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# Phase 2 Study of Temozolomide-based Chemoradiation Therapy for High-risk Low-grade Gliomas: Preliminary Results of Radiation Therapy Oncology Group 0424

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## Abstract

**Purpose—**Radiation Therapy Oncology Group (RTOG) 0424 was a phase 2 study of a high-risk low-grade glioma (LGG) population who were treated with temozolomide (TMZ) and radiation therapy (RT), and outcomes were compared to those of historical controls. This study was designed to detect a 43% increase in median survival time (MST) from 40.5 to 57.9 months and a 20% improvement in 3-year overall survival (OS) rate from 54% to 65% at a 10% significance level (1-sided) and 96% power.

**Methods and Materials—**Patients with LGGs with fewer than 3 risk factors for recurrence (age ≥40 years, astrocytoma histology, bihemispherical tumor, preoperative tumor diameter of ≥6 cm,



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or a preoperative neurological function status of >1) were treated with RT (54 Gy in 30 fractions) and concurrent and adjuvant TMZ.

**Results—**From 2005 to 2009, 129 evaluable patients (75 males and 54 females) were accrued. Median age was 49 years; 91% had a Zubrod score of 0 or 1; and 69%, 25%, and 6% of patients had 3, 4, and 5 risk factors, respectively. Patients had median and minimum follow-up examinations of 4.1 years and 3 years, respectively. The 3-year OS rate was 73.1% (95% confidence interval: 65.3%–80.8%), which was significantly improved compared to that of prespecified historical control values ($P<.01$). Median survival time has not yet been reached. Three-year progression-free survival was 59.2%. Grades 3 and 4 adverse events occurred in 43% and 10% of patients, respectively. One patient died of herpes encephalitis.

**Conclusions—**The 3-year OS rate of 73.1% for RTOG 0424 high-risk LGG patients is higher than that reported for historical controls ($P<.001$) and the study-hypothesized rate of 65%.

## Introduction

Until the long-term results of Radiation Therapy Oncology Group (RTOG) 9802 (1) became available, the role of chemotherapy in patients with low-grade gliomas (LGG) was not clearly established. Studies of recurrent LGG treated with single agents such as nitrosourea or temozolomide (TMZ) alone or with combination therapies such as procarbazine, lomustine (CCNU) and vincristine (PCV) demonstrated responses (2–6) without convincing survival benefit (7, 8). The Southwest Oncology Group phase 3 trial of radiation therapy (RT) with or without CCNU for incompletely resected LGGs reported a median survival time of 4.5 years versus 7.4 years favoring chemoradiation, but the trial closed early, and the difference was not statistically significant, potentially due to severe underpowering (9). RTOG 9802 phase 3 trial (1) randomized patients with newly diagnosed LGGs who were over age 40 or who had undergone a subtotal resection to RT with or without PCV. Initial reports described an increase in progression-free survival (PFS), but with median follow-up approaching 12 years, there is a categorical overall survival (OS) benefit for the PCV + RT arm compared to the RT-alone arm (median survival times [MSTs] of 13.3 and 7.8 years, respectively), thereby establishing chemo-radiation as a standard of care for high-risk LGG patients.

When RTOG 0424 opened, TMZ was considered a novel chemotherapy agent, although small trials in recurrent grade 2 and 3 gliomas had demonstrated its efficacy (10–12). Because of long-term toxicity concerns, accrual was restricted to high-risk LGGs. With the publication, in 2005, of the European Organization for Research and Treatment of Cancer (EORTC) 22,981/National Cancer Institute of Canada (NCI) CE3 trials (11) reporting a survival advantage for TMZ plus radiation compared to radiation alone, TMZ became the standard chemotherapy agent for glioblastoma (GBM), so there is now a need to identify the role of TMZ in concert with radiation therapy for LGGs.

This report describes the preliminary results of RTOG 0424, a phase 2 trial of 129 high-risk LGG patients with ≥3 risk factors, as defined by Pignatti et al (13), treated with radiation and concurrent and adjuvant TMZ. Analysis of the EORTC 22844 (12) trial by Pignatti et al (13) identified 5 prognostic factors (age >40 years, largest preoperative tumor diameter of

>6 cm, tumor crossing the corpus callosum, astrocytoma histology, and preoperative neurological function deficits) that were significant according to multivariable analysis at the 1% significance level. The validity of this model was tested by applying it to a set of LGG patients from the EORTC 22845 trial (14, 15). Patients with fewer than 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 by Pignatti et al (13) has been independently confirmed using data from the Surveillance Epidemiology and End Results (SEER) database (16); however, limitations of that work include lack of central pathologic validation of the local histologic diagnosis and unavailability of molecular markers analysis.

