoperative optimisation. Although surgery should not be significantly delayed, a brief preoperative optimisation utilising a multidisciplinary approach, including nutritional support, comorbidity management, and physiotherapy, could prevent adverse outcomes in sarcopenic patients. In the postoperative phase, TMT can assist in determining the need for ongoing nutritional support and physiotherapy to maintain functional capacity and improve quality of life during radiotherapy and chemotherapy.[30]

5.1. Certainty of evidence

We utilised the GRADE framework for prognostic factor research[21] to evaluate the certainty of evidence for each outcome measure stratified by intracranial condition. Here, we describe the key decisions taken to decide the level of confidence in our findings for each outcome measure (Table 1). In the Supplementary Material, we provide a detailed

Table 1
Grading of Recommendations Assessment, Development and Evaluation (GRADE) table assessing the quality of evidence for the association of each outcome measure with TMT.

Outcome measures	Number of participants	Number of studies	GRADE factors								Overall quality
			Phase of investigation	Study limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Moderate/large effect size	Dose effect	
Glioblastoma											
Overall survival	2885	10	1	No serious limitations	Serious limitations↓	No serious limitations	No serious limitations	No serious limitations	Absent	Unclear	Low (++)
Progression-free survival	1828	4	2	No serious limitations	Serious limitations↓	No serious limitations	No serious limitations	No serious limitations	Present↑	Unclear	High (++++)
Early discontinuation of treatment	328	1	2	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Serious limitations↓	Present↑	Unclear	High (++++)
Complications	438	2	1	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Serious limitations↓	Absent	Unclear	Low (++)
Brain metastases											
Overall survival	1374	5	1	No serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Absent	Unclear	Moderate (+++)
Progression-free survival	558	1	2	No serious limitations	No serious limitations	No serious limitations	Serious limitations↓	Serious limitations↓	Absent	Unclear	Low (++)
PCNSL											
Overall survival	171	2	1	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Serious limitations↓	Present↑	Unclear	Moderate (+++)
Progression-free survival	43	1	2	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Serious limitations↓	Present↑	Unclear	High (++++)

↓: downgrade quality; ↑: upgrade quality. Note: Phase 1 (exploratory) studies are of moderate quality; Phase 2 (validation) studies are of high quality.

explanation of the eight GRADE factors used to determine the certainty of the evidence for each outcome measure.

5.2. Glioblastoma

1. Overall survival

Only three out of the 10 studies[26,27,37] were validation studies (**moderate quality**). There was substantial study heterogeneity ($\tau^2 = 0.15$; $I^2 = 88\%$; $p < 0.00001$) (**downgrade**) likely due to the differences among these studies in patient age, length of follow-up, sub-type of glioblastoma included, and TMT threshold for sarcopenia (Supplementary Material). We concluded that the evidence base (that thicker TMT is associated with longer overall survival in glioblastoma) is of **low quality** (GRADE ++).

2. Progression free survival

Three out of the four studies[26,27,37] were validation phase 2 studies (**high quality**) Our meta-analysis showed a pooled hazard ratio of 0.40, which is a moderate effect size (**upgrade**). However, there was substantial between-study heterogeneity ($\tau^2 = 0.28$; $I^2 = 92\%$; $p = <0.00001$) (**downgrade**) likely due to the differences among these studies in, length of follow-up, sub-category of glioblastoma included, and TMT threshold (Supplementary Material). We concluded that the evidence base (that thicker TMT is associated with longer progression free survival in glioblastoma) is of **high quality** (GRADE ++++).

3. Early discontinuation

Only one study investigated the association between TMT and early discontinuation of treatment, and this was a phase two validation study[37] (**high quality**). This study reported a hazard ratio of 0.41, which is a moderate effect size (**upgrade**). However, due to the small number of studies, we assumed a possibility of publication bias (**downgrade**). We concluded that the evidence base (that thicker TMT is protective for early discontinuation of treatment in glioblastoma) is of **high quality** (GRADE ++++).

4. Complications

There were two studies, and one was an exploratory phase one study[35] while the other was a phase 2 validation study[37] (**moderate quality**). Due to the small number of studies, we assumed a possibility of publication bias (**downgrade**). We concluded that the evidence base (that thicker TMT is associated with reduced complications in glioblastoma) is of **low quality** (GRADE ++).

