International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Phase 2 Study of a Temozolomide-Based Chemoradiation Therapy Regimen for High-Risk, Low-Grade Gliomas: Long-Term Results of Radiation Therapy Oncology Group 0424

Barbara J. Fisher, MD,[*] Stephanie L. Pugh, PhD,[†] David R. Macdonald, MD,[*] Arnab Chakravatri, MD,[‡] Glenn J. Lesser, MD,[§] Sherry Fox, PhD, RN, CNRN,[‖] C. Leland Rogers, MD,[¶] Maria Werner-Wasik, MD,[#] Thomas Doyle, MD,[**] Jean-Paul Bahary, MD,[††] John B. Fiveash, MD,[‡‡] Joseph A. Bovi, MD,[§§] Steven P. Howard, MD,[‖‖] Hsiang-Hsuan Michael Yu, MD, ScM,[¶¶] David D'Souza, MD,[*] Nadia N. Laack, MD,[##] Igor J. Barani, MD,[***] Young Kwok, MD,[†††] Daniel R. Wahl, MD, PhD,[‡‡‡] Jon F. Strasser, MD,[§§§] Minhee Won, MA,[†] and Minesh P. Mehta, MD[‖‖‖]

***London Regional Cancer Program, London, Ontario, Canada; †NRG Oncology Statistics and Data Management Center, Philadelphia, Pennsylvania; ‡Ohio State University Comprehensive Cancer Center, Columbus, Ohio; §Comprehensive Cancer Center of Wake Forest University, Winston-Salem, North Carolina; ‖Cullather Brain Tumor Quality of Life Center, Richmond, Virginia; ¶Arizona Oncology Services Foundation, Scottsdale, Arizona; #Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; **Henry Ford Hospital, Detriot, Michigan; ††Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada; ‡‡University of Alabama at Birmingham Medical Center, Birmingham, Alabama; §§Froedtert and the Medical College of Wisconsin, Milwaukee,**

Corresponding author: Barbara J. Fisher, MD; E-mail: barbara.fisher@lhsc.on.ca

Presented in part at the Society for Neuro-oncology Annual Meeting 2018.

Igor J. Barani is currently at Barrow Neurological Institute, Phoenix, Arizona.

This project was supported by grants U10CA180868 (NRG Oncology Operations) and U10CA180822 (NRG Oncology Statistical and Data Management Center), and grant U24CA196067 (NRG Biospecimen Bank).

Disclosures: J.A.B. discloses consulting fees from Elekta, outside the submitted work. J.B.F. discloses research and education contracts with Varian Medical Systems, outside the submitted work. G.J.L. discloses the role of data and safety monitoring board chair with Stemline Therapeutics, consulting roles with BTG and Monteris, and being a clinical trial site for Incyte, NewLink Genetics, Vascular Biogenics, and Novartis, outside the submitted work. D.R.M. discloses nonfinancial clinical trial support to his cancer center for the Tg-511-15-01 study from Tocagen, Inc, and nonfinancial clinical trial support to his cancer center for the Radiation Therapy Oncology Group 3508/AbbVie M13-18 (Intellance 1) study from AbbVie, Inc, outside the submitted work. M.P.M. discloses consultant roles with Insys, Remedy, IBA, Varian, Celgene, AbbVie, AstraZeneca, Tocagen, and Blue Earth and serves on the board of directors of Oncoceutics, with stock options, outside the submitted work. S.L.P. discloses salary support paid to her institution from Pfizer-Astellas and Millenium, and grant salary support paid to her institution from the Patient-Centered Outcomes Research Institute and a PA CURE grant. J.F.S. discloses personal speaker's bureau fees from AstraZeneca, Bristol Myers Squibb, and Genomic Health, outside the submitted work. D.R.W. discloses grants from Agioes, Inc, and Innocrin, Inc, outside the submitted work. In addition, D.R.W. has a patent for a transcription-based algorithm to predict therapy response in glioblastoma pending.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Acknowledgments—We gratefully acknowledge the contributions of Stephen W. Coons, MD, and the late Christina A. Meyers, PhD, ABPP, to this project.

