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Post-chemoradiation volumetric response predicts survival in newly diagnosed glioblastoma treated with radiation, temozolomide, and bevacizumab or placebo


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Abstract

Background. In the current study we used contrast-enhanced T1 subtraction maps to test whether early changes in enhancing tumor volume are prognostic for overall survival (OS) in newly diagnosed glioblastoma (GBM) patients treated with chemoradiation with or without bevacizumab (BV).

Methods. Seven hundred ninety-eight patients (404 BV and 394 placebo) with newly diagnosed GBM in the AVAglio trial (NCT00943826) had baseline MRI scans available, while 337 BV-treated and 269 placebo-treated patients had >4 MRI scans for response evaluation. The volume of contrast-enhancing tumor was quantified and used for subsequent analyses.

Results. A decrease in tumor volume during chemoradiation was associated with a longer OS in the placebo group (hazard ratio [HR] = 1.578, P < 0.0001) but not BV-treated group (HR = 1.135, P = 0.4889). Results showed a higher OS in patients on the placebo arm with a sustained decrease in tumor volume using a post-chemoradiation baseline (HR = 1.692, P = 0.0005), and a trend toward longer OS was seen in BV-treated patients (HR = 1.264, P = 0.0724). Multivariable Cox regression confirmed that sustained response or stable disease was prognostic for OS (HR = 0.7509, P = 0.0127) when accounting for age (P = 0.0002), KPS (P = 0.1516), postsurgical tumor volume

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(P < 0.0001), O6-methylguanine-DNA methyltransferase status (P < 0.0001), and treatment type (P = 0.7637) using the post-chemoradiation baseline.

**Conclusions.** The post-chemoradiation timepoint is a better baseline for evaluating efficacy in newly diagnosed GBM. Early progression during the maintenance phase is consequential in predicting OS, supporting the use of progression-free survival rates as a meaningful surrogate for GBM.

**Keywords**

bevacizumab | clinical trials | GBM | glioblastoma | MRI | response assessment | T1 subtraction

**Importance of the study**

Significant questions remain regarding the usefulness of contrast enhancement in determining tumor response and failure within the context of newly diagnosed glioblastoma (GBM). Following initial surgical resection, for example, there may not be sufficient measurable enhancing disease to monitor treatment response. Additionally, the presence of pseudoprogression, or treatment-related inflammatory changes mimicking tumor growth,1-3 often confounds interpretation of tumor response in the upfront setting, particularly during concomitant radiation and temozolomide.4-8 Moreover, ongoing investigations into the use of anti-angiogenic agents for treatment of GBM raise additional doubts about the reliability of contrast enhancement as a meaningful surrogate for treatment efficacy.5-8

Clinicians have developed novel strategies to mitigate these challenges during routine clinical care; however, these approaches have not been thoroughly evaluated and have yet to be translated into routine use in multicenter clinical trials. For example, the postoperative MRI examination is often used as a baseline for upfront GBM clinical trials, but this scan often occurs without a standardized acquisition protocol because it is attained prior to enrollment and the scans are often confounded with post-surgical changes including blood products. To isolate contrast enhancement from blood products, or to identify true disease-related enhancement from occult enhancement during anti-angiogenic therapy, clinicians can use digital subtraction techniques,6,7 or "T1 subtraction maps," or wait for subsequent scans to better understand the current state of the disease. Because clinicians often observe transient imaging changes during chemoradiation due to pseudoprogression, pseudoresponse (in case of anti-angiogenic treatments), or true tumor progression, many choose to use the first post-chemoradiation MRI examination as a “new baseline” for evaluating subsequent changes during routine clinical care. Thus, there appears at least some level of divergence between how physicians evaluate treatment efficacy in routine clinical practice and how efficacy is measured during a clinical trial setting, likely owing to inadequate scientific evidence relating these differing strategies to clinical value or predicting long-term overall survival (OS).

