

Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539

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OBJECTIVE This is the first clinical outcomes report of NRG Oncology RTOG 0539, detailing the primary endpoint, 3-year progression-free survival (PFS), compared with a predefined historical control for intermediate-risk meningioma, and secondarily evaluating overall survival (OS), local failure, and prospectively scored adverse events (AEs).

METHODS NRG Oncology RTOG 0539 was a Phase II clinical trial allocating meningioma patients to 1 of 3 prognostic groups and management strategies according to WHO grade, recurrence status, and resection extent. For the intermediate-risk group (Group 2), eligible patients had either newly diagnosed WHO Grade II meningioma that had been treated with gross-total resection (GTR; Simpson Grades I–III) or recurrent WHO Grade I meningioma with any resection extent. Pathology and imaging were centrally reviewed. Patients were treated with radiation therapy (RT), either intensity modulated (IMRT) or 3D conformal (3DCRT), 54 Gy in 30 fractions. The RT target volume was defined as the tumor bed and any nodular enhancement (e.g., in patients with recurrent WHO Grade I tumors) with a minimum 8-mm and maximum 15-mm margin, depending on tumor location and setup reproducibility of the RT method. The primary endpoint was 3-year PFS. Results were compared with historical controls (3-year PFS: 70% following GTR alone and 90% with GTR + RT). AEs were scored using NCI Common Toxicity Criteria.

RESULTS Fifty-six patients enrolled in the intermediate-risk group, of whom 3 were ineligible and 1 did not receive RT. Of the 52 patients who received protocol therapy, 4 withdrew without a recurrence before 3 years leaving 48 patients evaluable for the primary endpoint, 3-year PFS, which was actuarially 93.8% ($p = 0.0003$). Within 3 years, 3 patients experienced events affecting PFS: 1 patient with a WHO Grade II tumor died of the disease, 1 patient with a WHO Grade II tumor had disease progression but remained alive, and 1 patient with recurrent WHO Grade I meningioma died of undetermined cause without tumor progression. The 3-year actuarial local failure rate was 4.1%, and the 3-year OS rate was 96%. After 3 years, progression occurred in 2 additional patients: 1 patient with recurrent WHO Grade I meningioma and 1 patient with WHO Grade II disease; both remain alive. Among 52 evaluable patients who received protocol treatment, 36 (69.2%) had WHO Grade II tumors and underwent GTR, and 16 (30.8%) had recurrent WHO Grade I tumors. There was no significant difference in PFS between these subgroups ($p = 0.52$, HR 0.56, 95% CI 0.09–3.35), validating their consolidation. Of the 52 evaluable patients, 44 (84.6%) received IMRT, and 50 (96.2%) were treated per protocol or

ABBREVIATIONS AE = adverse event; CGE = cobalt gray equivalent; CNED = continual no evidence of disease; CTV = clinical tumor volume; EBRT = external beam RT; EORTC = European Organisation for Research and Treatment of Cancer; GTR = gross-total resection; GTV = gross tumor volume; IMRT = intensity-modulated RT; MMSE = Mini-Mental State Examination; OAR = organ at risk; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PRV = planning risk volume; PTV = planning target volume; PTV_{PRV} = overlap between the PTV and the particular PRV of concern; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SD = stable disease; SRS = stereotactic radiosurgery; STR = subtotal resection; WHO = World Health Organization; 3DCRT = 3D conformal RT.

SUBMITTED May 10, 2016. **ACCEPTED** November 21, 2016.

INCLUDE WHEN CITING Published online October 6, 2017; DOI: 10.3171/2016.11.JNS161170.

with acceptable variation. AEs (definitely, probably, or possibly related to protocol treatment) were limited to Grade 1 or 2, with no reported Grade 3 events.

CONCLUSIONS This is the first clinical outcomes report from NRG Oncology RTOG 0539. Patients with intermediate-risk meningioma treated with RT had excellent 3-year PFS, with a low rate of local failure and a low risk of AEs. These results support the use of postoperative RT for newly diagnosed gross-totally resected WHO Grade II or recurrent WHO Grade I meningioma irrespective of resection extent. They also document minimal toxicity and high rates of tumor control with IMRT.

Clinical trial registration no.: NCT00895622 (clinicaltrials.gov).