Int J Radiation Oncol Biol Phys, Vol. 107, No. 4, pp. 720–725, 2020
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2020.03.027

*Wisconsin; [|||]University of Wisconsin Hospital, Madison, Wisconsin; [¶¶]H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [##]Mayo Clinic, Rochester, Minnesota; ***UCSF Medical Center — Mount Zion, San Francisco, California; [†††]University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, Maryland; [‡‡‡]University of Michigan Medical Center, Ann Arbor, Michigan; [§§§]Christiana Care Health Services, Inc, Wilmington, Delaware; and [||||||]Miami Cancer Institute, Kendall, Florida*

Received Dec 20, 2019. Accepted for publication Mar 17, 2020.

Purpose: To report the long-term outcomes of the RTOG 0424 study of a high-risk, low-grade glioma population treated with concurrent and adjuvant temozolomide (TMZ) and radiation therapy (RT).

Methods and Materials: For this single-arm, phase 2 study, patients with low-grade gliomas with ≥3 risk factors (age ≥40 years, astrocytoma, bihemispheric tumor, size ≥6 cm, or preoperative neurologic function status >1) received RT (54 Gy in 30 fractions) with TMZ and up to 12 cycles of post-RT TMZ. The initial primary endpoint *P* was overall survival (OS) at 3 years after registration. Secondary endpoints included progression-free survival (PFS) and the association of survival outcomes with methylation status. The initial 3-year report of this study was published in 2015.

Results: The study accrued 136 patients, of whom 129 were analyzable. The median follow-up for surviving patients was 9.0 years. The 3-year OS was 73.5% (95% confidence interval, 65.8%-81.1%), numerically superior to the 3-year OS historical control of 54% ($P < .001$). The median survival time was 8.2 years (95% confidence interval, 5.6-9.1). Five- and 10-year OS rates were 60.9% and 34.6%, respectively, and 5- and 10-year PFS rates were 46.8% and 25.5%, respectively.

Conclusions: The long-term results confirmed the findings from the initial report for efficacy, suggesting OS and PFS outcomes with the RT-TMZ regimen exceeded historical control groups treated with radiation alone. Toxicity was acceptable.

Introduction

Until the long-term results of RTOG 9802[1] became available, the role of chemotherapy (CT) in patients with low-grade gliomas (LGGs) was not clearly established. The RTOG 9802[1] phase 3 trial[1] for newly diagnosed subtotally resected LGGs or gross-totally resected patients aged >40 years randomized patients to radiation therapy (RT) versus RT plus adjuvant procarbazine, CCNU, and vincristine (PCV). With a median follow-up time approaching 12 years reported, an overall survival (OS) benefit for the PCV + RT arm over the RT-alone arm was observed. Median survival times (MSTs) were 13.3 years for PCV and radiation versus 7.8 years for radiation alone.

The analysis by Pignatti et al[2] of the European Organization for Research and Treatment of Cancer (EORTC) 22844[3] trial identified 5 prognostic factors (age ≥40 years, largest preoperative tumor diameter ≥6 cm, tumor crossing the corpus callosum, astrocytoma histology, and preoperative neurologic function deficits) on a multivariable analysis at the 1% significance level. Patients with ≤2 of these 5 factors had an MST of 7.7 years (95% confidence interval [CI], 6.6-9.3), whereas patients with ≥3 risk factors (high risk) had a significantly shorter MST of 3.2 to 3.6 years (95% CI, 3.0-4.0). The prognostic index from Pignatti et al[2] was independently confirmed by applying it to a set of patients with LGGs from the EORTC 22845[4,5] trial and using data from the Surveillance Epidemiology and End Results database.[6] Their work provided a historical control group of patients with LGG treated with surgery and radiation alone for comparison to the results of RTOG 0424.

The original RTOG 0424 concept was designed and submitted as a randomized comparison of RT versus RT plus temozolomide (TMZ), but because this concept was not approved by the National Cancer Institute, an alternative design using a nonrandomized historical cohort from the Pignatti et al[2] EORTC data set treated with surgery and radiation alone for comparison was prespecified, and a priori statistical analyses were used to determine a "positive signal."

This article describes the long-term results of a group of patients with high-risk LGG with ≥3 risk factors as defined by Pignatti et al[2] treated with RT and concurrent and adjuvant TMZ. This trial will likely be the only trial to provide prespecified, prospective, albeit indirect, comparative long-term survival results to evaluate the contribution of concurrent and adjuvant TMZ over and above RT alone in this patient population.