To address these practical questions we utilized contrast-enhanced T1 subtraction maps to increase lesion conspicuity, then tested whether early changes in contrast enhancement during chemoradiation or maintenance therapy are prognostic for OS in patients with newly diagnosed GBM treated with concomitant radiation and temozolomide with or without BV. Results suggest the first post-chemoradiation timepoint may be a better baseline for evaluating therapeutic efficacy in newly diagnosed GBM. Data suggest that early progression during the maintenance phase is more consequential in predicting OS, supporting the use of progression-free survival rates as a meaningful surrogate.

**Methods**

**Study Design, Treatment, and Patients**

A total of 921 patients were enrolled in AVAglio, a randomized, double-blind, placebo-controlled phase III trial...
sponsored by F. Hoffmann-La Roche (ClinicalTrials.gov
#NCT00943826; clinicaltrials.gov/ct2/show/NCT00943826)
and conducted at 120 sites in 23 countries. The proto-
col was approved by the applicable independent ethics
committee and institutional review board at each insti-
tution. All patients provided written informed consent
to participate. The study adhered to the principles of
the Declaration of Helsinki and the Guidelines for Good
Clinical Practice. Patient demographics are provided
in Table 1 and are available in Chinoth et al. Detailed
methodology for patient selection is outlined in the
Supplementary material.

Of the 921 patients initially enrolled, 458 were ran-
domized to the BV group and 463 to the placebo group
(Fig. 1), while 452 patients in the BV group and 459
patients in the placebo group received treatment. All
patients were 18 years of age or older and had newly
diagnosed supratentorial GBM on histological confirma-
tion. Patients were excluded if they had no detectable
disease at baseline (volume = 0 cc) or if they had recent
symptomatic intracranial hemorrhage or prior radiother-
apy, chemotherapy, or immunotherapy. After undergoing
surgical resection or biopsy, patients underwent concur-
rent RT (60 Gy administered as 2-Gy fractions 5 days/wk)
and oral TMZ (75 mg/m² of body surface area per day for
a maximum of 49 days) along with either intravenous
BV (10 mg/kg of body weight) or placebo every 2 weeks
(Fig. 1A). Patients then underwent a 28-day break in treat-
ment followed by maintenance with oral TMZ (150 mg/
m²/d on days 1 to 5 during the first cycle and 200 mg/m²/d
during subsequent cycles if unacceptable toxic effects did
not develop) plus either intravenous BV (10 mg/kg body
weight) or placebo, with no crossover between arms,
every 2 weeks for six 4-week cycles (24 wk). In the final
monotherapy phase, either BV (15 mg/kg body weight)
or placebo alone was administered every 3 weeks until
disease progression or development of adverse effects.
OS for these patients was measured from the date of ran-
domization in the trial. Additional details regarding the
clinical trial protocol and general efficacy outcomes are
available from Chinoth et al.²³

Magnetic Resonance Imaging

After surgical resection or biopsy, all patients received
imaging prior to the start of radiochemotherapy (postop-
erative), as well as 28 days after completion of concurrent
radiochemotherapy (post-chemoradiation). Patients also
received imaging approximately every 8 weeks during
the maintenance phase, every 3 weeks during the mono-
therapy phase, and at the time of disease progression.
At each MRI examination, patients received T1-weighted
MR images both before (T1) and after (T1+C) injection of
a gadolinium-based contrast agent. Any MRI examination
without a precontrast T1-weighted image was excluded
from the study. Additional anatomic MR images included
T2-weighted fluid-attenuated inversion recovery and
T2-weighted turbo spin echo images, but these were not
used in the current study.