RTOG 0424 was originally designed as a randomized phase 2 trial but was recommended by the National Cancer Intitute's Cancer Therapy Evaluation Program to move forward as a single-arm phase 2 trial because of accrual concerns, with the expectation that the results of RTOG 0424 could serve as the basis for a future phase 3 LGG trial. The Eastern Cooperative Oncology Group initiated the E3F05 phase 3 trial of TMZ plus radiation versus radiation alone for LGGs in 2009, but accrual to this trial was suspended in early 2014, and the trial will not be completed. Hence, RTOG 0424 is the only trial of TMZ plus radiation in LGGs to be completed within the foreseeable future.

Because RTOG 0424 is a singl-arm phase 2 study, compared to a historical control, it was designed with the survival bar set very high, that is, a 43% increase in MST and a 20% improvement in 3-year OS were required for statistical significance.

## Methods and Materials

Investigators initiated this trial after approval by a local institutional Human Investigations Committees and in accordance with the Helsinki Declaration (revised in 2000). Informed consent was obtained from each participant or their guardian.

Eligibility criteria for RTOG 0424 included supratentorial World Health Organization grade II astrocytoma, oligodendroglioma (O), or oligoastrocytoma (OA) confirmed by central pathology review with at least 3 of the following factors: age ≥ 40 years, preoperative tumor diameter of ≥6 cm, bihemispherical tumor, astrocytoma histology, and/or preoperative neurological function status of >1 (ie moderate to severe impairment). Patients could not have received prior chemotherapy or radiation therapy, must have been cancer-free for at least 5 years, must have enrolled <12 weeks from surgery with a pretreatment Zubrod score of 0 to 2, and have had adequate marrow, liver, and renal function. Pre- and postoperative brain magnetic resonance images (MRI) with and without contrast were required within 4 weeks of surgery.

This study opened in January 2005 and was amended in February 2006 to collect tissue for post-hoc determination of methylguanine-DNA methyl transferase (MGMT) promoter methylation status and quality-of-life and neurological functional status evaluation. The study closed in August 2009 with 136 patients entered. Seven patients were ineligible and were excluded (2 were excluded because of a stereotactic biopsy postamendment requiring

tissue submission, 3 because of inadequate imaging, 1 because of outdated laboratory studies, and 1 because of inadequate number of risk factors), which left a total of 129 patients for analysis.

Consenting eligible patients were assigned to 3-dimensional (3D) conformal radiation to 54 Gy in 30 fractions plus concurrent and adjuvant TMZ. The radiation target volume was based on the postoperative MRI T2-weighted image residual tumor and/or surgical cavity plus a 2-cm margin. Chemotherapy consisted of concurrent oral TMZ, 75 mg/m$^2$/day, during radiation therapy and up to 12 cycles of adjuvant TMZ, 150 to 200 mg/m$^2$/day, on days 1 to 5, repeated every 28 days with prophylaxis for *Pneumocystis carinii* infection. Dose modifications were permitted based on blood counts. TMZ was stopped at disease progression or for unacceptable toxicity.

Baseline examinations included physical examination, MRI of brain, full blood counts, and biochemistry assays. Patients were evaluated monthly postradiation during adjuvant TMZ therapy, at 4 months post-TMZ, and every 6 months thereafter. An MR brain scan was repeated 4 weeks postradiation and then every 3 months thereafter.

RTOG 0424 patients were considered to have a high-risk LGG according to the definition described by Pignatti et al (13). The historical MST for this high-risk group is 40.5 months with the caveat that a central pathology review was not initially performed in Europe in the late 1980s. RTOG 0424 was designed to detect a 43% increase in MST from 40.5 (13) to 57.9 months and improve the 3-year OS from 54% (13) to 65% at a significance level of 0.10 (one-sided). Assuming an exponential distribution of survival times, the primary hypothesis is equivalent to a 43% relative increase in MST (from 40.5 to 57.9 months) and 37% reduction in monthly hazard ratio (from 0.0171 to 0.12). The sample size calculation and primary analysis were based on a Z-test comparing the logarithm of the hazard ratio found in the study by Schoenfeld and Richter (17) (adjusted for a single-arm trial). The study initially required 36 deaths of 72 patients to ensure 80% power for the primary hypothesis. The sample size was later increased to 135 in order to ensure adequate power to detect a hazard ratio of 2.5 for MGMT (unmethylated vs methylated) status, at a 2-sided sided significance $\alpha$ level of 0.05 with an MGMT prevalence rate of at least 30%, and warranted power of 96% for the primary hypothesis.