<https://thejns.org/doi/abs/10.3171/2016.11.JNS161170>

KEY WORDS meningioma; WHO Grade II (atypical); radiotherapy; oncology

TREATMENT of patients with meningioma is most often based on clinical judgment, personal experience, institutional tradition, and retrospective series, all in the absence of Level 1 evidence. Practices have varied, and the establishment of a uniform approach has been hampered not only by the lack of prospective trials, but also, and rather importantly, by inconsistent grading criteria. In recent years, the latter has been addressed by the World Health Organization (WHO) with updated criteria in 2007 and 2016. Previous grading standards were not broadly accepted, but, based on a recently published secondary endpoint analysis of pathology concordance from NRG Oncology RTOG 0539, the WHO 2000 and 2007 standards appear to have been broadly followed, at least among institutions enrolling patients in NRG Oncology RTOG cooperative group trials.⁴⁰

Several cooperative group meningioma protocols have been launched, but they either have met with disappointing results or have failed to reach accrual goals.^{10,21,25,27} The Southwest Oncology Group (SWOG) completed a Phase III trial, with results published in 2015 by Ji and colleagues, assessing mifepristone, an antiprogesterin. That study (SWOG-S9005) randomized patients with progressive or recurrent meningioma to receive either oral mifepristone or placebo and showed no improvement in either failure-free or overall survival with mifepristone.²¹

Regarding radiation therapy (RT), prior evidence has been limited to Level IV or V.²⁵ Recently, however, 2 Phase II trials, this one from NRG Oncology RTOG and another from the European Organisation for Research and Treatment of Cancer (EORTC 22042–26042), completed accrual, and the data are undergoing analysis. This report describes the initial clinical outcomes from NRG Oncology RTOG 0539, a Phase II trial of observation for low-risk meningioma and of RT for intermediate- and high-risk meningioma. The trial opened in June 2009 and closed ahead of schedule with full accrual in August 2012. The schema and enrollment data are depicted in Fig. 1.

This report focuses on the intermediate-risk cohort (Group 2), composed of patients with newly diagnosed WHO Grade II meningioma treated with gross-total resection (GTR) or recurrent WHO Grade I meningioma, with or without resection of any extent. We address the study's primary endpoint, 3-year progression-free survival (PFS), as well as the mature secondary endpoints of 3-year overall survival (OS) and acute and late adverse events (AEs).

Methods

Institutional Review Board Approval, Consent, and Clinical Trial Registration

This cooperative group protocol was approved by the institutional review boards at each participating study site, and documentation was received at the Radiation Therapy Oncology Group (RTOG, now NRG Oncology) central office. Each patient signed an approved informed consent form before trial enrollment. This protocol (NRG Oncology RTOG 0539) is registered with ClinicalTrials.gov (<https://clinicaltrials.gov>). The ClinicalTrials.gov identifier is NCT00895622.

Selection Criteria

Adults 18 years of age or older with a unifocal, histologically documented intracranial meningioma, with no prior history of cranial RT, with Zubrod Performance Status 0–1 and without severe, active comorbidity were eligible for enrollment. Histology, including WHO 2007 tumor grade and subtype, was confirmed for each patient via central pathology review by one of the authors (A.P.). Following central review, patients were partitioned according to specific criteria into 3 groups: Group 1 (low risk), Group 2 (intermediate risk), and Group 3 (high risk), shown in Fig. 1.

Protocol Registration

Registration took place in 2 steps. Step 1 was initial registration, followed by submission of pathology specimens for central review. Step 2 registration, which occurred after central pathology review, entailed protocol group assignment. After this step, protocol-specified treatment began.

Tumor Grade and Resection Extent

This report pertains to patients assigned to the intermediate-risk group (Group 2), which includes patients with a newly diagnosed gross-totally resected WHO Grade II meningioma or a recurrent WHO Grade I meningioma irrespective of the resection extent. Resection extent was classified using Simpson criteria⁴³ and was based on the neurosurgeons' assessment and postoperative MRI findings, also centrally reviewed (by Bruce Dean—see *Acknowledgments*—and authors J.M. or A.A.). Gross-totally resected tumors included Simpson Grades I–III.

For patients with a newly diagnosed WHO Grade II

Phase II Trial of Observation for Low-Risk Meningioma and of Radiotherapy for Intermediate and High-Risk Meningioma