Tumor Segmentation

Contrast-enhanced T1-weighted subtraction maps were
calculated by standard techniques outlined by Ellingson et al.¹¹
Briefly, linear registration was performed between T1 and
T1+C images, including trilinear interpolation if image reso-

Table 1  Patient demographics (from Chinoth et al)²³

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Chemoradiation + Bevacizumab (N = 458)</th>
<th>Chemoradiation + Placebo (N = 463)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>57 (20–84)</td>
<td>56 (18–79)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>282 (62%) / 176 (38%)</td>
<td>298 (64%) / 165 (36%)</td>
</tr>
<tr>
<td>KPS at baseline (% of patients)</td>
<td>80-100 (67%)</td>
<td>90-100 (70%)</td>
</tr>
<tr>
<td>MGMT status (% of patients)</td>
<td>Methylated (26%)</td>
<td>Methylation status (% of patients) 26%</td>
</tr>
<tr>
<td></td>
<td>Unmethylated (49%)</td>
<td>Methylated (15%)</td>
</tr>
<tr>
<td></td>
<td>Missing (25%)</td>
<td>Unmethylated (51%)</td>
</tr>
<tr>
<td>Primary vs secondary GBM</td>
<td>Primary (452/458)</td>
<td>Primary (461/463)</td>
</tr>
<tr>
<td></td>
<td>Secondary (6/458)</td>
<td>Secondary (2/458)</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>10.6 mo</td>
<td>6.2 mo</td>
</tr>
<tr>
<td>Median OS</td>
<td>16.8 mo</td>
<td>16.7 mo</td>
</tr>
</tbody>
</table>
Hypothesis Testing and Statistical Analysis

Initial change in tumor volume during chemoradiation with or without concomitant BV

To test whether the initial change in tumor volume during chemoradiation with or without concomitant BV was predictive of OS in newly diagnosed GBM, we first examined whether the absolute change in tumor volume before and after chemoradiation with or without concomitant BV was linearly correlated with OS. We hypothesized that patients with large decreases in tumor volume would have a longer OS. We also explored whether a sustained decrease in tumor volume was a better predictor of OS compared with patients exhibiting either an unsustained decrease (initial decrease followed by rebound consisting of an increase in volume greater than baseline) or increase in tumor volume using similar univariate and multivariate analyses.

Volumetric response during maintenance (adjuvant) phase using post-chemoradiation baseline

Next, we tested whether evaluation of volumetric changes evolving during the maintenance phase, after completion of chemoradiation, was a significant predictor of OS. We
used both univariate and multivariate analyses to examine whether patients with a sustained decrease in tumor volume during the maintenance phase had a significant survival advantage compared with patients exhibiting an increase in tumor volume or an unsustained decrement in volume from the post-chemoradiation baseline.

**Volumetric equivalent Response Assessment in Neuro-Oncology (RANO) response during chemoradiation or maintenance phase with or without concomitant BV**

To test whether early response or failure using the RANO criteria could be used to predict OS we implemented “volumetric equivalent” RANO response categories based on thresholds described previously. A series of univariate and multivariate analyses were conducted to examine the association between radiographic responders (partial response [PR] and complete response [CR] corresponding to decreased enhancing tumor volume >65%) and those with stable (SD) or progressing disease (PD, defined as >40% increase in tumor volume) using both postsurgical and post-chemoradiation baselines. Additionally, a separate analysis was conducted to compare survival between sustained responders and nonresponders or unsustained responders. Lastly, we performed univariate and multivariate analyses comparing patients with early PD, including unsustained PR or CR along with sustained SD, with patients exhibiting continually shrinking or stable tumor.

All multivariable analyses controlled for age, KPS, O6-methylguanine-DNA methyltransferase (MGMT) methylation status, and treatment arm. log-rank analysis on Kaplan–Meier data and Cox proportional hazards regression models were used to model the relationship between radiographic variables and OS under a variety of conditions. No adjustments for multiple comparisons were performed. All statistical tests were performed using GraphPad Prism v6.0h, Stata v12, or Matlab (R2017a; Mathworks).