OS and PFS were analyzed as time-to-event data using the Kaplan-Meier product limit method (18). The log-rank test (19) was used to compare OS rates among different patient characteristics, and the associated hazard ratio was estimated by Cox proportional hazard model (20). All *P* values are 2-sided and have not been adjusted for multiple comparisons. For this initial report, the analysis focused on the entire cohort, rather than on molecular subgroupings because MGMT analysis was a post-hoc amendment. With the recognition that additional molecular markers such as 1p19q (21, 22), isocitrate dehydrogenase (IDH) (22), and PTEN promoter methylation (23) are also prognostically significant in this group of patients, a comprehensive molecular analysis is underway and will be reported separately.

## Results

Pretreatment characteristics are presented in Table 1. Sixty-nine percent, 24.8%, and 6.2% of patients had 3, 4, or 5 risk factors, respectively, a distribution similar to that (70%, 29%, and 1%, respectively) in the study by Pignatti et al (13). There were no differences in survival for patients with different numbers of risk factors.

Radiation therapy was delivered according to protocol (target volume received 90%–110% of the prescribed total dose of radiation therapy) in 123 of 129 patients (95.3%). Chemotherapy was delivered according to protocol (no modifications or delays in the prescription of chemotherapy) in 98 of 129 patients (80%). Three additional patients received >80% of the protocol dose of TMZ.

The median follow-up time for all patients and all surviving patients were 4.1 and 5.0 years, respectively. Figure 1 shows the OS of all patients treated in the RTOG 0424 study. The 3-year OS rate is 73.1% (95% CI, 65.3%–80.8%), significantly higher than the historical control OS rate of 54% (13) at a 0.1 significance level (one-sided; $P = .001$). The corresponding monthly hazard rate is 0.009, significantly lower than the null hypothesis rate of 0.0171, with Z-statistic of −3.938 and $P<.001$. There have been 52 deaths to date, 36 due to tumor progression, 8 due to unrelated causes, and 7 due to unknown causes. The 5-year OS rate is 57.1% (95% CI: 47.7%–66.5%), and the MST has not yet been reached.

Figure 1 also illustrates the PFS curves for all patients. The 3-year PFS was 59.2% (95% CI: 50.7%–67.8%), and median PFS was 4.5 years (95% CI: 3.5–NA). It should be noted that RTOG 0424 opened in 2004, when the inflammatory response associated with TMZ and RT was not well recognized and Revised Assessment in Neurooncology (RANO) criteria were not used (24).

We conducted a Cox model assessment of the association between OS or PFS and the following prognostic factors: histology (oligodendroglioma/oligoastrocytoma vs astrocytoma), neurologic function (no deficit vs minor vs moderate or major deficit), tumor size (<5 cm vs >5 cm), age (<40 years vs > 40 years), tumor crossing the midline (yes or no), and extent of surgery (biopsy vs resection). Only histology was significantly associated with OS ($P = .0027$; hazard ratio [HR] = 0.385; 95% CI: 0.207–0.718), and PFS ($P = .0339$; HR = 0.572; 95% CI: 0.341–0.95). The other factors were not significantly associated with either OS or PFS.

Adverse events (AEs) were reported according to CTCAE version 3.0 (25) as definitely, probably, or possibly related to treatment; 55 patients (42.6%) experienced grade 3 AE, 13 patients (10.1%) experienced grade 4 AE, and 1 patient experienced a grade 5 infection (herpes encephalitis) possibly related to TMZ or steroids. Details of possible treatment-related AEs are listed in Table 2. No grade 5 hematological or neurological toxicities were reported, but 1 patient who experienced an episode of cerebral ischemia related to a clotting disorder has recovered. Although AEs with TMZ and RT are higher than would be expected with radiation therapy alone, serious late toxicities such as second malignancy, leukemia, hepatic failure, symptomatic leukoencephalopathy, or brain necrosis have not been reported, and we continue to diligently follow patients.

## Discussion

Optimal management of LGG patients remains controversial because of tumor heterogeneity and variability of natural history. Multiple prognostic factors have been reported, including age, histology, tumor size, performance status, extent of resection, mini-mental status, and molecular characteristics (21–37). Retrospective studies of the kinetics of LGGs indicate continuous growth of variable speed (38), with most ultimately undergoing anaplastic transformation (39). A subset of LGGs clearly manifests more aggressive clinical behavior, requiring earlier intervention (13, 33, 40). RTOG 0424 tries to address the question of whether these high-risk patients would benefit from more aggressive upfront treatment.

