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A phase I/II trial of 5-fraction stereotactic radiosurgery with 5-mm margins with concurrent temozolomide in newly diagnosed glioblastoma: primary outcomes

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Abstract

Background. We sought to determine the maximum tolerated dose (MTD) of 5-fraction stereotactic radiosurgery (SRS) with 5-mm margins delivered with concurrent temozolomide in newly diagnosed glioblastoma (GBM).

Methods. We enrolled adult patients with newly diagnosed glioblastoma to 5 days of SRS in a 3 + 3 design on 4 escalating dose levels: 25, 30, 35, and 40 Gy. Dose limiting toxicity (DLT) was defined as Common Terminology Criteria for Adverse Events grades 3–5 acute or late CNS toxicity, including adverse radiation effect (ARE), the imaging correlate of radiation necrosis.

Results. From 2010 to 2015, thirty patients were enrolled. The median age was 66 years (range, 51–86 y). The median target volume was 60 cm^3 (range, 14.7–137.3 cm^3). DLT occurred in 2 patients: one for posttreatment cerebral edema and progressive disease at 3 weeks (grade 4, dose 40 Gy); another patient died 1.5 weeks following SRS from postoperative complications (grade 5, dose 40 Gy). Late grades 1–2 ARE occurred in 8 patients at a median of 7.6 months (range 3.2–12.6 mo). No grades 3–5 ARE occurred. With a median follow-up of 13.8 months (range 1.7–64.4 mo), the median survival times were: progression-free survival, 8.2 months (95% CI: 4.6–10.5); overall survival, 14.8 months (95% CI: 10.9–19.9); O^6-methylguanine-DNA methyltransferase hypermethylated, 19.9 months (95% CI: 10.5–33.5) versus 11.3 months (95% CI: 8.9–17.6) for no/unknown hypermethylation ($P = 0.03$), and 27.2 months (95% CI: 11.2–48.3) if late ARE occurred versus 11.7 months (95% CI: 8.9–17.6) for no ARE ($P = 0.08$).

Conclusions. The per-protocol MTD of 5-fraction SRS with 5-mm margins with concurrent temozolomide was 40 Gy in 5 fractions. ARE was limited to grades 1–2 and did not statistically impact survival.

Key Points

1. For newly diagnosed GBM, a 1-week course of chemoradiotherapy was well tolerated.
2. Radiotherapy dose was escalated per protocol to 40 Gy in 5 fractions.
3 Adverse radiation effect did not negatively impact overall survival.

Importance of the Study

In patients with newly diagnosed GBM, the authors performed a prospective dose escalation study to determine that the MTD of 5-fraction radiotherapy with concurrent temozolomide was 40 Gy in 5 fractions. Adverse radiation effect, the primary toxicity of a shortened treatment regimen, was limited to grades 1–2 and did not impact quality of life. Compared with the standard of care 6-week course of chemoradiotherapy, this 1-week treatment course allowed better patient access to specialized care. In the era of exploring the role of immunotherapy in GBM, hypofractionated radiotherapy (ie, larger doses per day in fewer fractions) should be investigated further, as it may both increase the immunostimulatory effect of radiotherapy through greater release of tumor antigens as well as decrease the immunosuppression seen through radiotherapy-induced lymphopenia.

With standard of care radiotherapy of 60 Gy in 30 fractions with concurrent and adjuvant temozolomide (TMZ)[1] with tumor treating fields,[2] overall survival (OS) for patients with newly diagnosed glioblastoma (GBM) is poor, with a median survival of up to 21 months and a 5-year survival of 13%.[2]

Given that a 6-week course of radiotherapy may represent up to 10% of some patients' remaining life, a shortened radiation fractionation schedule is desirable. Previous prospective trials in GBM that have shortened treatment times through hypofractionated irradiation (ie, fewer fractions of a larger dose per fraction) were of radiobiologically less dose and in patients with poor performance status or advanced age.[3–5] Alternatively, other prospective studies[6–9] explored hypofractionation as a means to increase the radiobiologic dose. A hypofractionated radiotherapy paradigm holds the potential of shortened treatment times, improved quality of life, better access to specialized care centers, and potentially improved tumor outcomes with increased cell kill and less tumor repopulation.[6,10] Furthermore, in the era of immunotherapy, shortened radiotherapy courses may both increase the immunostimulatory effect of treatment while decreasing the immunosuppression seen with prolonged irradiation courses.

