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Original Research Article

# Cervical body composition on radiotherapy planning computed tomography scans predicts overall survival in glioblastoma patients

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ABSTRACT

*Background and purpose:* Glioblastoma (GBM) patients face a strongly unfavorable prognosis despite multimodal therapy regimens. However, individualized mortality prediction remains imprecise. Harnessing routine radiation planning cranial computed tomography (CT) scans, we assessed cervical body composition measures as novel biomarkers for overall survival (OS) in GBM patients.

*Materials and methods:* We performed threshold-based semi-automated quantification of muscle and subcutaneous fat cross-sectional area (CSA) at the levels of the first and second cervical vertebral body. First, we tested this method's validity by correlating cervical measures to established abdominal body composition in an open-source whole-body CT cohort. We then identified consecutive patients undergoing radiation planning for recent GBM diagnosis at our institution from 2010 to 2020 and quantified cervical body composition on radiation planning CT scans. Finally, we performed univariable and multivariable time-to-event analyses, adjusting for age, sex, body mass index, comorbidities, performance status, extent of surgical resection, extent of tumor at diagnosis, and MGMT methylation.

*Results:* Cervical body composition measurements were well-correlated with established abdominal markers (Spearman's rho greater than 0.68 in all cases). Subsequently, we included 324 GBM patients in our study cohort (median age 63 years, 60.8% male). 293 (90.4%) patients died during follow-up. Median survival time was 13 months. Patients with below-average muscle CSA or above-average fat CSA demonstrated shorter survival. In multivariable analyses, continuous cervical muscle measurements remained independently associated with OS.

*Conclusion:* This exploratory study establishes novel cervical body composition measures routinely available on cranial radiation planning CT scans and confirms their association with OS in patients diagnosed with GBM.

## Introduction

Despite considerable scientific advances, diagnosis of a glioblastoma (GBM) remains associated with high mortality, resulting in a median survival of less than two years [1,2]. Over time, prognostic risk factors have been established, most importantly isocitrate dehydrogenase-1 (IDH-1) mutation [3]. Given the outsized influence of this marker, only IDH-wildtype tumors remain classified as GBM in the most recent re-definition of World Health Organization (WHO) guidelines [4]. Other prognostic factors including $O^6$-Methylguanine-DNA Methyltransferase (MGMT) methylation status [5], body mass index (BMI) [6], age [7], performance status [8], and extent of tumor resection [9] have also been explored. However, mortality risk prediction remains in need of improvement [10,11].

Body composition measurements have recently been introduced into risk prediction algorithms for cancer patients in a diverse set of tumors

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including in gastrointestinal [12], lung [13,14], renal [15] and hematologic [16] malignancies. Most studies rely on measurements based on computed tomography (CT) scans at the level of the third lumbar vertebra (L3) which have been defined as the gold standard [17] and have been found to represent total body muscle mass [18]. However, investigations try to increasingly use different vertebral levels in an effort to harness routinely available local CT imaging [19,20].

In GBM, associations between CT-based body composition and prognosis have not been previously investigated. Meanwhile, numerous recent studies suggest a relationship between GBM outcome and temporal muscle thickness (TMT), a one-dimensional measure derived from diagnostic magnetic resonance imaging (MRI) [21–24]. Fat measurements or two-dimensional body composition quantifications have not been attempted.

We developed this cohort study to assess the prognostic potential of CT-derived two-dimensional muscle and fat measurements using routinely available data from radiation planning CT scans in GBM patients. We first assessed the validity of our measurements by comparing these newly quantified cervical markers with standardized measures at the L3 level in a cohort of whole-body CT scans. We then performed measurements in a cohort of GBM patients, hypothesizing that radiation planning CT-based body composition measures may be associated with overall survival (OS) in this patient group.

## Materials and methods

This retrospective study was approved by the ethics committee of the Medical Association of Westphalia-Lippe (2021-685-f-S).

### *Validation cohort*

Pre-therapeutic positron-emission tomography (PET)-CT scans from the ACRIN 6668 NSCLC FDG PET study [25] accessible through the Cancer Imaging Archive (TCIA) [26] were downloaded. We then used the CT scan series to perform body composition measurements. The open-source 3D Slicer Software (version 4.13.0) was used for segmentation.

First, after uploading the CT scans into the workstation, images were reformatted to standardize patient positioning: Head tilt along the frontal axis was corrected by orienting the nasal septum in a vertical plain. Head tilt along the sagittal axis was corrected by similarly orienting the dens axis in a vertical plain.

We chose to quantify cervical muscle at the levels closest to the cranium, i.e., at the levels of the first (C1) and second cervical vertebral body (C2). At each level, a single axial image visualizing the vertebral arch was selected. As oropharyngeal mucosa proves difficult to accurately differentiate from muscle given similar levels of radiodensity on non-contrast scans we decided to perform segmentations in the retrocervical region, largely similar to previous studies at the C3 level [27]. Thus, all muscle and fat compartments located dorsally of the vertebral arch were included. Previously reported cutoff values were used for measurement of muscle (-29 to + 150 Hounsfield units) and fat tissue (-190 to -30 Hounsfield units). Segmentations are visualized in Fig. 1. In sum, the following muscle groups were included: the trapezoid, sternocleidomastoid, levator scapulae and the autochthonous muscles (M. longissimus capitis, splenius capitis, splenius cervicis, semispinalis capitis) also encompassing the short neck musculature (M. rectus capitis posterior major, obliquus capitis superior et inferior). Fat tissue located dorsally of the parotid glands and outside of the muscle facia – i.e., between muscles and skin – was defined as subcutaneous fat tissue. Measurements were not attempted if scans were visually deemed unsuitable by the readers and the supervisors. All measurements were performed by a trained analyst (B.O.T.) while its reproducibility was independently analyzed by a second trained analyst (A.S.T.) using a control sample of 38 scans. Interreader agreement was determined similar to previous studies [28].