The results of single-arm phase 2 trials must be compared with historical controls. There are 2 historical papers which have reported analyses of the results of high-risk LGG patients treated with radiation alone, Pignatti et al (13) and Daniels et al (32). The survival results for high-risk LGGs treated with TMZ and radiation therapy in RTOG 0424 significantly exceeded those reported by Pignatti et al (13) with increases >43% in MST and >20% in 3-year OS. Problems with historical radiation treatment studies can include changes in surgery, imaging and radiation planning, and delivery over time. Hence, RTOG 0424 required not only equivalency of survival but a 43% improvement in MST and 20% improvement in 3-year OS for results to be statistically significant. Two other major criticisms of the analysis by Pignatti et al (13) are, first, the lack of a central pathology review, which could have resulted in the inclusion of anaplastic tumors, thereby deflating the survival rate, and second, the fact that the analysis involved European patients. There may be philosophical differences in timing of treatment intervention in LGG patients between the United States and Europe, leading to the phenomenon of lead-time bias. In the United States, radiation therapy is more commonly administered postoperatively at the time of diagnosis, especially for high-risk patients, whereas in Europe, treatment with surgery and radiation therapy is more likely to be deferred until tumor or symptom progression, although categorical data backing these assumptions are lacking. Nevertheless, it is possible that RTOG 0424 may have included patients treated earlier, yielding an artificially longer survival. Gorlia et al (40) estimated the differences between initiation of treatment for European and U.S. patients to be 16 weeks, that is, the estimate of the delay in treatment from first symptom in EORTC patients was 30 weeks compared to 14 weeks for the U.S. study patients in North Central Cancer Treatment Group (NCCTG) 86-72-51 and RTOG 9802 trials. The survival of the RTOG 0424 patients still significantly exceeds that of patients in the study by Pignatti et al (13), even allowing for the addition of the lead time.

With regard to the pathology review issue, Gorlia et al (40) performed a retrospective central pathology review of some of the EORTC 22844/22845 patients used in the analysis by Pignatti et al (13). A total of 390 LGG patients from the EORTC 22844/22,845 studies were reviewed, and 308 were confirmed to have grade 2 LGG (79% agreement). A new prognostic model introduced by Gorlia et al (40) identified 4 new independent prognostic factors: time since first symptom, Medical Research Council (research funding organization of the United Kingdom) score (neurological or cognitive functional deficit), astrocytoma histology, and tumor size >5 cm. This model was validated with U.S. phase 3 LGG patients from NCCTG 86-72-51 and RTOG 9802 trials, and 3 independent prognostic factors were

found for the U.S. studies: MRC score, astrocytoma, and tumor size but not time since first symptom. Despite pathological differences between the EORTC and NCCTG/RTOG groups, data from both groups yielded 3 risk cohorts with comparable survival curves within each of the 3 risk groups for the EORTC 22844/22845 versus NCCTG86-72-51/RTOG 9802 patients.

Although RTOG 0424 was not designed for comparison using the EORTC survival calculator, we wanted to duplicate the analysis performed with the EORTC and Intergroup data by Gorlia et al (40). We, therefore, took the data from RTOG 0424 patients and entered it into the online EORTC LGG survival calculator (http://www.eortc.be/tools/lggcalculator/calculator.aspx), developed based on the reanalysis by Gorlia et al (40). There were some differences between the 2 studies. In order to enter RTOG 0424 data into the EORTC survival calculator, tumor size had to be reclassified as <5 cm versus ≥5 cm (rather than <6 cm vs ≥6 cm), and 5 histopathological categories had to be reassigned to 2 categories (ie astrocytoma vs oligodendroglioma and oligoastrocytoma [O/OA]). The astrocytoma-dominant patients from RTOG 0424 were entered into the survival calculator as O/OAs rather than astrocytomas, although the behavior of these tumors may be more similar to that of astrocytomas.