With this background, in 2010, we initiated a phase I/II trial investigating shortening of the radiotherapy course to determine the maximum tolerated dose (MTD) of 5-fraction radiotherapy with 5-mm margins delivered with concurrent and adjuvant TMZ in adult patients with newly diagnosed supratentorial GBM.

Materials and Methods

Patient Population

Patients older than 18 years with newly diagnosed, pathologically confirmed, supratentorial GBM were candidates for this institutional review board–approved prospective trial (clinicaltrials.gov: NCT01120639). Eligibility criteria included an expected survival of more than 12 weeks, adequate organ function to receive TMZ, ability to give informed consent, and a maximum final planning target volume (PTV) of 150 cm^3. Patients were excluded if they had previous cranial irradiation, infratentorial tumor extension, or multifocal or leptomeningeal disease or were pregnant or unable to have MRI or CT scans or give informed consent.

Radiation and Chemotherapy Treatment

Following surgery, enrolled patients underwent treatment planning for hypofractionated stereotactic radiosurgery (SRS) with the CyberKnife (Accuray) as previously described.[11] As defined by the postsurgical MRI performed within 2 weeks of SRS, the gross tumor volume (GTV) consisted of the tumor resection cavity, residual enhancing tumor, and nodular non-enhancing tumor. The clinical target volume (CTV) was defined by adding a 5-mm margin to the GTV, not extending beyond anatomic borders of tumor spread such as the calvarium, falx, and tentorium. No attempt was made to specifically include peritumoral edema. The final PTV was the same as the CTV, with 0-mm margin (see Fig. 1).

The 5-fraction SRS dose was escalated in a standard 3 + 3 design at 4 dose levels: 25 Gy, 30 Gy, 35 Gy, and 40 Gy. A 45 Gy level was initially planned, but was omitted prior to accrual of patients at that dose due to reports of high toxicity at similar biologically effective doses.[9] Patients enrolled onto 2 treatment arms based on the final size of the PTV: arm 1 with PTV 0.1 to < 60 cm^3 (roughly equivalent to a 5 cm sphere) and arm 2 with PTV 60 to 150 cm^3 (equivalent to a 6.6 cm sphere).

The prescription isodose line covered at least 95% of the PTV; undercoverage to 90% was allowed near organs at risk. Normal organ dose constraints were 98% of the optic pathways received less than 27.5 Gy and brainstem maximum dose of 30 Gy in 5 fractions, undercovering the PTV to meet these limits.

Patients received SRS in 5 consecutive days over 7 elapsed days, with extension over a weekend allowed. Daily concomitant TMZ at a dose of 75 mg/m^2 started the day prior to the first SRS treatment; therefore 8 total days were prescribed. Although not protocol defined, patients received standard adjuvant TMZ at 150–200 mg/m^2 daily, 5 days every 28 days for at least 6 months.

Patient Assessment and Toxicity Reporting

Following chemoradiotherapy, follow-up occurred 1 month later, then every 2 months, including physical exam and MRI.