Additionally, standardized measurements at the L3 level on the same scan were performed similar to previous studies [16] resulting in fat or muscle cross-sectional areas (in $cm^2$).

### *Glioblastoma cohort*

Consecutive adult patients undergoing radiotherapy planning for pathologically confirmed GBM at our institution, a large tertiary care brain tumor center, between January 1st, 2010, and December 31st, 2020, were included. Only patients without previous irradiation to the

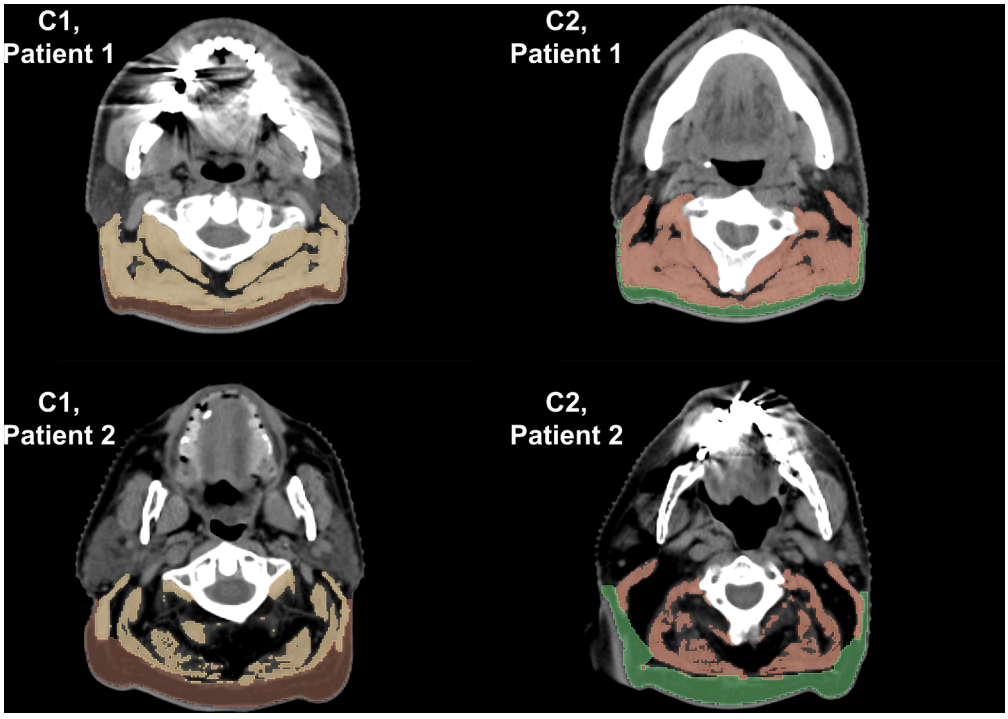


**Fig. 1.** Cervical body composition measurements. Quantified skeletal muscle area was located dorsally of the C1 and C2 vertebrae. Additionally, subcutaneous adipose tissue area was computed. Here, representative measurements are demonstrated for levels C1 and C2 for two male patients. 56-year-old Patient 1 demonstrates high-muscle area while measurements in 63-year-old patient 2 are reduced. Patient 1 survived for another 20 months. Patient 2 passed away after only 3 months. Note that the metal artifacts did not preclude analyses in these cases.

cranium were considered. Similarly, only IDH-1 negative tumors qualified for screening, reflecting recent modifications in GBM definition. Patients were included irrespective of prior surgical procedure. We only included patients with a primary GBM diagnosis whereas patients with recurring GBM were excluded.

Patient data (demographics, co-morbidities, tumor, and treatment details) and outcomes were abstracted from an intra-institutional neurosurgical database as well as the cancer registry of the Western German Cancer Center (Westdeutsches Tumorzentrum, WTZ), a prospectively maintained resource. OS was defined as the primary outcome with survival time in months calculated from radiation planning CT to date of last contact or death as of June 2nd, 2022. Macroscopic tumor volume in $cm^3$ was measured based on preoperative contrast-enhanced T1-weighted MRI images. Extent of resection was determined based on postoperative MRI images and abstracted from the radiological report or, if not explicitly stated, assessed by radiation oncologists (H.T.E., F.M. T.). Cases with removal of more than 95% of the contrast-enhancing lesion were deemed "gross total resections" (GTR) while all other resections were considered "subtotal resections" (STR), similar to previous definitions [29–31].

Patient CT scans were downloaded from the ARIA Oncology Information System (Varian Medical Systems, Inc., Palo Alto, CA, USA). Cervical measurements were performed as described above. The analyst (B.O.T.) was blinded to outcomes during measurements. Again, fat or muscle cross-sectional areas in $cm^2$ were obtained. These parameters were then directly used for analyses. For group definition, we defined a low-muscle or low-fat group comprised of males or females with below-median muscle or fat measurements relative to their sex ("low-muscle/low-fat group"). This group was compared to the remaining patients with above-median muscle or fat measurements relative to their sex ("high-muscle/high-fat group") [20].