Low-risk LGG patients were effectively excluded from the RTOG 0424 trial. There were only 12 patients in the RTOG 0424 patient group who were reclassified as low-risk according to the definition by Gorlia et al (40), a number too small to analyze. Therefore, only intermediate- and high-risk groups were created from this process (n = 117 patients). Figure 2 illustrates the OS curves for the RTOG 0424 patients reclassified into intermediate- and high-risk groups. Table 3 summarizes the MSTs, projected 5-year OS rates, and 3-year PFS data from RTOG 0424 patients reclassified into intermediate- and high-risk groups based on the EORTC calculator and compares these results to those reanalyzed by Gorlia et al (40) of the EORTC 22844 and 22845 and NCCTG 86-72-51 and RTOG 9802 trials. These numbers seem to indicate a slightly better survival for the intermediate-risk patient group in RTOG 0424, although median follow-up for RTOG 0424 is only 4.1 years, which may be too preliminary to allow for a direct comparison of 5-year OS rates. The RTOG 9802 and RTOG 9402 trials reported that the addition of chemotherapy to radiation therapy altered the 10-year OS rate rather than the 3-year OS rate. The survival for the high-risk group (primarily large astrocytomas) appears to be equivalent.

Another historical control comparator which can be used is the analysis performed by Daniels et al (33). That study reported an independent validation of the EORTC analysis by Pignatti et al (13), using patient data from the U.S. NCCTG 86-72-51 phase 3 trial, and defined 2 risk groups by using the EORTC risk factors reported by Pignatti et al (13), high-risk patients with ≥3 risk factors who had a poorer MST (3.9 years) than low-risk patients with ≤2 factors (10.8 years), a difference which was statistically significant with a *P* value of <.001. Thus, the EORTC-defined risk factors reported by Pignatti et al (13) on non-centrally reviewed LGGs appear to identify a similar high-risk group of centrally reviewed LGGs with an MST of <4 years from a U.S. trial. The median survival reported by Daniels et al (33) was 3.9 years, whereas at 3.9 years, 68.4% of patients in RTOG 0424 were still alive.

Based upon comparison with older historical controls (13, 33), the preliminary survival rates of RTOG 0424 are high, even discounting lead time and central pathology review biases, and there could be several other possible explanations. A maldistribution of molecular markers important in determining response to TMZ and RT could potentially explain the results. Patients with methylated glioblastoma (41) and those with codeleted anaplastic oligodendroglioma (21) tend to have prolonged OS with chemoradiation than with radiation alone. IDH mutations are correlated with a higher rate of response to TMZ (26). Second, there may be an element of radiation sensitization associated with TMZ (42). In the trial by Stupp et al (11), concurrent and adjuvant TMZ administered with radiation yielded a higher percentage of long-term survivors than radiation for GBM. The combination of TMZ and radiation appeared to alter the natural history of 8% of GBM patients who remained alive 5 years after treatment. Third, it is possible that early intervention with chemo-radiation may alter the natural evolution of some LGGs. A comparison with the reanalysis by Gorlia et al (40) is very preliminary but may indicate an advantage for the intermediate risk LGG patients.

## Conclusions

There is emerging information showing that the addition of chemotherapy to radiation therapy for LGGs has survival benefits (1). The 3-year OS rate of 73.1% for eligible patients treated in RTOG 0424 is higher than a priori specified historical controls (13, 33) treated with radiation therapy alone ($P<.001$). Prospective molecular marker analysis is awaiting National Cancer Institute Clinical Trial Evaluating Program approval. These data should be considered as hypothesis generating, lending strong support for further studies of combined chemo-radiation in LGGs and for the use of TMZ in combination with radiation therapy to treat LGGs.

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## Summary

There is emerging evidence that addition of chemo-therapy to radiation therapy has survival benefits for patients with low-grade gliomas (LGGs). The 3-year overall survival rate of 73.1% for eligible high-risk LGG patients treated with radiation and concurrent and adjuvant temozolomide in Radiation Therapy Oncology Group 0424 is significantly higher than the a priori specified historical controls treated with radiation alone ($P<.001$) with acceptable toxicity.