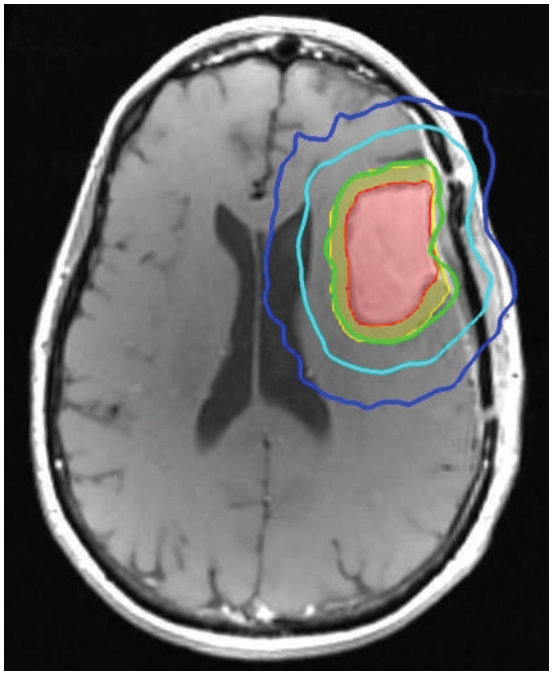

Fig. 1 A representative 5-fraction, 5-mm margin radiotherapy treatment plan. The left frontal resection cavity (red contour) with a 5-mm margin (yellow contour) form the final planning target volume (PTV) which was covered by the 35 Gy prescription isodose line (green). Shown are the 50% dose (cyan) and 25% dose (blue) isodose lines.

A dose limiting toxicity (DLT) was defined as a treatment-related (with possible, probable, or definite attribution) Common Terminology Criteria for Adverse Events (CTCAE) v3 grades 3–5 CNS toxicity occurring within 30 days of SRS, with lifelong assessment for late (defined as after 30 days) SRS-related adverse radiation effect (ARE), the imaging correlate of radiation necrosis. The MTD was the highest dose where 0–1 out of 6 patients at that dose level per arm had an acute or late CNS grades 3–5 toxicity.

Given the difficulty in interpreting posttreatment imaging in patients with GBM, new contrast enhancement or enlargement was scored as: (i) progressive disease, if ultimately determined to be recurrent tumor, (ii) pseudoprogression, if ARE appeared within 5 months and ultimately resolved, or (iii) ARE. As the final determination of ARE or progressive disease occurring after the initial appearance of increased enhancement, the time to event of ARE or progressive disease was backdated to the day of the first scan showing imaging changes. The highest symptom grade of ARE was scored per CTCAE, including asymptomatic imaging changes (ie, grade 1 ARE). An elective hospital admission for surgical resection to determine recurrent tumor versus radiation necrosis did not, of itself, constitute a grade 3 event; toxicity was scored per clinical symptoms prior to resection.

Statistical Methods

The primary endpoint of this phase I/II study was to determine the MTD and DLT for 5-fraction SRS concurrent with TMZ using a 3 + 3 study design. Secondary endpoints included short- and long-term adverse effects, OS, and quality of life (previously reported[12]). Progression-free survival (PFS) was defined as the date of diagnosis to time of disease progression or death, censored at the time of last clinical follow-up or imaging. OS was measured from the date of diagnosis until death, censored at the time of last clinical follow-up or imaging.

OS and PFS were estimated with Kaplan–Meier methodology. Categorical predictors such as status of O^6-methylguanine-DNA methyltransferase (MGMT) were tested with the log-rank test. For continuous predictors such as age and PTV, the OS and PFS outcomes were analyzed in a Cox proportional hazards model. The time to ARE was analyzed using competing risk methods with death as competing risk; categorical predictors were tested using Gray's, test and continuous predictors were tested in a Cox proportional hazards model with death as a competing risk. The correlation between toxicity outcomes and continuous predictors such as dose and PTV was analyzed using logistic regression models; the association between toxicity outcomes and categorical predictors such as MGMT status was analyzed using Fisher's exact test. All tests were two-sided with an alpha level of 0.05; and all analyses were performed using SAS v9.4.

Patient Characteristics

We enrolled 30 patients from August 2010 to October 2015 (see Appendix 1, a Consolidated Standards of Reporting Trials [CONSORT] figure). The median age was 66 years (range, 51–86 y) with a median KPS of 80 (range, 50–100) (see Table 1). Gross total resection, defined by residual contrast enhancement on an MRI within 48 hours after surgery, was achieved in 12 patients (40%). Thirteen patients (43%) had MGMT promoter hypermethylation, 15 (50%) had no hypermethylation, and 2 were unknown.

Treatment Characteristics

The median time from surgery to SRS was 4.1 weeks (range, 1.8–19.7 wk). The median GTV was 27 cm^3 (range, 4–81 cm^3) with a median PTV of 60 cm^3 (range, 14.7–137.3 cm^3). Twenty-seven (90%) patients were treated with adjuvant TMZ for a median of 7 cycles (range, 2–16 cycles).