5.3. Brain metastases

1. Overall Survival

Only one of the five studies[24] is a phase two validation study (**moderate**). There were no further upgrade/downgrades across the other seven GRADE criteria. Thus, we concluded that the evidence base (that thicker TMT is associated with longer overall survival in brain metastases) is of **moderate quality** (GRADE +++).

2. Progression free survival

One phase 2 validation study[24] (**high Quality**). However, the precision of the study could not be determined due to a lack of reporting of the number of events or the event ratio (**downgrade**). Additionally, due to the small number of studies, we assumed a possibility of publication bias (**downgrade**). Consequently, we deemed that the evidence base (that thicker TMT is associated with longer progression free survival in

brain metastases) is of **low quality** (GRADE ++).

5.3.1. Primary CNS lymphoma

1. Overall Survival

There were two studies, and one was an exploratory phase one study[8] while the other was a phase 2 validation study[35] (**moderate quality**). Our meta-analysis showed a pooled hazard ratio of 0.34, which is a moderate effect size (**upgrade**). However, due to the small number of studies, we assumed a possibility of publication bias (**downgrade**). Therefore, we concluded that the evidence base (that thicker TMT is associated with longer OS in primary CNS lymphoma) is of **moderate quality** (GRADE +++).

2. Progression Free Survival

One phase 2 validation study[35] (**high quality**) which reported a hazard ratio of 0.23, which is a moderate effect size (**upgrade**). However, due to the small number of studies, we assumed a possibility of publication bias (**downgrade**). Thus, we concluded that the evidence base (that thicker TMT is associated with longer PFS in primary CNS lymphoma) is of **high quality** (GRADE ++++).

5.4. Limitations

Certain limitations should be factored in when interpreting this review. Firstly, although all the included studies had a low risk of bias, all the studies were retrospective, and the majority (11 studies) were single-centred. Additionally, we were unable to formally assess the presence and effect of publication bias due to the small number of studies per outcome measure. Secondly, as most of the included studies were conducted in Austria (6 studies) and other European countries (total of 11 studies), the findings of our review might not be generalisable. Lastly, amongst other sources of heterogeneity, there was variation in the TMT threshold values, and this may have affected the accuracy of our analysis. To translate the prognostic utility of TMT to clinical practice, there is a need to design large international prospective multicentre clinical trials and to utilise existing imaging databases to establish standardised TMT cut-off values. These trials should be prioritised in currently underrepresented continents.

6. Conclusion

In general, across various intracranial intra-axial malignancies, patients who are not sarcopenic (i.e., those with thicker TMT) have better survival outcomes and are less prone to discontinuing treatment secondary to drug toxicity. In most cases, the quality of evidence ranged from moderate to high, suggesting that TMT has the potential to be a valuable prognostic tool for risk-benefit considerations in the management of these patients. However, for TMT to be more useful clinically, there is a need to establish a standardised TMT cut-off value for sarcopenia, and this could be achieved by conducting large international multicentre prospective validation studies and utilising existing imaging databases.

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Availability of data and material (data transparency)

Extracted data from the studies included in this review are presented in the Supplementary Material.

Code availability (software application or custom code)

Not Applicable.

Ethics approval (include appropriate approvals or waivers)

Not Applicable.

Consent to participate (include appropriate statements)

Not Applicable.

Consent for publication (include appropriate statements)

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Ethical approval

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CRediT authorship contribution statement

Olatomiwa Olukoya: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Temidayo Osunronbi:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization, Validation, Investigation. **Damilola A. Jesuyajolu:** Writing – review & editing, Data curation, Validation, Investigation. **Blossom C. Uwaga:** Writing – review & editing, Data curation, Validation, Investigation. **Ayomide Vaughan:** Writing – review & editing, Data curation, Validation, Investigation. **Oluwabusayo Aluko:** Writing – review & editing, Data curation, Validation, Investigation. **Temitayo O. Ayantayo:** Writing – review & editing, Data curation, Validation, Investigation. **Jeremiah O. I. Daniel:** Writing – review & editing, Data curation, Validation, Investigation. **Samuel O. David:** Writing – review & editing, Data curation, Validation, Investigation. **Habiblah A. Jagunmolu:** Writing – review & editing, Data curation, Validation, Investigation. **Alieu Kanu:** Writing – review & editing, Data curation, Validation, Investigation. **Ayomide T. Kayode:** Writing – review & editing, Data curation, Validation, Investigation. **Tobi N. Olajide:** Writing – review & editing, Data curation, Validation, Investigation. **Lewis Thorne:** Writing – review & editing, Supervision, Validation, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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