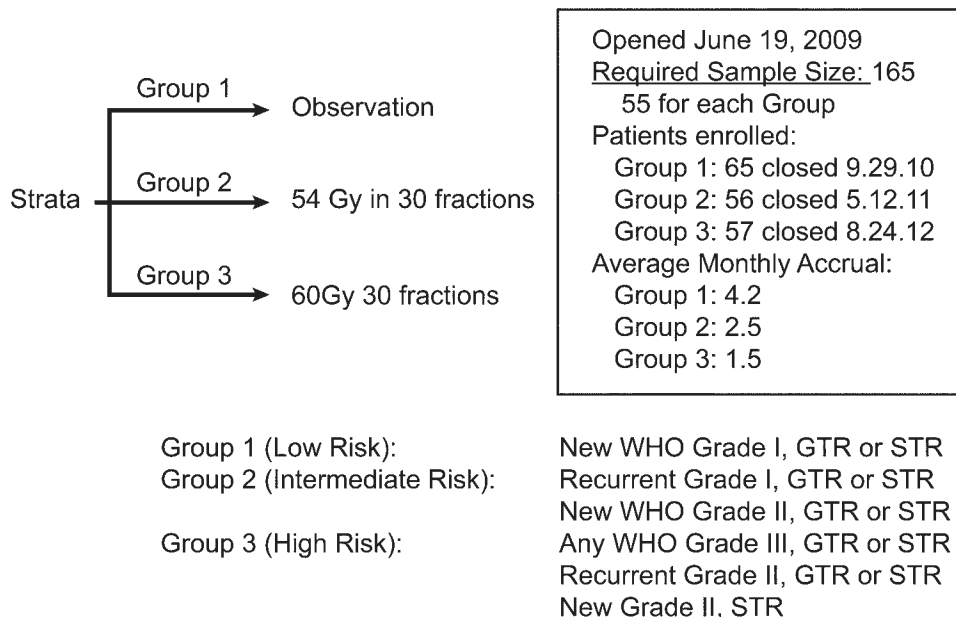


FIG. 1. Protocol schema, accrual data, and subgroup definitions.

meningioma, initial registration and central pathology review must have been completed within 24 weeks of surgery. This interval was designed to permit sufficient time for imaging at 3–4 months after surgery to confirm GTR. In the setting of a recurrent WHO Grade I tumor, there were no such constraints, and although additional resection or biopsy was encouraged, it was not a prerequisite. For patients with WHO Grade I meningioma, recurrence or progression leading to eligibility for protocol enrollment was defined clinically and radiographically at the enrolling institution, with documentary MRI submission as a prerequisite. No patient with a newly diagnosed WHO Grade I meningioma, irrespective of resection grade, was enrolled in Group 2. If further biopsy or resection was performed for recurrent tumor, submission of such specimens was mandated. The diagnosis of recurrence based solely on imaging findings was permitted, but if no additional resection was performed, submission of specimens from the prior resection was required, and tumor grade was centrally confirmed on the basis of those specimens.

Preoperative and postoperative MRI examinations were required for each patient with a WHO Grade II meningioma. For those with recurrent WHO Grade I meningioma, pre- and postoperative MRI examinations were required if surgery was performed; however, only the follow-up imaging documenting recurrence was needed if additional surgery was not undertaken.

Radiation Therapy

Every Group 2 patient received radiation therapy (RT); 3D conformal RT (3DCRT), intensity-modulated RT (IMRT), or proton therapy was permitted. The dose was 54 Gy in 30 fractions of 1.8 Gy each, delivered on consecutive weekdays. The gross tumor volume (GTV) was the

tumor or resection bed for all Group 2 patients, plus any nodular enhancement in the recurrent/progressive WHO Grade I subgroup. The GTV was determined on the basis of pre- and postoperative MRI; multiplanar T1-weighted postcontrast and precontrast T1- and T2-weighted and FLAIR images were required. Neither cerebral edema nor the dural tail were included within the GTV, but hyperostotic bone or directly invaded bone was included. The clinical target volume (CTV) was the GTV + 1 cm. It was permissible to reduce the CTV margin to 0.5 cm around natural barriers to tumor growth such as uninvolved skull. The planning target volume (PTV) was the CTV + 3 to 5 mm, depending on the daily RT localization method and reproducibility. A planning risk volume (PRV) was defined for each organ at risk (OAR)—this being the OAR + 3 mm. OAR dose limits were defined in terms of point dose ($> 0.03 \text{ cm}^3$): lenses 5 Gy, retinae 45 Gy, optic nerves 50 Gy, optic chiasm 54 Gy, and brainstem 55 Gy.

In concept, a PTV accounts for variations in setup and reproducibility. Thus, altering PTV margins to reduce OAR dose is not approved in cooperative group trials. However, in this trial and in the interest of diminishing side-effect risk in cases for which the absolute benefit of RT has not been established with Level 1 evidence, a risk-adaptive modification was permitted. If an OAR was in immediate proximity to a PTV such that the dose to the OAR could not be constrained within protocol limits, a second PTV (termed the PTV_{PRV}), could be fashioned. The PTV_{PRV} was defined as the overlap between the PTV and the particular PRV of concern. If this modification was undertaken, then it was mandated that the dose to the PTV_{PRV} be as close as permissible to 54 Gy while not exceeding the OAR dose limit. Figure 2 provides an example of the use of a PTV_{PRV}. Target volumes and OARs