Results

Toxicity

Protocol-defined treatment-related DLTs occurred in 2 patients (Table 2): one patient was admitted 3 weeks following SRS (grade 4, arm 2, dose 40 Gy. Attribution: definite—tumor progression, possible—SRS treatment); another

patient died 2 weeks after SRS (grade 5, arm 1, dose 40 Gy. Attribution: definite—postsurgical hemorrhage, possible—SRS treatment). As these represented 1 of 6 patients on those 2 treatment arms of 40 Gy, the protocol-defined MTD was 40 Gy. All toxicities are shown in Appendix 2.

Table 1 Patient and treatment characteristics

Characteristics	Number (Range or Percentage)
Patient Characteristics	
Total patients enrolled	30
Age, y, median	66 (51–86)
Karnofsky performance status (KPS), median	80 (50–100)
Male	15 (50%)
Gross total resection	12 (40%)
Subtotal resection	15 (50%)
Biopsy only	3 (10%)
MGMT Promoter Status	
Hypermethylated	13 (43%)
Unmethylated	15 (50%)
Unknown	2 (7%)
SRS Treatment Characteristics	
Time, median weeks, from surgery to SRS	4.1 (1.8–19.7)
Gross tumor volume (GTV) (median cm^3)	27 (4–81)
Planning target volume (PTV) (median cm^3)	60 (15–137)
Prescription isodose line (median %)	82 (77–86)
Conformity index, median	1.1 (1.0–1.5)
Adjuvant TMZ Given (%)	90%
Number of Adjuvant TMZ Cycles (median)	7 (2–16)

Pseudoprogression occurred in 5 patients (17%) at a median time of 2.8 months (range, 0.8–3.4 mo) following SRS. Pseudoprogression occurred in 38% of the 13 patients with MGMT promoter hypermethylation compared with 0% with no/unknown hypermethylation ($P = 0.009$). Eight patients (27%) developed ARE (grade 1, $n = 2$; grade 2, $n = 6$) at a median time of 7.6 months (range, 3.2–12.6 mo). No patient had grades 3–5 ARE. ARE was not associated with radiotherapy dose (odds ratio = 1.02, $P = 0.83$) or PTV volume (odds ratio = 0.98, $P = 0.17$). MGMT hypermethylation status was associated with a higher incidence of ARE (46.2% vs 11.8%, $P = 0.049$). Pathology on 5 patients who had resection of imaging changes revealed progressive disease in 4 and radiation necrosis in 1. Ultimately, 26 (86%) patients were treated with bevacizumab, started in 5 (17% of all 30 patients) for symptomatic pseudoprogression, 3 (10%) for ARE, and 18 (60%) for progressive tumor.

Patient Outcomes

With a median clinical follow-up of 13.8 months (range, 1.7–64.4 mo), 29 (97%) patients have documented progression and 26 (87%) have died. The median OS (Fig. 2) for all patients was 14.8 months (95% CI: 10.9–19.9 mo), with a median PFS of 8.2 months (95% CI: 4.6–10.5 mo). The median OS was 19.9 months (95% CI: 10.5–33.5 mo) for patients with MGMT hypermethylation compared with 11.3 months (95% CI: 8.9 – 17.6 mo) for no/unknown hypermethylation ($P = 0.031$) (Fig. 2).

Patients who developed ARE had improved OS, with a median of 27.2 months (95% CI: 11.2–48.3 mo) compared with a median survival of 11.7 months (95% CI: 8.9–17.6 mo) among those who did not develop ARE, although this difference was not statistically significant ($P = 0.08$) (Fig. 3). A patient with grade 2 ARE whose surgical pathology revealed radiation necrosis is the long-term survivor on this trial, currently alive at 64 months. ARE occurred in 46.2% of MGMT hypermethylated patients versus 11.8% if no/unknown hypermethylation ($P = 0.049$). To analyze if ARE can overcome the prognostic effect of MGMT status, the

Table 2 Acute (within 30 days of SRS) and late (after 30 days) treatment-related CNS toxicity