Finally, TMT (in mm) was measured on pre-operative MRI scans, as described previously [21–24].

### *Statistical analysis*

We used descriptive statistics for patient characteristics. We analyzed correlations between body composition measurements at different levels using spearman correlations. Intraclass correlation coefficients were utilized to evaluate inter-reader agreement.

Univariable relationships between parameters and OS were estimated using the Kaplan-Meier method and assessed for statistical significance with the log-rank test. Cox proportional hazard models were developed for multivariable analyses including pre-defined variables previously associated with survival in GBM patients: Sex [32], BMI [6], extent of resection (biopsy vs. subtotal vs. total resections) [9], comorbidities and age (using the Charlson Comorbidity Index [CCI]) [33], postoperative performance status [8], tumor size at time of diagnosis [34], number of lesions at time of diagnosis (one vs. multiple) [35], bilateral glioblastoma (vs. unilateral) [36], and MGMT methylation status [5]. Analyses were performed using body composition measures at each level as continuous variables (in $cm^2$) as well as group definitions ("low-muscle group" vs. "high-muscle group").

All analyses were conducted using STATA (version 13.0, StataCorp, College Station, TX). A type-1 error rate of 5% was assumed for all confidence intervals and hypothesis tests.

## Results

### *Measurement validation*

A total of 193 patients (123 males, 70 females) qualified for analysis in the validation cohort. Exclusions are detailed in Supplementary Figure 1. Correlations between L3 and C1/C2 measurements were rated good for muscle (C1: spearman's rho = 0.78, $p < 0.001$; C2: rho = 0.82, $p < 0.001$) and fat tissue (C1: rho = 0.68, $p < 0.001$; C2: rho = 0.69, $p < 0.001$). Correlations between C1 and C2 levels were excellent (muscle: rho = 0.91, $p < 0.001$; fat tissue: rho = 0.94, $p < 0.001$). Scatter plots are shown in Fig. 2.

Inter-reader agreements were excellent for measurements at both levels (intraclass correlation coefficients greater than 0.965, Supplementary Table 1).

### *Patient characteristics in the GBM cohort*

We included 324 of 331 (97.9%) consecutively screened patients. Three patients were excluded due to previously received radiation therapy for a different primary brain tumor. Two patients were excluded for missing data on the extent of the resection. One patient was excluded for dental implant-related metal artifacts precluding accurate measurements at both levels. In one patient, C1 and C2 levels were not visualized on planning CT. In one case for C1 and eleven cases for C2, artifacts or limited field of view precluded measurement of one but not the other level and we decided to keep these patients included in the study. Fig. 3 summarizes inclusion and exclusion criteria.

The majority of patients (60.8%) were male and had previously undergone a resection (46.0% total, 38.6% subtotal resection) vs. a biopsy (15.4%). 53.4% of tumors demonstrated MGMT methylation. Patient, tumor, and treatment characteristics are detailed in Table 1.

After the radiation planning CT scan, most patients (84.3%) underwent standardized treatment with 60 Gy of irradiation in 2 Gy fractions. Some patients received different treatment regimens including hypofractionation due to deteriorating clinical status (n = 15), a higher total dose (66 Gy) to compensate for a pause in the radiation treatment following post-surgical complications (n = 1) or a premature termination of radiation treatment due to worsening of symptoms and/or the patient's preference (n = 26). 2 patients (0.6%) died before radiation treatment was commenced.

Overall mortality amounted to 90.4% (293 of 324 patients) over a median follow-up of 13 months. Median survival time was 13.1 months (95% confidence interval 11.3–14.8 months).

### *Body composition measurements*

**Supplementary** Fig. 2 demonstrates histograms of continuous body composition measurements. Median muscle CSA was higher at C2 compared to C1 while median fat CSA was higher at C1 compared to C2. Both measures were also higher in male compared to female patients ($p < 0.001$ for all). Median fat CSA for males and females was 15.4 $cm^2$ and 12.3 $cm^2$ at the C1 and 14.3 $cm^2$ and 10.8 $cm^2$ at the C2 level. Median muscle CSA for males and females were 31.4 $cm^2$ and 21.7 $cm^2$ at the C1 and 35.6 $cm^2$ and 23.4 $cm^2$ at the C2 level, respectively. These cutoffs served to categorize patients into low-muscle and high-muscle or -fat groups. Patient characteristics in Table 1 are also demonstrated by stratified low-muscle and high-muscle groups based on C1 level measurements. Patients in the low-muscle group were more likely to be of older age and had a higher CCI, a higher ECOG score (all $p < 0.001$) and a higher weight ($p = 0.022$) and BMI ($p = 0.005$).

### *Univariable analyses for body composition measurements and survival*

In univariable log-rank calculations, shorter survival was found in the low-muscle group compared to the high-muscle group for both C1 and C2 (Fig. 4). Median OS was 10.4 months in the low-muscle and 15.1 months in the high-muscle group ($p = 0.014$) for C1 and 10.2 vs. 15.1 months ($p = 0.012$) for C2. Conversely, the low-fat group survived longer compared to the high-fat group at both levels. Median OS was 14.8 months in the low-fat and 11.0 months in the high-fat group ($p = 0.012$) for C1 and 14.7 vs. 11.3 months ($p = 0.066$) for C2.