**Results**

No difference in OS was observed between treatment groups in patients with imaging available at both the pre- and post-chemoradiation timepoints (Fig. 2A; log-rank, \( P = 0.1219, \text{HR} = 0.8883 \)); however, a significant difference in the change in tumor volume between these 2 timepoints was observed (Fig. 2B; t-test, \( P < 0.0001 \)), suggesting BV patients had a significantly larger decrease in enhancing tumor volume after initial therapy compared with placebo (−9.7 cc vs +1.2 cc change, respectively). Intriguingly, investigation into the relationship between initial change in tumor volume during concurrent chemoradiation and resulting OS resulted in dramatically different results between the 2 treatment arms (Fig. 2C). As expected, a strong association was observed between significant decreases in tumor volume and increased OS in patients within the placebo group (Fig. 2C; linear regression, \( P = 0.0019; \text{slope} = -7.83 \text{cc change in volume for every day of increased OS} \)); however, an opposite association between change in tumor volume and OS was observed within the BV group, suggesting patients with the largest decrease in tumor volume actually had worse prognosis (Fig. 2C; linear regression, \( P = 0.0007; \text{slope} = +8.64 \text{cc change in volume for every day of increased OS} \)).

**Volumetric Equivalent RANO Response During Chemoradiation with or without Concomitant Bevacizumab**

Classification of initial change in tumor size into “volumetric equivalent” RANO response categories indicated a higher proportion of patients with PR (42.2%) and CR (6.5%) within the BV arm compared with the placebo arm (12.1% and 1.6%, respectively). Log-rank test for trends indicated a significant increase in median OS with better response when examining all subjects pooled together (Fig. 2D; log-rank test for trends, \( P < 0.0001 \); median OS = 436 days, 509 days, 580 days, and 642 days for PD, SD, PR, and CR, respectively). Stratification of patients by treatment indicated this trend was present in the placebo arm (Fig. 2E; log-rank test for trends, \( P < 0.0001 \); median OS = 434 days, 540 days, 687 days, and 1064 days for PD, SD, PR, and CR, respectively) but not the BV arm (Fig. 2F; log-rank test for trends, \( P = 0.2869 \); median OS = 491 days, 485 days, 589 days, and 638 days for PD, SD, PR, and CR, respectively).

**Initial Change in Tumor Volume During Chemoradiation with or without Concomitant Bevacizumab**

No survival differences were observed between pooled patients exhibiting a sustained decrease in tumor volume compared with patients exhibiting an unsustained or increased tumor size while using the postsurgical scan as the baseline for evaluation (Fig. 3A; log-rank, \( P = 0.1919, \text{HR} = 1.133 \)). The same trend was observed in both the placebo (Fig. 3B; log-rank, \( P = 0.2787, \text{HR} = 1.103 \)) and BV arm (Fig. 3C; log-rank, \( P = 0.4637, \text{HR} = 1.103 \)). Multivariable Cox regression demonstrated a significant association between continuous measures of initial change in tumor burden and OS (Supplementary Table S1; Cox, \( P < 0.0001, \text{HR} = 1.0142 \)) after accounting for treatment arm (Cox, \( P = 0.8024 \)), age (Cox, \( P < 0.0001, \text{HR} = 1.0209 \)), KPS (Cox, \( P = 0.1647 \)), MGMT methylation status (Cox, \( P < 0.0001, \text{HR} = 0.4227 \)), and continuous measures of postsurgical, residual contrast-enhancing tumor volume (Cox, \( P < 0.0001, \text{HR} = 1.0229 \)). Additional models investigating continuous measures in percentage change in tumor volume (Cox, \( P = 0.8549 \)) did not show a significant association after accounting for other covariates.

Patients were then stratified into initial “radiographic responders” (PR or CR) or “radiographic nonresponders” (SD or PD) based on volumetric equivalent calculations to the RANO criteria using the postoperative baseline. Univariate log-rank analysis of data pooled across treatment arms suggested that patients with radiographic response had significantly longer OS compared with nonresponders (Supplementary Fig. S1A; log-rank, \( P = 0.0058, \text{HR} = 1.260 \)). This effect was stronger when examining the placebo arm alone (Supplementary Fig. S1B; log-rank, \( P = 0.0155, \text{HR} = 1.508 \)); however, it is important to note
that only 13.7% of patients demonstrated a response in this treatment arm. Consistent with trends observed when analyzing absolute changes in tumor size, patients on the BV arm who experienced radiographic response (PR or CR) did not demonstrate a significant survival advantage compared with patients exhibiting SD or PD (Supplementary Fig. S1C; log-rank, $P = 0.2615$).