		Toxicity and CTCAE Grade (number)			
Treatment Arm		Dose 25 Gy	Dose 30 Gy	Dose 35 Gy	Dose 40 Gy
Arm 1: <60 cm^3	Number enrolled	$n = 3$	$n = 3$	$n = 3$	$n = 6$
	Acute grades 3–5 toxicity	0	0	0	G5 = 1 [a]
	Late adverse radiation effect (grade)	G1 = 1	0	G1 = 1 G2 = 2*	G2 = 1
Arm 2: 60–150 cm^3	Number enrolled	$n = 3$	$n = 3$	$n = 3$	$n = 6$
	Grades 3–5 acute toxicity	0	0	0	G4 = 1 [a]
	Late adverse radiation effect (grade)	0	G2 = 1	G2 = 1	G2 = 1
Grades 3–5 treatment-related CNS toxicity per dose level (a DLT)		0%	0%	0%	17%
Grades 1–5 treatment-related CNS toxicity per dose level		17%	17%	67%	33%

*One patient with G2 toxicity (arm 1, 35 Gy dose level) had surgery for histologic diagnosis of radiation necrosis.
[a]See description in text about the 2 DLTs on the 40 Gy arms.
Abbreviation: G = grade.

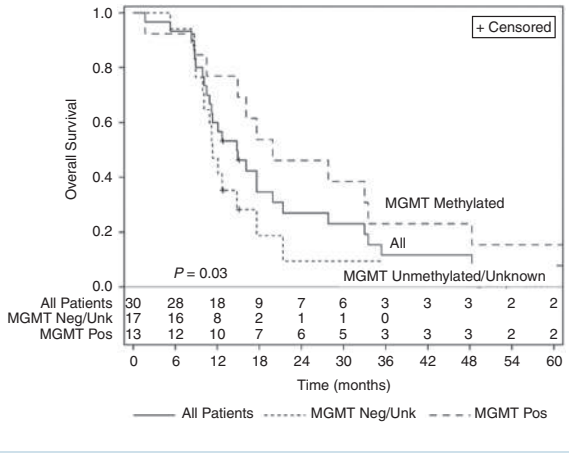

Fig. 2 The median OS for all patients (solid line) was 14.8 months (95% CI: 10.9–19.9). The median OS for tumors with MGMT promoter hypermethylation (dashed line) was 19.9 months (95% CI: 10.5–33.5) versus 11.3 months (95% CI: 8.9 – 17.6) for no/unknown MGMT hypermethylation (dotted line) ($P = 0.03$).

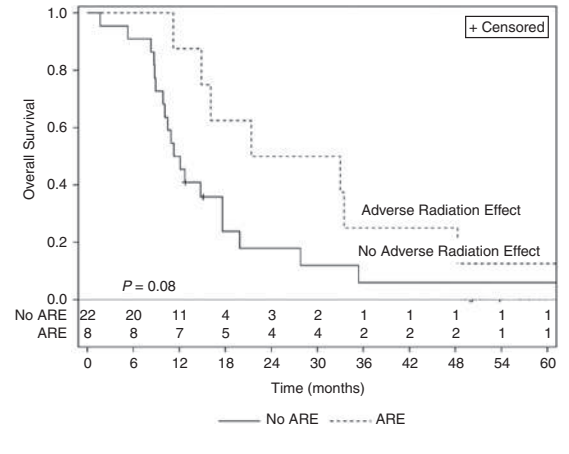

Fig. 3 Median OS for patients that developed ARE, the imaging correlate of radiation necrosis ($n = 8$, dashed line), was 27.2 months (95% CI: 11.2–48.3 mo) compared with 11.7 months (95% CI: 8.9–17.6 mo) in those without ARE ($n = 22$, solid line) ($P = 0.08$).

median OS for patients was 33.3 months for MGMT+/ARE + versus 17.6 months MGMT+/ARE– ($P = 0.31$), and 16.3 months MGMT–/ARE+, 11.3 months MGMT–/ARE– ($P = 0.65$).