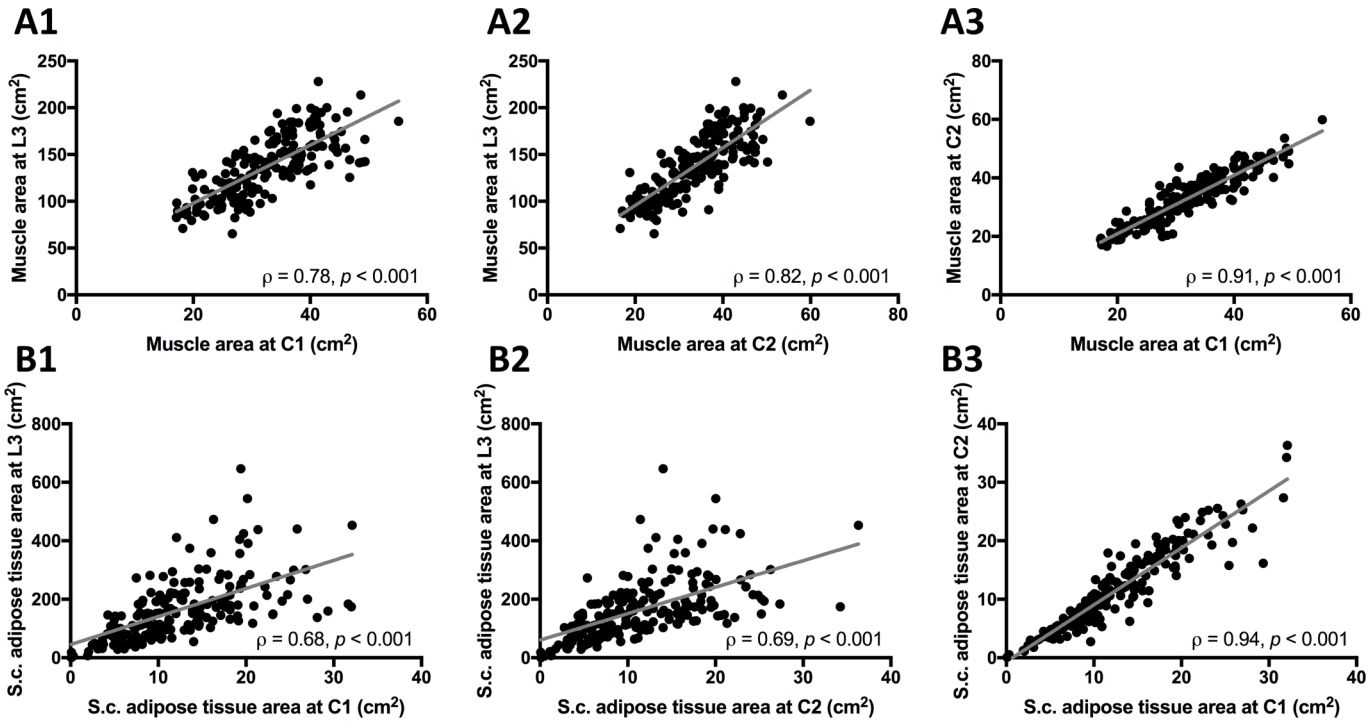


**Fig. 2.** Correlation between measurements at the level of the first cervical (C1), second cervical (C2) and third lumbar vertebra (L3). Spearman correlation coefficients and respective *p* values are presented. Muscle (panels A1-3) and fat (panels B1-3) measurements were correlated.