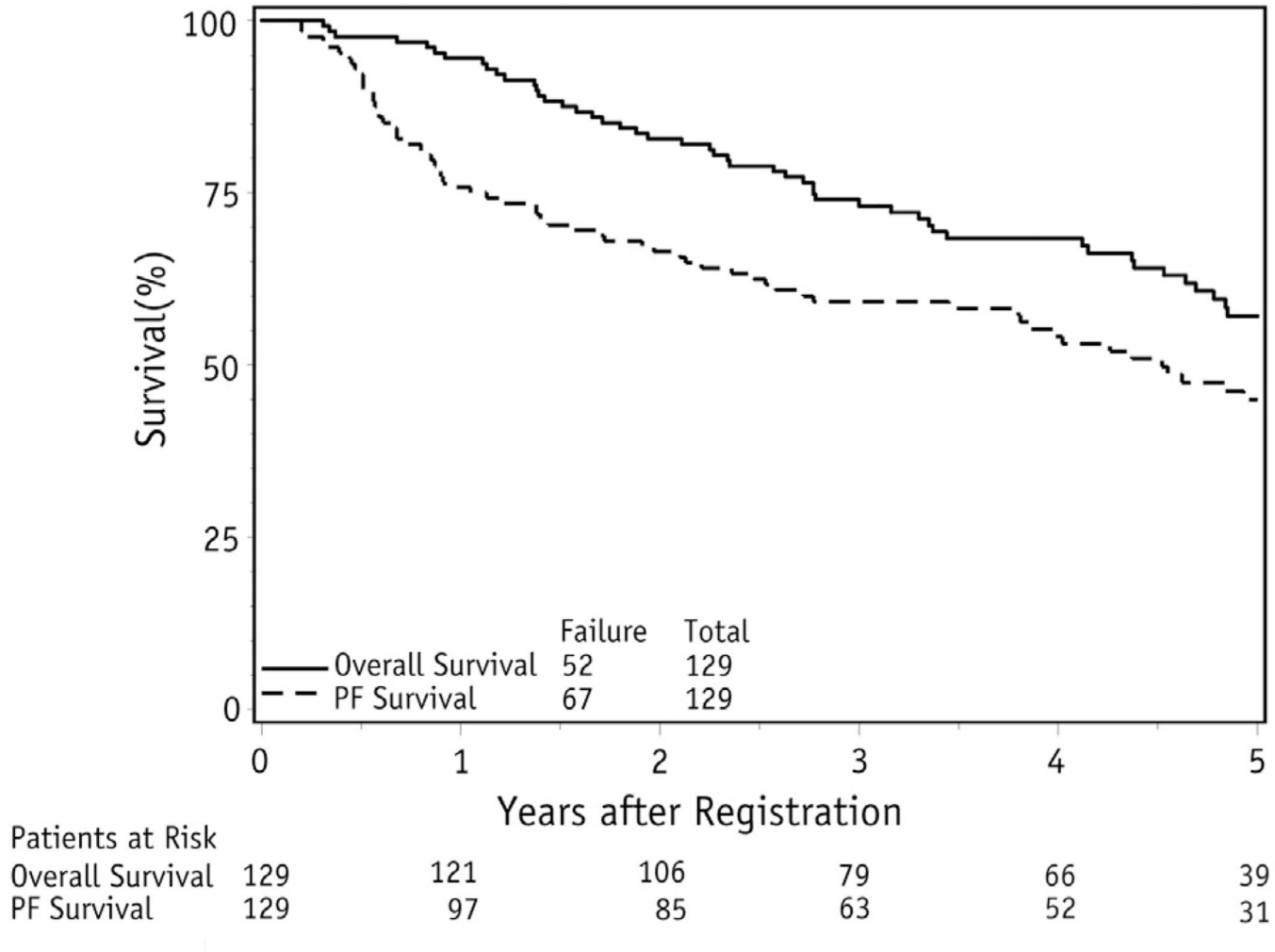


**Fig. 1.**
Overall and progression-free survival of RTOG 0424 patients.

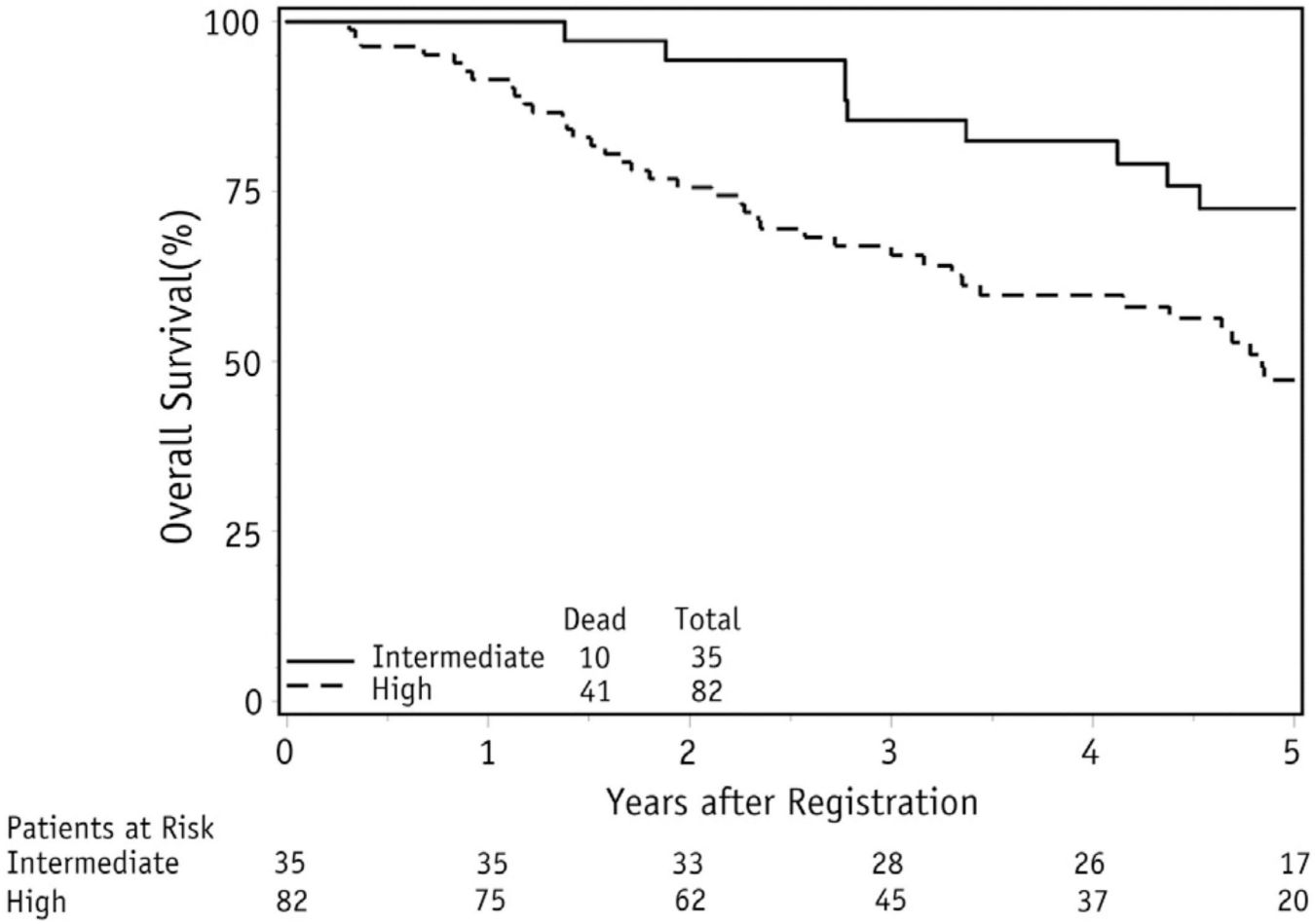


**Fig. 2.**

Overall survival of RTOG 0424 patients reclassified according to the EORTC LGG prognostic model. LGG = low-grade glioma.

## Table 1

Pretreatment characteristics (n = 129)

| | |
|---|---|
| Median age | 49 |
| Minimum age–maximum age | 20–76 |
| Q1–Q3 | 41–58 |
| Sex | |
| Males | 75 (58.1%) |
| Females | 54 (41.9%) |
| Race | |
| American Indian/Alaska Native | 1 (0.8%) |
| Asian | 2 (1.6%) |
| Black or African American | 4 (3.1%) |
| Native Hawaiian or Other Pacific Islander | 1 (0.8%) |
| White | 121 (93.8%) |
| Ethnicity | |
| Hispanic or Latino | 6 (4.7%) |
| Not Hispanic or Latino | 114 (88.4%) |
| Unknown (individuals who did not report ethnicity) | 9 (7.0%) |
| Zubrod performance status | |
| 0 | 59 (45.7%) |
| 1 | 58 (45.0%) |
| 2 | 12 (9.3%) |
| Neurological function | |