Patients with gross total tumor resection had a median OS of 27.2 months (95% CI: 9.9–48.3 mo) compared with 12.7 months (95% CI: 8.9–17.6 mo) for subtotal resection and 8.8 months (95% CI: 5.3–14.9 mo) for biopsy only ($P = 0.02$). Other factors were not correlated with OS: age, $P = 0.16$; dose, $P = 0.39$; KPS, $P = 0.07$; and pseudoprogression, $P = 0.39$.

Considering patient access to specialized care, of note, the 30 patients enrolled on this 1-week treatment protocol lived farther away from our comprehensive cancer center compared with a contemporaneous cohort of 50 patients treated during the same time period with standard 6 weeks of radiotherapy (mean of 150 vs 44 miles [$P = 0.047$]), with 68% vs 38% living greater than 30 miles away).

Discussion

Despite improvement in survival seen in recent prospective trials,[1,2] patients with GBM treated with standard of care chemoradiotherapy over 6 weeks have a poor prognosis, and "innovative treatments for glioblastoma are needed."[2] Hypofractionated radiotherapy (ie, larger doses of irradiation per day over a shorter treatment course) has many potential advantages: (i) the patient burden of commuting for daily treatment is lessened, (ii) a shorter treatment course may allow better access to specialized centers of care, (iii) a greater radiobiologic dose may improve outcomes, (iv) a shortened treatment course has less societal cost than the current standard of care, (v) with larger doses per day, a different radiobiology may exist,[13] (vi) when combined with immunotherapy, hypofractionation may provide a greater immunostimulatory effect,[14] and (vii) a shortened course may minimize lymphopenia and the immunosuppressive effect of prolonged treatment courses.[15] Therefore, we sought to determine the MTD of hypofractionated radiotherapy in 1 week, with concurrent and adjuvant TMZ. We found that the per protocol MTD for patients with a final target volume of up to 150 cm^3 (defined as the tumor plus a 5-mm margin) was 40 Gy in 5 fractions. Given that the only 2 DLTs occurred at the 40 Gy dose, one may conservatively consider 35 Gy in 5 fractions for future trials.

For newly diagnosed GBM in patients of advanced age or poor performance status, randomized data support hypofractionated radiotherapy courses of less than 6 weeks with a smaller radiobiologic dose. Trials of radiotherapy alone in selected patients found that 40 Gy in 15 fractions had equivalent OS to 60 Gy in 30 fractions[3] and that 25 Gy in 5 fractions was non-inferior to 40 Gy in 15 fractions.[4] Furthermore, conventional 6 weeks of treatment was associated with worse survival compared with a hypofractionated regimen of 34 Gy in 10 fractions.[16] The addition of standard concurrent and adjuvant TMZ with 40 Gy in 15 fractions, compared with the same radiotherapy alone, improved OS without unexpected toxicity.[17] Thus, dose-reduced, concurrent hypofractionated chemoradiotherapy is a standard of care in those with poor performance status or advanced age.

As an alternative to conventional fractionation, prospective, single arm trials have explored hypofractionated radiotherapy to escalate the equivalent dose to greater than 60 Gy over 6 weeks for younger patients with good performance status.[7–9,18–23] A series of 3 trials from the University of Colorado established the safety of 60 Gy in 10 fractions with concomitant and adjuvant TMZ and bevacizumab.[24] However, the final trial[9] was closed early due to a 50% incidence of radiation necrosis, attributed potentially to larger

treatment volumes (median PTV of 127 cc). Compared with our trial, this trial had a larger target margin of 10 mm and greater equivalent dose.[25,26] With a 5-mm margin and a median PTV volume of 60 cc, we observed 8 cases (27%) of grades 1–2 radiation necrosis. Ultimately, 87% of patients received bevacizumab, but only 12% for radiation necrosis. We did not find an association between radiation necrosis and tumor size or dose level.