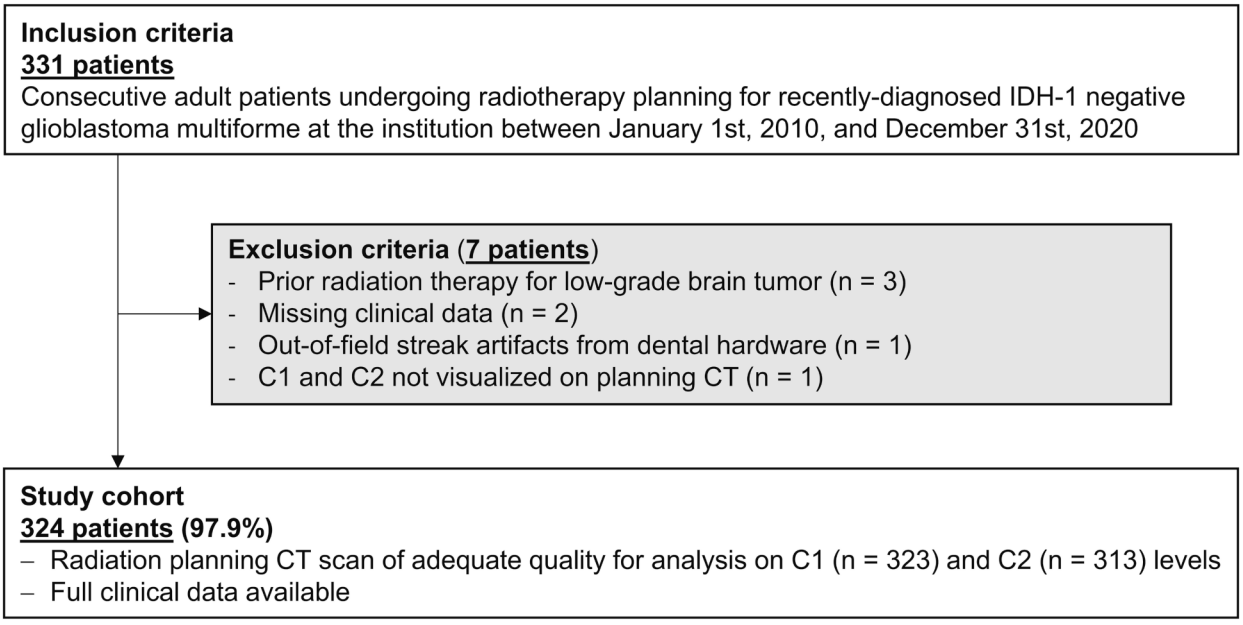


**Fig. 3.** Glioblastoma cohort inclusion and exclusion criteria. IDH-1: isocitrate dehydrogenase 1. C1: first cervical vertebra. C2: second cervical vertebra. CT: computed tomography.

*Multivariable analyses including novel body composition measurements*

We then performed multivariable Cox proportional hazard regressions, adjusting for parameters known to be associated with survival. Here, both muscle groups and continuous muscle measurements were independently associated with OS (Table 2). Low muscle measurements were associated with reduced survival. Conversely, associations were lost for subcutaneous fat tissue in a multivariable setting for group and continuous measurements (Table 2).

*Associations with ECOG score*

We subsequently assessed associations between muscle and fat measurements and performance status, as reflected in the ECOG score (**Supplementary** Fig. 3). Muscle and fat measurements did not show strong relationships with ECOG scores. We only found weak to moderate negative associations between muscle and ECOG score in males and weak positive associations between fat and ECOG score in females.

**Table 1**
Patient characteristics. Median and interquartile range, mean and standard deviation or number and percentage are given, as appropriate. Data are presented for all included patients (n = 324) and for patients with below-average (n = 162) and above-average (n = 161) muscle measurements at the first cervical vertebra (C1; measurements were not available in n = 1 patient).

| | All (n = 324) | C1 low muscle group (n = 162) | C1 high muscle group (n = 161) | *p* value |
|---|---|---|---|---|
| **General patient characteristics** | | | | |
| **Age**, years, median (range) | 63 (21–89) | 67 (25–89) | 60 (21–85) | **<0.001** |
| **Body mass index**, kg/m$^2$, median (range) | 26.0 (13.7–58.8) | 25.4 (13.7–42.0) | 26.6 (17.8–58.8) | **0.005** |
| **Height**, cm, median (range) | 174 (148–198) | 174 (150–198) | 174 (148–195) | 0.72 |
| **Weight**, kg, median (range) | 80 (43–188) | 79 (43–130) | 81 (48–188) | **0.022** |
| **Male**, n (%) | 197 (60.8) | 98 (60.5) | 98 (60.9) | 0.95 |
| **Patient comorbidities** | | | | |
| **Charlson Comorbidity Index**, median (range) | 4 (2–12) | 5 (2–12) | 4 (2–11) | **<0.001** |
| **Eastern Cooperative Oncology Group (EGOG) Score**, n (%) | | | | **<0.001** |
| ECOG 0–1 | 235 (72.5) | 120 (63.0) | 132 (82.0) | |
| ECOG 2–4 | 89 (27.5) | 60 (37.0) | 29 (18.0) | |
| **Tumor characteristics & treatment details** | | | | |
| **MGMT methylation status**, n (%) | | | | 0.62 |
| Un-methylated | 151 (46.6) | 73 (45.1) | 77 (47.8) | |
| Methylated | 173 (53.4) | 89 (54.9) | 84 (52.2) | |
| **Extent of resection**, n (%) | | | | 0.32 |
| Gross total resection (GTR) | 149 (46.0) | 71 (42.8) | 77 (47.8) | |
| Subtotal resection (STR) | 125 (38.6) | 69 (42.6) | 56 (34.8) | |
| Biopsy | 50 (15.4) | 22 (13.6) | 28 (17.4) | |
| **Radiation dose,** Gy | 60 (0–66) | 60 (0–60) | 60 (0–66) | 0.37 |
| **Standard dose (60 Gy) applied**, n (%) | 273 (84.3) | 135 (83.3) | 137 (85.1) | 0.67 |
| **Tumor size at time of diagnosis,** cm$^3$ | 30.6 (0.3–170.9) | 32.9 (1.7–170.9) | 28.9 (0.3–140.6) | 0.11 |
| **Bilateral tumor manifestation**, n (%) | 45 (13.9) | 20 (12.3) | 25 (15.5) | 0.41 |
| **Number of lesions at time of diagnosis**[1], n (%) | | | | 0.11 |
| Single lesion | 246 (75.9) | 129 (79.6) | 116 (72.1) | |
| Multiple lesions | 78 (24.1) | 33 (20.4) | 45 (28.0) | |

[1] Contrast-enhancing lesions on T1-weighted preoperative magnetic resonance imaging scans.

*Comparison with temporal muscle thickness*

Finally, we performed correlation analyses between TMT and cervical muscle measurements. Preoperative MRI imaging allowed for successful TMT measurements in 307 of 324 patients (94.7%). The median time difference between preoperative MRI and postoperative radiation planning CT added up to 22 days (range 7–81 days). Correlations were only moderately strong between TMT and C1 (spearman's rho = 0.40, $p < 0.001$) and C2 (rho = 0.44, $p < 0.001$, **Supplementary Fig. 4**). Upon inclusion of both measures into the multivariable model, both TMT and cervical muscle measurements were significantly associated with OS (Supplementary Table 3).