As indicated, the trial was originally proposed as a randomized, phase 2 trial but was approved by the National Cancer Institute to move forward as a single-arm, phase 2 trial, with the expectation that the results could serve as the basis for a future phase 3 trial. Prior to the results becoming available, the Eastern Clinical Oncology Group initiated a randomized comparison of RT versus RT and concurrent/adjuvant TMZ in LGG, but this trial was suspended without meeting accrual objectives because of the publication of the RTOG 9802[1] trial, which rendered an RT-alone arm futile in this disease. By the time the RTOG

9802[1] trial results became available, RTOG 0424 had completed accrual.

Methods and Materials

Investigators initiated this trial after approval by local institutional review boards. Informed consent was obtained from each participant. Eligibility was confirmed by central pathology review. With respect to other neoplasms, patients were required to have been cancer free for 5 years without prior CT or RT, to have been enrolled into the study within 12 weeks of craniotomy, and to have a pretreatment Zubrod score of 0 to 2 with adequate marrow, liver, and renal function and 3 to 5 of the following factors: age $\geq$40 years, preoperative tumor diameter $\geq$6 cm, bihemispheric tumor, astrocytoma histology, and/or preoperative neurologic function status $>$1 (ie, moderate to severe impairment).

Consenting patients were assigned to conformal RT of 54 Gy in 30 fractions plus concurrent and adjuvant TMZ. The RT target volume was based on the postoperative magnetic resonance imaging (MRI) T2/FLAIR image sequences, identifying the residual tumor and/or surgical cavity as the gross tumor volume, adding a 1.5-cm margin corrected for anatomic restrictions to define the clinical target volume, and adding 5 mm for the planning target volume. The dose of concurrent oral TMZ was 75 mg/m^2/d during radiation therapy, and up to 12 cycles of post-radiation TMZ were delivered at 150 to 200 mg/m^2/d on Days 1 to 5, repeated every 28 days with pneumocystis carinii prophylaxis. Dose modifications were permitted based on blood counts. TMZ was stopped at disease progression, for unacceptable toxicity, or upon patient refusal.

Patients were evaluated monthly after radiation during adjuvant TMZ, at 4 months post-TMZ, and every 6 months thereafter. An MRI of the brain was repeated 4 weeks post-radiation after completion of radiation therapy, every 3 months during CT, every 6 months for 2 years, and annually thereafter. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events version 3.0.[7]

This trial was designed as a single-arm, phase 2 study to determine whether the regimen under investigation improved survival compared with the EORTC high-risk LGG population (Pignatti et al[2] historical control), using prespecified statistical thresholds for survival improvement. Secondary endpoints were progression-free survival (PFS) and toxicity. Neurocognitive and quality-of-life testing was performed but will be reported separately.

OS was defined as the time from registration until death, regardless of cause. PFS is defined as the time from registration until progressive disease or death from any cause, where progressive disease is defined as a 25% or greater increase in the cross-sectional area of enhancing or nonenhancing tumor on consecutive MRI scans, or any new area(s) of tumor. Both OS and PFS were analyzed as time-to-event data, and patients who did not experience the event of interest were analyzed as censored observations at the time of last follow-up.

The Kaplan–Meier product limit method[8] was used to estimate OS and PFS rates. A 1-sided Z-test was used to test the significance in OS between the logarithm of the estimated hazard rate (λ_{EST}) and the hypothesized hazard rate ($\lambda_{HYP} = .0171$, 3-year survival 54%), with a variance equal to the reciprocal of the number of deaths observed within 3 years. The null hypothesis would be rejected at a significance level of 0.1 when the test statistic Z had a value of less than -1.28. The log-rank test[9] was used to compare OS between different patient characteristics, and the associated hazard ratio (HR) was estimated by Cox proportional hazard model.[10] Cox models incorporating stepwise selection were used to adjust for sex, age, histology, surgery, neurologic function, Zubrod score, O^6-methylguanine–DNA methyltransferase (MGMT) DNA-repair gene status, and tumor crossing the midline. As in the primary paper, because most patients had resection and the largest preoperative tumor diameter was $\geq$5 cm, the extent of resection (biopsy vs resection) and tumor size ($<$5 vs $\geq$5 cm) were not included as covariates.