Next, patients were stratified based on whether they maintained a sustained or confirmed response (CR or PR) based on the volume changes on the subsequent scan after the initial response. In general, patients with a sustained response (CR or PR) did not demonstrate a significant survival advantage when pooled across treatment arms (Supplementary Fig. S1D; log-rank, $P = 0.885$, HR = 1.022) using the postsurgical baseline timepoint. This was true for both the placebo (Supplementary Fig. S1E; log-rank, $P = 0.6198$, HR = 1.133) and BV arm (Supplementary Fig. S1F; log-rank, $P = 0.0928$, HR = 1.046) when evaluated separately.

Early progression, defined as an unsustained CR, PR, or SD, from the postsurgical baseline timepoint also was not prognostic compared with patients exhibiting a sustained CR, PR, or SD state when evaluated for all patients (Fig. 3D; log-rank, $P = 0.5468$, HR = 1.091) or patients stratified into the placebo (Fig. 3E; log-rank, $P = 0.1356$, HR = 1.303) or BV treatment arms (Fig. 3F; log-rank, $P = 0.5710$, HR = 0.8446).

Cox multivariable regression comparing sustained radiographic responders to nonresponders while controlling for treatment, age, postoperative residual tumor volume, MGMT methylation status, and KPS confirmed the univariate observations, suggesting that MGMT status (Supplementary Table S2; Cox, $P < 0.0001$, HR = 0.3554), age (Cox, $P = 0.0002$, HR = 1.0197), and postoperative tumor volume (Cox, $P < 0.0001$, HR = 1.0170) were significant prognostic factors for OS, while radiographic response (Cox, $P = 0.5398$, HR = 0.9217), treatment arm ($P = 0.9003$, HR = 1.0153), and KPS ($P = 0.2066$, HR = 0.8548) were not. A Cox multivariable regression model suggested that patients with early progression, defined as an unsustained CR, PR, or SD, as well as early PD, from the postsurgical baseline timepoint, trended toward shorter OS
Fig 3 Initial volumetric response during the concurrent phase and the impact on OS in newly diagnosed GBM treated with or without concomitant bevacizumab. (A) Kaplan–Meier curves for OS in all patients stratified by whether they exhibited a sustained decrease in tumor volume (log-rank, P = 0.1919). (B) Kaplan–Meier curves for OS in patients in the placebo arm stratified by whether they exhibited a sustained decrease in tumor volume (log-rank, P = 0.2787). (C) Kaplan–Meier curves for OS in patients in the bevacizumab arm stratified by whether they exhibited a sustained decrease in tumor volume (log-rank, P = 0.4637). (D) Kaplan–Meier plots for OS in all patients, pooled across treatment arms, stratified by early progression during the concurrent phase (log-rank, P = 0.5468). (E) Kaplan–Meier plots for OS in patients on the placebo arm stratified by early progression during the concurrent phase (log-rank, P = 0.1356). (F) Kaplan–Meier plots for OS in patients on the bevacizumab arm stratified by early progression during the concurrent phase (log-rank, P = 0.5710). PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response.

(Supplementary Table S3; Cox, P = 0.0761) when accounting for other covariates.