## Discussion

In our study, we implemented and validated cervical body composition measures obtained from routine radiation planning CTs as novel biomarkers associated with OS in GBM patients. Patients with low muscle or high fat measurements experienced shorter OS compared to those with high muscle or low fat measurements. Muscle measurements at levels C1 and C2 were independently associated with OS in multivariable models. These findings indicate that body composition parameters obtained from routine cranial radiation planning CT scans may help to improve the prediction of death in GBM patients.

Our study introduces the concept of body composition into the context of brain tumor radiation planning CT imaging. As radiation treatment is routinely recommended in GBM patients, radiation planning imaging is widely available in this cohort. Radiation planning scans have recently been used to evaluate non-cancerous features in lung [37] and head and neck cancer [38]. This novel approach takes advantage of routine imaging generated as part of clinical radiation therapy preparation, underlining the value of radiotherapy-related data for prognostication.

Here, we proceeded to implement novel measurements at the C1 and C2 levels in outcome prediction for GBM patients, consistently demonstrating that muscle measurements are novel risk predictors associated with OS. Fat parameters showed univariable associations with OS, but relationship was lost in multivariable modelling, indicating that cervical fat measurements do not improve existing risk stratification, contrary to muscle measurements. Measurements were investigated in a group-based setting based on cutoffs to demonstrate that these measurements may help identify specific groups at risk for shorter survival. However, multivariable testing also involved continuous body composition measurements, leveraging the availability of more granular data. Ultimately, the continuous nature of the measurements may allow for a more individualized approach in prognostication.

Body composition measures have been extensively investigated in abdominal malignancies based on the availability of standardized L3 measurements [19]. More recently, thoracic imaging has similarly been utilized to demonstrate associations between body composition and mortality in cancer patients [39]. Cervical imaging has not been investigated to a similar degree, resulting in a lack of understanding and standardization. Some studies noted reproducibility of muscle measurements at the level of the third [40] and fifth [41] cervical vertebra and introduced measurements to head and neck cancer patients [27,42,43]. Here, we provide data to show that body composition measurements at the level of C1 and C2 are feasible, reproducible and are correlated with standardized measurements from L3. Correlations between muscle measurements at C1/2 and L3 was strong and on par with correlations in the thorax [44]. Meanwhile, fat tissue measurements differed somewhat more strongly, possibly due to the old age of non-contrast CT scans used. Modern, high-quality CT scans will likely enable more accurate measurements and may result in stronger correlations.

During patient screening, exclusion rates were minimal. Metal dental hardware may limit analyses in individual cases due to streak artifacts, but this phenomenon only precluded measurements in a single patient.

Our pre-specified model considered the most relevant established risk factors for mortality in our patient cohort, including sex, BMI, performance status, multilesional tumors vs. single lesions, comorbidities and age (combined in the CCI), tumor size, extent of resection, bilateral tumor extent, and MGMT methylation. In accordance with previous findings [5,6,8,29,32,33,35,36], most of these parameters were associated with survival. Interestingly, tumor size and number of lesions held no prognostic relevance in a multivariable setting, potentially due to the inclusion of "postoperative resection status" and "bilateral tumor extent" as related and more relevant risk factors.

Multiple studies have shown the value of TMT in GBM patients [21–24] while only a single small-scale study disagreed [45]. Notably,