The Pignatti et al[2] data have been criticized as being inadequate owing to several limitations in terms of information available on tumor characteristics. Therefore, for the purpose of survival reporting in this updated report, a reclassification based on the pooled intergroup LGG analyses is provided. The EORTC, together with RTOG and the National Cancer Clinical Trials Group (NCCTG), reanalyzed outcomes in patients with LGG treated on several clinical trials, resulting in a definitive publication of the pooled analysis by Gorlia et al in 2013.[11] Data from RTOG 0424 were entered into the online EORTC LGG survival calculator based on the aforementioned 2013 Gorlia Intergroup LGG pooled, updated, and reanalyzed database (http://www.eortc.be/tools/lggcalculator/calculator.aspx). To enter the data into the EORTC survival calculator, tumor size had to be reclassified as $<$5 cm versus $\geq$5 cm, and 5 histopathologic categories had to be reassigned into 2 categories: astrocytoma versus oligodendroglioma/oligoastrocytoma.

Results

This study opened on January 26, 2005, and closed on August 11, 2009, after reaching its accrual target. The study was amended in February 2006 to include MGMT determination and neurocognitive testing, and the sample size increased to 135 patients. This analysis includes all data received through October 2017. Seven patients were excluded owing to ineligibility, leaving a total of 129 eligible patients for this analysis. The median follow-up time for all patients was 6.8 years and 9.0 years for all living patients, 4 years longer than previously reported. Out of the 129 eligible patients in this study, 75 (58.1%) had

centrally tested MGMT status available from the DNA methylation analysis. Fifty-seven of these 75 patients (76.0%) had methylated MGMT status, and 18 (24.0%) were MGMT unmethylated.

The distribution of high-risk factors was 69%, 24.8%, and 6.2% for 3, 4, or 5 risk factors, respectively, which is similar to the Pignatti et al[2] study (70%, 29%, and 1%). There was no difference in long-term survival for patients based upon the numbers of risk factors.

The MST was 8.2 years (95% CI, 5.6-9.1). The 3-year OS rate was 73.5% (95% CI, 65.8%-81.1%), superior to the historical control[2] 3-year OS of 54% ($P < .001$). Five- and 10-year OS rates were 60.9% (95% CI, 52.4-69.4) and 34.6% (95% CI, 25.1-44.1), respectively (Fig. 1); 5- and 10-year PFS rates were 46.8% (95% CI, 38.2-55.5) and 25.5% (95% CI, 17.0-34.0), respectively (Fig. 2). The 3-year PFS was 59.2% (95% CI, 50.7-67.8%), and median PFS was 4.5 years (95% CI, 3.5-n.a). Investigator-reported cause of death among a total of 76 deaths to date was as follows: 53 patients (69.7%) of brain tumor, 1 patient of complications of protocol treatment, and the remaining 22 patients for other, unknown, or missing reasons. OS and PFS data are summarized in Table 1 and Figure 3 (OS only) based on the intergroup EORTC/NCCTG/RTOG risk-stratified online calculator.

MGMT methylation and sex (in favor of females) were the only variables to remain statistically significant after stepwise selection for OS (HR = 3.06; 95% CI, 1.64-5.75; $P < .001$ and HR = 0.53; 95% CI, 0.28-0.98; $P = .44$, respectively) and PFS (HR = 2.41; 95% CI, 1.32-4.40; $P = .015$ and HR = 0.50; 95% CI, 0.28-0.87; $P = .004$, respectively). OS and PFS data are summarized in Table 1 and Figure 3 (OS only) based on the intergroup EORTC/NCCTG/RTOG risk-stratified online calculator.[11]

There were 57 patients (44.2%) with a reported grade 3 AE; 13 patients (10.1%) with a grade 4 AE; and 1 patient (0.8%) with a reported grade 5 infection (herpes encephalitis), possibly related to TMZ or steroids. There were no grade 5 hematological or neurologic toxicities. One patient

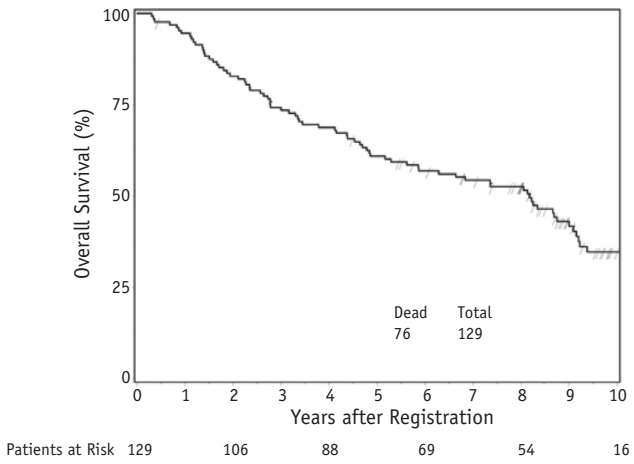

Fig. 1. Overall survival of RTOG 0424 patients.