| No symptoms | 31 (24.0%) |
| Minor symptoms | 51 (39.5%) |
| Moderate symptoms (fully active) | 35 (27.1%) |
| Moderate symptoms (required assistance) | 12 (9.3%) |
| Histology from central review | |
| Astrocytoma | 71 (55.0%) |
| Oligoastrocytoma, astro-dominant | 14 (10.9%) |
| Oligoastrocytoma, astro = oligo | 1 (0.8%) |
| Oligoastrocytoma, oligo-dominant | 14 (10.9%) |
| Oligodendroglioma | 29 (22.5%) |
| Surgery | |
| Biopsy | 20 (15.5%) |
| Partial resection | 79 (61.2%) |
| Total resection | 24 (18.6%) |
| Other | 6 (4.7%) |
| Number of high-risk factors | |
| 3 | 89 (69.0%) |
| 4 | 32 (24.8%) |
| 5 | 8 (6.2%) |

| | |
|---|---|
| Individual high-risk factors | |
| Age ≥ 40 y | 103 (79.8%) |
| Largest preoperative tumor diameter of ≥6 cm | 102 (79.1%) |
| Tumor crossed the midline | 69 (53.5%) |
| Tumor subtype astrocytoma/mixed (astro-dominant) | 85 (65.9%) |
| Preoperative neurological function status of >1 | 64 (49.6%) |