Adverse radiation effect represents a spectrum, ranging from asymptomatic imaging findings to severe symptoms requiring hospitalization and surgical resection. We found that patients who developed ARE had a non-statistically ($P = 0.08$) improved median survival of 27 versus 12 months, similar to other hypofractionated[7,27] or conventionally fractionated studies.[28] Notably, we previously reported that ARE was not associated with a decline in patient-reported quality of life on this protocol.[12]

As highlighted by Hingorani et al, hypofractionated radiotherapy may hold the "hope for the future"[10] from a radiobiologic perspective. A larger dose per fraction may overcome the histology-specific radioresistance seen with the smaller daily doses of conventionally fractionated radiotherapy.[29] The putative GBM cancer stem cells are considered similarly radioresistant.[30,31] Preclinical data suggest that hypofractionated doses better overcome glioma cell repopulation compared with conventional fractionation.[13] The prospective trial by Omuro et al suggested that a hypofractionated course of 36 Gy in 6 fractions over 2 weeks with concurrent TMZ and bevacizumab may overcome the negative prognostic impact of MGMT methylation status, with a median survival of 18 months for methylated and 22 months for unmethylated patients ($P = 0.56$).[21] Unfortunately, our trial did not corroborate these results: MGMT remained prognostic, with a median survival of 11.3 months for no/unknown hypermethylation versus 19.9 months for hypermethylated MGMT ($P = 0.03$).

In the era of trials exploring the role of immunotherapy in GBM, hypofractionated radiotherapy may be advantageous to conventionally fractionated regimens. Larger daily radiotherapy doses may release more tumor antigens, be more immunostimulatory than conventional radiotherapy, and more effectively prime the immune system.[14,32,33] Additionally, prolonged radiotherapy courses may be counterproductive to immunotherapy, given its known immunosuppressive effects such as in preparatory regimens for stem-cell transplants. Prospective data of conventional chemoradiotherapy for GBM found that lymphopenia appears associated with worse survival, primarily attributed to early tumor progression rather than infection.[34] Furthermore, studies calculating the flow dynamics of the peripheral blood through the brain during a typical irradiation course suggest that the entire circulating blood lymphocyte compartment is irradiated in a 6-week radiotherapy course.[15] In other solid tumors, hypofractionation over a shorter course appears to decrease the rate of lymphopenia.[35] A preliminary analysis suggests less lymphopenia in our 1-week trial compared with a conventional 6-week course of chemoradiotherapy.[36]

We acknowledge the limitations of our small study population, the 3 + 3 trial design, and the heterogeneity of patients when accounting for all prognostic factors such as extent of resection, MGMT status, age, and tumor size. Given these small numbers, any reported subgroup analyses are considered strictly exploratory, to be refuted or confirmed in larger trials. Additionally, given that patients on this trial had irradiation targeting only the resection bed and gross tumor with a 5-mm margin, with no edema purposely targeted, formal patterns of failure analyses are ongoing to determine if tumor recurred outside of 5 mm but within the 20 mm of a conventional radiotherapy field.

In conclusion, the protocol defined that MTD for hypofractionated radiotherapy over 5 consecutive days with 5-mm margins in targets up to 150 cm^3 with concurrent TMZ was 40 Gy in 5 fractions. However, given the grade 5 toxicity at 40 Gy, although felt to be independent from treatment, one may consider a lower dose level of 35 Gy in 5 fractions as the regimen for future trials, particularly if combined with agents that may potentiate radiation toxicity, such as tumor treating fields or immunotherapy. Although 27% of patients developed ARE, all were grades 1–2 and did not impact quality of life,[12] with a statistically insignificant improved OS. Thus, rather than representing the primary toxicity of hypofractionated radiotherapy, ARE in the bevacizumab era, especially if not symptomatic, may be clinically desirable. Lastly, a shortened treatment protocol may be beneficial as our field explores the role of immunotherapy for GBM and may improve patient outcomes through better access to comprehensive cancer centers.[37]

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

glioblastoma | radiosurgery | newly diagnosed | hypofractionated | prospective

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Authorship statement. Study design: SGS, CYHC, JRA. Acquisition of data: all authors. Statistical analysis: RvE Interpretation of the data: MA, SGS, CYHC. Drafting of the initial manuscript: MA, RvE, SGS, CYHC. Review and revision of the manuscript: all authors. Approval of the final manuscript: all authors. This study was presented, in part, at the American Society for Radiation Oncology annual meeting 2016 and International Stereotactic Radiosurgery Society congress in 2017.

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