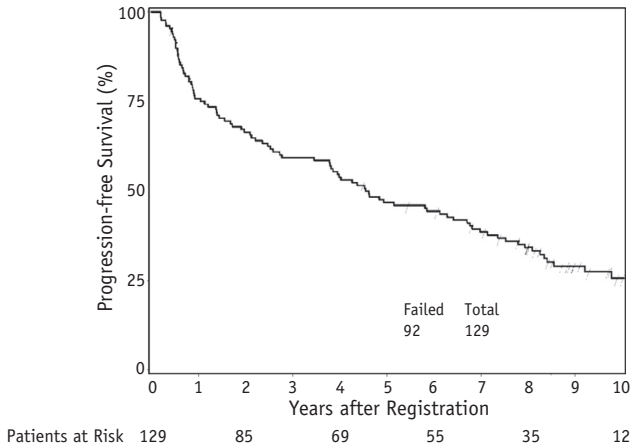

Fig. 2. Progression-free survival of RTOG 0424 patients.

experienced an episode of cerebral ischemia related to a clotting disorder but recovered. There has been 1 patient with a second malignancy (a nasopharyngeal tumor right at the edge of the radiation volume).

Discussion

RTOG 0424 attempted to address the question of whether patients with high-risk LGG as defined by previously reported adverse risk factors[2,12] would benefit from more aggressive treatment with combined CT and radiation. Unfortunately, a comparison with a high-risk group of patients with LGG entered into RTOG 9802[1] trial was not possible because insufficient information was collected during the RTOG 9802[1] trial concerning high-risk factors such as tumor size and bihemispheric involvement. In addition, imaging studies were not available for RTOG 9802[1] patients. The patients with high-risk LGG entered into the RTOG 0424 trial were not directly comparable to patients with LGG entered into the RTOG 9802[1] trial because of the eligibility requirement of RTOG 0424 that patients had to have 3 or more high-risk factors (age >40 years, astrocytoma histology, bihemispheric tumor, neurologic signs, and/or size >6 cm). No other trials in this patient population occurred at a time similar to RTOG 0424.

Daniels et al[12] performed an independent validation of the Pignatti et al EORTC analysis[2] using patient data from the NCCTG86-27-51[13] phase 3 trial and defined 2 risk groups using the EORTC[2] risk factors: high-risk patients with ≥3 risk factors with a statistically significantly ($P < .001$) poorer MST (3.9 years) and low-risk patients with ≤2 factors with an MST of 10.8 years. Thus, it appears that the EORTC-defined risk factors[2] on non−centrally reviewed LGGs identify a similar high-risk group of centrally reviewed LGGs with an MST of <4 years from the NCCTG trial. At 3.9 years, the OS of patients in RTOG 0424 was 68.4% (95% CI, 60.1%-76.6%) versus 50% reported by

Table 1 Comparison of survivals: RTOG 0424 versus Gorlia et al[*,11]

Intermediate-risk patients	Survival	Patients/events, n	RTOG 0424 (95% CI) survival	Gorlia[11] EORTC survival (95% CI)	RTOG survival (95% CI)
	MST	35/22	8.8 (5.9-11.1)	7.6 (6.2-8.9)	7.2 (5.2-11.1)
	5-year OS	35/22	74.3 (59.8-88.8)	72.2 (62.1-80.0)	61.8 (51.5-70.5)
	Median PFS	57/40	6.4 (4.5-7.5)	4.7 (3.7-5.9)	3.6 (3.1-4.8)
	3-year PFS	57/40	73.7 (62.3-85.1)	71.2 (61.8-78.7)	61.5 (51.9-69.9)
High-risk patients	MST	82/52	5.3 (3.4-8.7)	4.8 (3.8-6.3)	5.5 (2.6-7.2)
	5-year OS	82/52	51.1 (40.2-61.9)	49.9 (40.3-58.8)	50.0 (39.1-60.0)
	Median PFS	60/47	2.0 (0.9-4.0)	3.3 (2.2-3.5)	1.7 (0.8-4.1)
	3-year PFS	60/38	43.3 (30.8-55.9)	51.9 (42.5-60.4)	42.4 (30.2-54.1)

Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; MST = median survival time; OS = overall survival; PFS = progression-free survival.