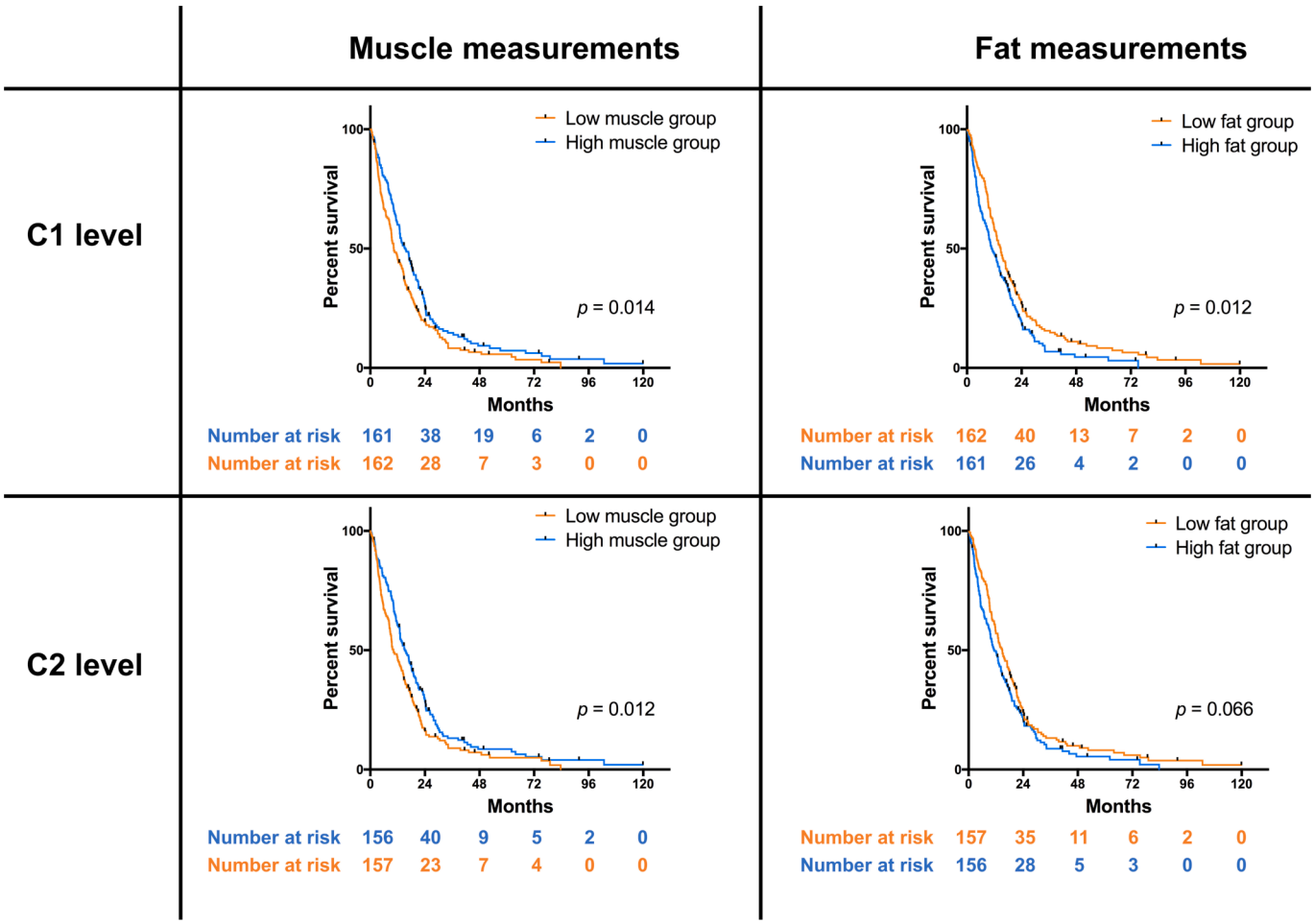


**Fig. 4.** Kaplan Meier plots demonstrate relationship between overall survival and low-muscle or fat area group (orange) and high-muscle or fat area group (blue), according to C1 measurements (upper row) and C2 measurements (lower row). Low-muscle group patients experienced significantly shorter survival compared to high-muscle group patients ($p = 0.014$ for C1, median survival 10.4 vs. 15.1 months; $p = 0.012$ for C2, median survival 10.2 vs. 15.1 months), while low-fat group patients experienced longer survival ($p = 0.012$ for C1, median survival 14.8 vs. 11.0 months; $p = 0.066$ for C2, median survival 14.7 vs. 11.3 months).

our study shows that cervical muscle measurements and TMT may reflect different body composition characteristics given only limited correlation. In our combined model, both measures significantly contributed to GBM risk prognostication independently of each other. Combining multiple different non-cancerous imaging features is increasingly given consideration in efforts to improve risk prognostication [37]. In this setting, we propose the combination of TMT and cervical muscle measurements for prediction of survival in GBM patients. We hypothesize that future research in other imaging features may identify additional prognostic factors to further improve the existing model.

Improving cervical muscle measurements themselves may also offer intriguing future potential. Our two-dimensional measures can easily be expanded to include three dimensions, e.g., by encompassing the entire C1-C2 segment. CT-based 3D body composition has previously been established via convolutional networks [46]. Given the capacity for population-scale body composition analysis using deep learning algorithms [47], there is substantial potential to both expand and simplify measurement acquisition. Fully automated algorithms eliminate measurement time and may facilitate implementation of measurements in clinical practice.

Radiation planning CT scans are generally performed post-surgery. However, up-front surgery remains the gold standard in GBM patients, so we do not believe that pre-operative availability of parameters would impact clinical decision-making. This was reflected in our model as the extent of resection remained a key prognostic factor. We believe the immediate clinical value of our findings lies in a better understanding of individualized prognosis for patients and caregivers. Enhanced prognostic capabilities may allow for well-timed intensification of palliative support in end-of-life settings, potentially improving patient quality of life in this critical period. Here, measurements may support the clinician's qualitative "eyeball test" with quantitative data. They may also enhance patient decision-making by providing a better prognostic understanding to caregivers and patients.

Interestingly, there was only limited association between physical status, as reflected in the ECOG score, and muscle and fat measurements. This indicates that body composition measurements are not a close surrogate for performance status but may include additional information. Numerous other parameters have previously been identified that influence body composition markers, including nutrition [48], hormonal status [49], inflammatory status [50], stress [51], sleep [52], socioeconomic status [53], and genetics [54]. Thus, in our view, these body composition measures reflect a multitude of individual factors which in their sum show the potential to enhance GBM prognostication.