Volumetric Response During Maintenance (Adjuvant) Temozolomide with or without Concomitant Bevacizumab Using a Post-Chemoradiation Baseline

In general, a sustained decrease in tumor volume during the maintenance (adjuvant) treatment phase with TMZ with or without BV resulted in a favorable prognosis (Fig. 4). Stratification of patients based on a sustained decreasing tumor volume (Fig. 4A; log-rank, P = 0.0006, HR = 1.391) or whether they had progressive disease during this period appeared to be the strongest predictor (Fig. 4D; log-rank, P < 0.0001, HR = 1.498), whereas sustained response did not reflect a long-term survival advantage (Supplementary Fig. S2A; log-rank, P = 0.7296, HR = 1.050). Patients in the placebo arm treated with TMZ during the maintenance phase who displayed a sustained decrease in tumor volume had significantly longer survival (Fig. 4B; log-rank, P = 0.0005, HR = 1.692), whereas patients treated with TMZ and BV during the same period who exhibited a decrease in tumor volume tended to have longer survival (Fig. 4C; log-rank, P = 0.0724, HR = 1.264). Patients demonstrating a sustained response (CR or PR) in the placebo (Supplementary Fig. S2B; log-rank, P = 0.0849, HR = 1.690) or BV arm (Supplementary Fig. S2C; log-rank, P = 0.4972, HR = 0.8963) did not exhibit significantly longer survival; however, patients exhibiting early progression or an unsustained response treated with either TMZ alone (Fig. 4E; log-rank, P = 0.0002, HR = 1.737) or with concomitant BV (Fig. 4F; log-rank, P = 0.0374, HR = 1.345) had a significantly worse outcome.

Consistent with univariate observations that a sustained response, defined as a confirmed PR or CR, does not translate into a significant survival advantage using univariate analyses, multivariable Cox regression analysis did not establish a relationship between sustained response and OS (Supplementary Table S4; Cox, P = 0.200) when also accounting for covariates including age (P = 0.0002, HR = 1.0196), MGMT status (P < 0.0001, HR = 0.3531), KPS
Fig. 4  Volumetric responses during the maintenance phase using a post-chemoradiation baseline and the impact on OS in newly diagnosed GBM treated with or without concomitant bevacizumab. (A) Kaplan–Meier plots for OS in all patients, pooled across treatment arms, stratified by sustained decrease in tumor volume during the maintenance phase (log-rank, \( P = 0.0066 \)). (B) Kaplan–Meier plots for OS in patients on the placebo arm stratified by sustained decrease in tumor volume during the maintenance phase (log-rank, \( P = 0.0005 \)). (C) Kaplan–Meier plots for OS in patients on the bevacizumab arm stratified by sustained decrease in tumor volume during the maintenance phase (log-rank, \( P = 0.0724 \)). (D) Kaplan–Meier plots for OS in all patients, pooled across treatment arms, stratified by early progression during the maintenance phase (log-rank, \( P < 0.0001 \)). (E) Kaplan–Meier plots for OS in patients on the placebo arm stratified by early progression during the maintenance phase (log-rank, \( P = 0.0002 \)). (F) Kaplan–Meier plots for OS in patients on the bevacizumab arm stratified by early progression during the maintenance phase (log-rank, \( P = 0.0374 \)).

Table 2  Multivariable Cox regression model results for patients with early failure during maintenance phase (post-chemoradiation baseline), treatment arm, age, KPS, and MGMT status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-chemoradiation failure vs disease control (PD vs SD/PR/Cr)</td>
<td>(-0.2864 \pm 0.1149)</td>
<td>0.7509</td>
<td>(0.5995–0.9406)</td>
<td>0.0127</td>
</tr>
<tr>
<td>Postsurgical tumor volume (continuous, cc)</td>
<td>0.0173</td>
<td>1.0175</td>
<td>(1.0122–1.0228)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment (placebo vs bevacizumab)</td>
<td>0.0171</td>
<td>1.0173</td>
<td>(0.8151–1.2697)</td>
<td>0.8786</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.0193</td>
<td>1.0195</td>
<td>(1.0090–1.0301)</td>
<td>0.0002</td>
</tr>
<tr>
<td>KPS (50–80 vs 90–100)</td>
<td>(-0.1768 \pm 0.1233)</td>
<td>0.8380</td>
<td>(0.6581–1.0670)</td>
<td>0.1516</td>
</tr>
<tr>
<td>MGMT status (methylated vs unmethylated)</td>
<td>(-1.0072 \pm 0.1286)</td>
<td>0.3652</td>
<td>(0.2838–0.4700)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: \( N = 478 \) of 606 patients had all variables available for multivariate Cox analysis.