* RTOG 0424 patients were run through the EORTC low-grade glioma calculator to determine their risk group.

Daniels et al.[12] The difference between the MST of the EORTC[2] patients with high-risk LGG and those reported by Daniels et al[12] is only 4 to 5 months, which would be compatible with an estimate in the delay in RT administration from first symptom in EORTC[2] patients compared to that in the NCCTG86-27-51[12]/RTOG[1] patients (ie, 12 vs 30 weeks).

Gorlia et al[11] performed a retrospective central pathology review of 390 patients with LGG from the EORTC 22844 and 22845[3-5] studies, confirming grade II LGG in 308 (79% agreement). A new prognostic model identified new independent prognostic factors: time since first symptom, Medical Research Council score (neurologic/cognitive functional deficit), astrocytoma histology, and tumor size $\geq$5 cm. This model was validated using patient data from the phase 3 NCCTG86-27-51[13] and RTOG[1] trials, resulting in the identification of the following independent prognostic factors: Medical Research Council score, astrocytoma, and tumor size. Although there were pathologic differences between the EORTC[11,12,14] studies and NCCTG86-27-51[13]/RTOG,[1] data from both groups yielded 3 risk cohorts with comparable survival curves within each of the 3 risk groups for EORTC[3-5] versus NCCTG86-27-51[13]/RTOG.[1]

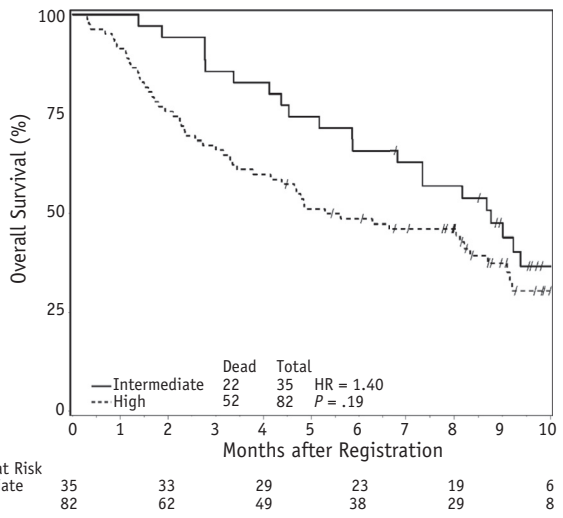

Fig. 3. Overall survival of RTOG 0424 patients by European Organization for Research and Treatment of Cancer (EORTC) risk group analysis (intermediate- vs high-risk group as per EORTC low-grade glioma online calculator).

Low risk patients were effectively excluded from the RTOG 0424 trial. Table 1 summarizes the MSTs, projected 5-year OS, and 3-year PFS data from RTOG 0424 intermediate- and high-risk groups based on running patient characteristics through the EORTC calculator and comparing these results to those of the EORTC 22844/22845[3-5] and NCCTG86-27-51[13]/RTOG[1] trials. Although RTOG 0424 was not designed for comparison using the EORTC survival calculator, these numbers seem to indicate better survival for the intermediate-risk patient group in RTOG 0424 and equivalent survival for the high-risk group. Figure 3 illustrates the OS curves for the intermediate- and high-risk groups from RTOG 0424.

Using these various classification schemes, outcomes from the RTOG 0424 study are analogous to other validated large-scale data sets and better than RT alone. This report represents the only prospective cooperative group study in patients with high-risk LGG to systematically assess long-term survival and other outcomes yet to be reported (quality of life and neurocognitive function) in what has become the de facto standard of care therapy for this group of patients.