Whether muscle or fat are modifiable variables, e.g., by exercise, remains unclear and warrants investigation. Exercise interventions are becoming more common in GBM patients [55–57] and prospective studies are currently underway to assess whether structured exercise programs may prolong survival. Additionally, diet, general physical activity and inflammatory status may also be modifiable variables [48,58,59]. In this setting, our retrospective study underscores the potential relevance of investigating these interventions in this patient

**Table 2**
Multivariable Cox proportional hazard regression of overall survival in glioblastoma patients including novel muscle measures. Tumor size was calculated from preoperative contrast enhanced T1 magnetic resonance imaging. Extent of resection was calculated as biopsy, subtotal resection (STR; more than 5% of contrast-enhancing mass remaining on post-op MRI) and gross total resection (GTR; <5% of contrast-enhancing mass remaining on post-op MRI). ECOG: Eastern Cooperative Oncology Group. MGMT: $O^6$-Methylguanine-DNA Methyltransferase.

| | C1 high muscle group (vs. low-muscle group [reference]) n = 323 | | C2 high muscle group (vs. low-muscle group [reference]) n = 313 | | C1 muscle area (in $cm^2$) n = 323 | | C2 muscle area (in $cm^2$) n = 313 | |
|---|---|---|---|---|---|---|---|---|
| | HR (CI) | *p* | HR (CI) | *p* | HR (CI) | *p* | HR (CI) | *p* |
| **Muscle measurement** | 0.73 (0.56–0.94) | **0.014** | 0.75 (0.59–0.97) | **0.028** | 0.97 (0.95–0.99) | **0.008** | 0.97 (0.95–0.99) | **0.004** |
| **Body mass index**, $kg/m^2$ | 1.03 (1.01–1.06) | **0.005** | 1.03 (1.01–1.06) | **0.005** | 1.04 (1.02–1.06) | **0.001** | 1.04 (1.02–1.06) | **0.001** |
| **Sex** | | | | | | | | |
| Female | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| Male | 1.11 (0.87–1.43) | 0.391 | 1.14 (0.88–1.47) | 0.311 | 1.54 (1.1–2.17) | **0.013** | 1.73 (1.18–2.52) | **0.005** |
| **Charlson Comorbidity Index**, points | 1.12 (1.05–1.2) | **0.001** | 1.12 (1.04–1.2) | **0.002** | 1.11 (1.03–1.19) | **0.004** | 1.1 (1.03–1.18) | **0.008** |
| **ECOG Score** | | | | | | | | |
| 0–1 | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| ≥2 | 1.55 (1.17–2.04) | **0.002** | 1.55 (1.17–2.04) | **0.002** | 1.52 (1.15–2.01) | **0.003** | 1.52 (1.15–2) | **0.004** |
| **Tumor size at time of diagnosis,** $cm^3$ | 1 (0.99–1) | 0.594 | 1 (1–1) | 0.788 | 1 (0.99–1) | 0.524 | 1 (0.99–1) | 0.607 |
| **Number of lesions at time of diagnosis**[1] | | | | | | | | |
| 1 | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| 2 or more | 1.28 (0.93–1.75) | 0.127 | 1.21 (0.88–1.66) | 0.234 | 1.23 (0.9–1.68) | 0.188 | 1.22 (0.89–1.68) | 0.211 |
| **Tumor extent** | | | | | | | | |
| Unilateral | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| Bilateral | 1.44 (1.19–1.73) | **<0.001** | 1.42 (1.17–1.71) | **<0.001** | 1.43 (1.18–1.72) | **<0.001** | 1.42 (1.17–1.71) | **<0.001** |
| **MGMT methylation status** | | | | | | | | |
| Un-methylated | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| Methylated | 0.61 (0.48–0.78) | **<0.001** | 0.61 (0.48–0.77) | **<0.001** | 0.61 (0.48–0.78) | **<0.001** | 0.6 (0.47–0.77) | **<0.001** |
| **Extent of resection** | | | | | | | | |
| GTR | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | | Ref. 1.00 | |
| STR | 1.18 (0.9–1.56) | 0.221 | 1.21 (0.92–1.6) | 0.165 | 1.18 (0.9–1.55) | 0.225 | 1.23 (0.93–1.61) | 0.145 |
| Biopsy | 2.47 (1.69–3.61) | **<0.001** | 2.53 (1.72–3.72) | **<0.001** | 2.53 (1.73–3.68) | **<0.001** | 2.59 (1.77–3.8) | **<0.001** |

[1] Contrast-enhancing lesions on T1-weighted preoperative MRI scans.

cohort. However, notably, interventions need to be supervised by dedicated professionals and individualized according to patient preferences, disease status, treatment and symptoms, thus conforming to the "adapted physical therapy" concept [60].

There are some notable limitations to this study. First, the retrospective design did not allow for assessment of muscle strength and function or for analysis of exercise levels relative to imaging measures. Second, a single-center design may carry inherent biases, especially in a retrospective setting. However, a significant number of GBM patients was included in our analysis and patient characteristics were in line with previous studies. Third, for validation and C1/2-L3 correlation analyses, we relied on cancer patient data from lung cancer patients as whole-body CT scans of healthy participants are not routinely available. However, we chose pre-therapeutic scans of non-metastatic lung cancer, a tumor entity unlikely to affect body composition on C1/C2 or L3 levels disproportionately. Finally, this implementation study only assessed and established muscle measurements at a single timepoint. Future studies may allow for longitudinal assessments in patients undergoing re-irradiation. However, only selected patients typically undergo re-irradiation [61].

In conclusion, in this exploratory study, we implement cervical body composition parameters including muscle and subcutaneous fat tissue cross-sectional area at levels C1 and C2 and demonstrate validity and reproducibility of measurements. We proceed to demonstrate that muscle measurements are independent prognostic parameters for overall survival in glioblastoma patients. As these parameters are readily available from radiation planning CT scans, muscle parameters could be harnessed to improve prognostication in this patient cohort.

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## 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.

## Data availability statement:

All data generated and analyzed during this study are included in this published article (and its supplementary information files).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100621.

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