\((P = 0.2390)\), treatment \((P = 0.8063)\), and postoperative tumor volume \((P < 0.0001, HR = 1.0169)\).

Multivariable Cox regression demonstrated a significant survival advantage in examining patients with a sustained decrease in tumor volume during the maintenance phase with respect to the post-chemoradiation baseline (Supplementary Table SS; Cox, \( P = 0.0437, HR = 0.7758 \) for patients without a sustained decrease) when accounting for other covariates including age \((P = 0.0003; HR = 1.0201)\), MGMT status \((P < 0.0001, HR = 0.3538)\), KPS \((P = 0.2104, HR = 0.8540)\), treatment arm \((P = 0.9561, HR = 1.0065)\), and postsurgical tumor volume \((P < 0.0001, HR = 1.0175)\).

In addition, multivariate analyses suggested that patients with early tumor progression, defined as having early PD or sustained PR, CR, or SD within the maintenance phase with respect to the post-chemoradiation baseline, had a significantly shorter OS compared with patients exhibiting a sustained response or stable disease (Table 2; Cox, \( P = 0.0127, HR = 0.7509 \) for patients with sustained PR, CR, or SD after accounting for age \((P = 0.0002, HR = 0.7010)\).
HR = 1.0195), MGMT status (P < 0.0001, HR = 0.3652),
KPS (P = 0.1516, HR = 0.8380), treatment arm (P = 0.8796,
HR = 1.0173), and postsurgical residual tumor volume (P < 0.0001, HR = 1.0175). Together, these results suggest that
early evidence of tumor growth during the maintenance
phase, relative to the post-chemoradiation examination, is
a strong predictor of OS in newly diagnosed GBM.

Discussion

Contrast enhancement on computed tomography (CT) or
MRI has been the gold standard for brain tumor detection,
diagnosis, clinical monitoring, and response assessment to
new therapies for more than 40 years. The first article to use
contrast-enhanced CT to visualize intracranial tumors was
published in 1974,19 but it wasn’t until the early 1990s that
clinical use of contrast-enhanced T1-weighted MRI became
relatively routine, after studies showed comparable lesion
measurements with CT.20,21 Although contrast enhancement
on CT or MRI has been used routinely in the clinic, questions
have remained regarding the optimal timing of measure-
ments and overall utility of contrast-enhancing tumor volume
measurements in predicting long-term outcomes and deter-
mining drug efficacy in the context of newly diagnosed GBM.

The current study is consistent with multiple previous inves-
tigations demonstrating that postsurgical contrast-enhancing
tumor volume is a significant, independent prognostic factor
for OS in newly diagnosed GBM. Although both postsurgical
contrast-enhancing volume22-26 and extent of resection16-18
appear to be prognostic, studies suggest that postsurgical
residual tumor volume may be a stronger predictor of OS.26
Additionally, postsurgical residual volume may be a more
practical measurement to obtain, since presurgical MRI scans
are often not available or collected as part of clinical trials,
partly because patients are not enrolled until after surgery and
subsequent diagnosis. Despite the abundant evidence sug-
gestig that residual tumor size may predict OS, the current
study may be the largest to date (N = 798) using a homoge-
nous approach to quantify enhancing tumor volume without
contamination from postsurgical blood products.