Additionally, the RTOG 9802[1] and RTOG 9402[15] trials reported that the addition of CT to radiation therapy alters the 10-year OS rate. RTOG 0424 opened in 2004 when the inflammatory response (pseudoprogression) associated with TMZ and RT was not well recognized, and this may have resulted in falsely low PFS because response assessment in neuro-oncology criteria were not used.[13]

Based on comparison with older historical controls,[2,12] the preliminary survival rates of RTOG 0424 are high, and there could be several possible explanations. First, isocitrate dehydrogenase mutations are correlated with a higher rate of response to TMZ[16] and MGMT promoter methylation has been reported to be an independent

prognostic biomarker of high-risk LGG treated with temozolomide and radiation therapy[17] A comprehensive analysis of these markers in RTOG 0424 tumors is currently underway. Second, there may be an element of radiosensitization associated with TMZ, suggesting that the effect could be real.[18,19] Third, it is possible that early intervention with CT-RT may alter the natural evolution of some LGGs.

Conclusions

The long-term survival results of RTOG 0424 support the initial conclusions of this study with respect to historical controls treated with radiation alone.[2,11] The expected median survival of high-risk LGG treated with RT alone, based on the EORTC/NCCTG/RTOG pooled data, can be estimated to be approximately 7.2 to 7.6 years for intermediate-risk patients and 4.8 to 5.5 years for high-risk patients. In this trial, for a similar group of patients treated with RT plus TMZ, we observed an MST of 8.2 years (95% CI, 5.6-9.1) years. Whether PCV is superior to TMZ remains an open question.

References

1. Buckner J, Shaw E, Pugh S, et al. Radiation and procarbazine, CCNU and vincristine in low-grade glioma. *NEJM* 2016;374:1344-1355.
2. Pignatti F, Van Den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol* 2002;20:2076-2084.
3. Karim A, Maat B, Hatlevoli R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) study 22844. *Int J Radiat Oncol Biol Phys* 1996;36:549-556.
4. Karim A, Afra D, Cornu P, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BR04: an interim analysis. *Int J Radiat Oncol Biol Phys* 2002;52:316-324.
5. Van den Bent M, Afra D, De Witte O, et al. Long-term efficacy of early versus delayed radio-therapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomized trial. *Lancet* 2005;366:985-990.
6. Knisely J, Lally B, Zerlterman D. Validation of the European Organization for Research and Treatment of Cancer (EORTC) prognostic factors for low grade gliomas utilizing the Surveillance, Epidemiology and End Results (SEER) database. *Int J Radiat Oncol Biol Phys* 2005;63:S262-S263.
7. Trotti A, Dimitrios C, Setser A, et al. CTCAE v 3.0: Development of a comprehensive grading system for adverse events of cancer treatment. *Semin Radiat Oncol* 2003;13:176-181.
8. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn* 1958;53:457-481.
9. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J Royal Statist Soc* 1972;135:185-207.
10. Cox DR. Regression models and life-tables. *J Royal Statist Soc* 1972;34:187-220.
11. Gorlia T, Wu W, Wang M, et al. New validated prognostice models and prognostic calculators in patients with low-grade gliomas diagnosed by central pathology review: A pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. *Neurooncol* 2013;15:1568-1579.
12. Daniels T, Brown P, Felten S, et al. Validation of EORTC prognostic factors for adults with low-grade glioma: A report using Intergroup 86-72-51. *Int J Radiat Oncol Biol Phys* 2011;81:218-224.
13. van den Bent M, Wefel J, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): Assessments of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol* 2011;12:583-593.
14. Shaw E, Arusell R, Scheithauer B, et al. Prospective randomized trial of low- versus high-dose radiation therpay in adult supratentorial low-grade glioma: intial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/East Cooperative Oncology Group study. *J Clin Oncol* 2002;20:2267-2276.
15. Carincross J, Wang M, Shaw E, et al. Phase III trial of chemo-radiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol* 2013;31:331-343.
16. Yan H, Williams Parsons D, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 2009;360:765-773.
17. Bell E, Zhang P, Fisher B, et al. Association of MGMT methylation promotor status with survival outcomes in patients with high-risk glioma treated with radiotherapy and temozolomide: an analysis from the NRG/RTOG 0424 trial. *JAMA Oncol* 2018;4:1405-1409.
18. Gieger G, Fu W, Kao G, et al. Temozolomide-mediated radiosensitization of human glioma cells in a zebrafish embryonic system. *Cancer Res* 2008;68:3396-3404.
19. Stupp R, Mason W, Van Den Bent M, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide (TMZ) versus radiotherapy (RT) alone on survival in glioblastoma in a randomized phase III study. Five-year analysis of the EORTC-NCIC study. *Lancet Oncol* 2009;10:459-466.