*Abbreviation:* Q1–Q3 = XXXX.

## Table 2

Number of patients with an adverse event by category and grade related to protocol treatment (n = 129)

| | Grade | | |
|---|---|---|---|
| **Category** | **3** | **4** | **5** |
| Allergy/immunology | 1 | 0 | 0 |
| Auditory/ear | 0 | 0 | 0 |
| Cardiac arrhythmia | 0 | 0 | 0 |
| Cardiac general | 0 | 0 | 0 |
| Coagulation | 0 | 0 | 0 |
| Constitutional symptoms | 11 | 0 | 0 |
| Death | 0 | 0 | 1 |
| Dermatology/skin | 5 | 0 | 0 |
| Endocrine | 0 | 0 | 0 |
| Gastrointestinal | 7 | 0 | 0 |
| Hemorrhage/bleeding | 0 | 1 | 0 |
| Hepatobiliary/pancreas | 1 | 0 | 0 |
| Infection | 6 | 1 | 1* |
| Lymphatics | 0 | 1 | 0 |
| Metabolic/laboratory | 15 | 0 | 0 |
| Musculoskeletal/soft tissue | 6 | 2 | 0 |
| Ocular/visual | 1 | 0 | 0 |
| Pain | 10 | 0 | 0 |
| Pulmonary/upper respiratory | 2 | 0 | 0 |
| Renal/genitourinary | 0 | 0 | 0 |
| Sexual/reproductive function | 0 | 0 | 0 |
| Vascular | 1 | 3 | 0 |
| Hematological | 31 | 10 | 0 |
| Neurological | 9 | 4 | 0 |

*Died of herpes encephalitis possibly related to protocol treatment.

**Table 3**

Overall and progression-free survival for RTOG 0424 patients reclassified according to EORTC intermediate and high-risk groups compared with historical controls of Gorlia et al (40)

| Gorlia et al (40) risk category | Survival | No. of patients/no. of events | Study 0424 survival (95% CI) | EORTC trial survival (95% CI) | RTOG/NCCTG trials survival (95% CI) |
|---|---|---|---|---|---|
| OS Model | | | | | |
| Intermediate risk | MST OS (y) | 35/10 | N (5.9–N) | 7.6 (6.2–8.9) | 7.2 (5.2–11.1) |
| | 5-year OS (%) | 35/10 | 72.5 (57.1–87.9)* | 72.2 (62.1–80.0) | 61.8 (51.5–70.5) |
| High risk | MST OS (y) | 82/39 | 4.8 (3.5–N) | 4.8 (3.8–6.3) | 5.5 (2.6–7.2) |
| | 5-year OS (%) | 82/39 | 47.2 (35.3–59.2)* | 49.9 (40.3–58.8) | 50.0 (39.1–60.0) |
| PFS Model | | | | | |
| Intermediate risk | Median PFS (y) | 57/25 | 5.2 (4.5–N) | 4.7 (3.7–5.9) | 3.6 (3.1–4.8) |
| | 3-year PFS (%) | 57/25 | 73.6 (62.2–85.1) | 71.2 (61.8–78.7) | 61.5 (51.9–69.9) |
| High risk | Median PFS (y) | 60/38 | 2.0 (0.9–4.0) | 3.3 (2.2–3.5) | 1.7 (0.8–4.1) |
| | 3-year PFS (%) | 60/38 | 43.1 (30.5–55.7) | 51.9 (42.5–60.4) | 42.4 (30.2–54.1) |

*Abbreviations:* EORTC = European Organization for Research and Treatment of Cancer; MST = median survival time; N = not yet reached; NCCTG = North Central Cancer Treatment Group; OS = overall survival; PFS = progression-free survival; RTOG = Radiation Therapy Oncology Group.

*Kaplan-Meier estimate.

*Int J Radiat Oncol Biol Phys*. Author manuscript; available in PMC 2016 March 01.