Results from the current study suggest the post-chemo-
radiation MRI examination may be a better baseline for
evaluating therapeutic efficacy compared with the postsur-
gical, pre-chemoradiation examination. Although results are
biased toward patients who can tolerate chemoradiation
and are able to obtain at least 3 MRI examinations
during the maintenance phase, the use of the post-chemo-
radiation timepoint as the baseline has a number of practical and scientific advantages. First, use of the post-
chemoradiation timepoint as the baseline reduces ambi-
guity associated with postsurgical changes, off-protocol
(pre-study) scan parameter variation, and potential vari-
ation of timing after surgical intervention, which may be
hours to days, or variation in timing from surgery to start
of therapy, as some tumor growth may occur between
surgery and the start of cytoxic therapy. Additionally,
there would inherently be less emphasis on the transient
changes known to occur during chemoradiation (ie, pseudo-
progression) or transient changes that may occur with
new experimental therapeutics including anti-angiogenic
agents (ie, pseudoresponse) or immunotherapies (ie,
inflammatory changes). Moreover, the use of the first post-
chemoradiation timepoint as the baseline more accurately
reflects current clinical management of patients with newly
diagnosed GBM, as questions regarding the interpretation
of transient changes during chemoradiation often occur.
Perhaps most importantly, scientific results from the cur-
rent study support use of the post-chemoradiation time-
point as the baseline for evaluating changes in tumor size
as a meaningful, treatment agnostic predictor of long-term
survival both in standard therapy and in combination with
anti-angiogenic agents.

Another principal observation in the current study is
the limited value of early radiographic response in newly
diagnosed GBM. Data using either the postsurgical or
post-chemoradiation timepoint as a baseline for evalu-
ation showed no survival benefit for patients who had a
confirmed or sustained partial or complete radiographic
response (>65% decrease in tumor volume) compared
with patients exhibiting stable or progressing disease.
Importantly, results did suggest a significant survival
disadvantage in patients with early radiographic pro-
gression, independent of treatment arm, age, KPS, and
MGMT status, particularly when using the post-chemo-
radiation timepoint as a baseline and when including
patients with measurable disease after surgery (Fig. 4).
Together, these data corroborate previous views that
objective response rates are not clinically meaningful in
newly diagnosed GBM, and may suggest that a measure
of early progression-free survival or treatment failure
rates during the maintenance phase (eg, progression-
free survival rates) may be extremely useful for predict-
ing long-term outcome, independently of other clinical
variables.

An interesting finding in the current study was that simple
measures of absolute increasing versus decreasing
tumor volume appeared to be informative in terms of pre-
dicting OS, particularly when probing univariate results.
The ability to quickly evaluate whether a tumor is growing or
shrinking as a meaningful and early measure of treat-
ment efficacy was the basis of the early Levin criteria39
and is more consistent with clinical management of GBM
patients, where progression is typically noted after evi-
dence of continual tumor growth and not after this growth
has reached an empirical threshold. Despite this observa-
ion, survival differences in patients with growing versus
shrinking tumors were not maintained after evaluating
using a multivariate Cox regression model including com-
mon clinical variables, suggesting that this may not be the
most sensitive method for evaluating efficacy and predict-
ing OS in newly diagnosed GBM.

Study Limitations

There are a few limitations that should be addressed. Since
postsurgical scans are often acquired out of the trial and
with nonstandardized acquisition parameters, the results
from the endpoint comparisons may have been influ-
enced by these technical differences. Additionally, if pre-
and postcontrast T1-weighted images were not acquired
identically, there is a chance that the resulting enhancing
tumor measurements on T1 subtraction maps could be
inaccurate.
Conclusion

In summary, results from the current study suggest that the post-chemoradiation time point may be a better baseline for evaluating therapeutic efficacy in newly diagnosed GBM compared with the postsurgical time point often used as the baseline in upfront trials, particularly in standard-of-care chemoradiation and chemoradiation plus therapies that may transiently modulate vascular permeability like BV. Data suggest that early progression during the maintenance phase is more consequential than early radiographic response in predicting OS, supporting the use of progression-free survival rates as a meaningful surrogate for outcome in newly diagnosed GBM. Further evaluation in future clinical trials is essential to confirm these observations.

Supplementary Material

Supplementary material is available at Neuro-Oncology online.

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