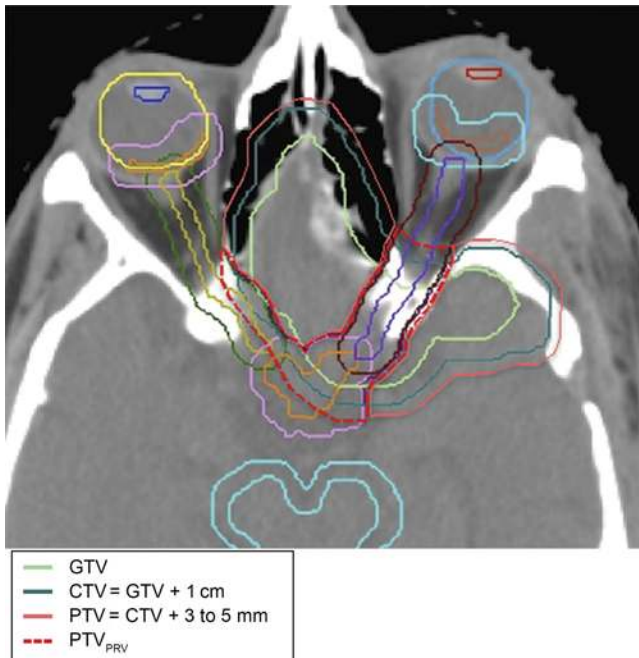


FIG. 2. Planning CT with OAR, PRV, GTV, CTV, PTV, and PTV_{PRV} contours for a patient whose WHO Grade II meningioma surrounded the anterior optic apparatus. The PTV prescription dose was 54 Gy in 30 fractions. With this example, the PTV_{PRV} prescription was lower to satisfy the optic nerve point dose constraint, while still allowing for the prescribed 54 Gy to the larger PTV.

were reviewed centrally, but this was accomplished after treatment completion.

Patient Assessment

Pretreatment evaluation included a history and physical with a neurological examination, documentation of steroid use and dosage, documentation of treatment with other hormonal agents, and MRI. Required MRI sequences were multiplanar T1-weighted postcontrast and precontrast T1- and T2-weighted and FLAIR. All patients were required to have had MRI within 12 weeks before Step 2 registration. Both pre- and postoperative MRI studies were required for all newly diagnosed patients. In the setting of recurrent or progressive meningioma without salvage surgery, MRI documentation of recurrence or progression was required. The determination of progression was at the discretion of the enrolling institution. Postoperative MRI studies must have been completed within 12 weeks of surgery, although additional confirmatory imaging was permitted so long as initial registration and central pathology review were completed within 24 weeks of surgery.

A posttreatment clinical assessment was required 1 month after RT, every 3 months for 3 years, and then at least yearly for 10 years. Mini-Mental State Examination (MMSE) and documentation of corticosteroid and other hormonal agent use followed the same schedule. Response was evaluated according to criteria similar to RECIST (Response Evaluation Criteria in Solid Tumors), modified to better apply to meningioma. Continual no evidence of disease (CNED) was ascribed when there was no measurable meningioma, stable disease (SD) when measurable

tumor remained unchanged or increased in maximum diameter by less than 20%, and progressive disease (PD) when tumor increased in any diameter by 20% or more. Neurological progression was defined as new or progressive neurological deficits without measurable growth; this was not observed in any patient. Adverse event evaluations and brain MRI were stipulated at 3 months post-RT, then at least every 6 months for 3 years, then at least yearly for 10 years.

Statistical Methodology

The primary endpoint of this Phase II trial was PFS at 3 years (3-year PFS) after registration. For this initial evaluation, we report the primary endpoint and secondary endpoints of 3-year OS and AEs. The protocol opened for enrollment on June 19, 2009. The full study closed on August 24, 2012, but accrual to the intermediate-risk cohort (Group 2) was completed on May 12, 2011 (see Fig. 1). The analysis date for the present report was January 5, 2016. Findings regarding pathological concordance have been published separately.⁴⁰

Based on historical data, the expected 3-year PFS for this intermediate-risk cohort was estimated at 70% with GTR alone and at 90% following GTR + RT.⁴² With a 1-sided significance level of 0.05, a sample of 50 eligible patients would provide a statistical power of over 95% to detect the projected 20% absolute increase using a 1-sample test on proportion, while providing a greater number of patients for the histopathological and molecular correlative part of the study. The study required the accrual of 55 patients to adjust for a 10% ineligibility rate.

PFS was measured from the date of study entry to the date of progression or death, or otherwise the date of the last follow-up on which the patient was reported alive and free of disease progression. OS was measured from the date of study entry to the date of death, or otherwise the date of the last follow-up on which the patient was reported alive. Outcomes were estimated using the Kaplan-Meier method. Time to tumor progression was calculated using the cumulative incidence function, with death without progression treated as the competing risk. The incidence rates of Grade 2+ acute and late AEs for dermatological/skin, neurological, and ocular/visual (excluding alopecia) categories, individually and combined, were reported for all eligible patients who received protocol treatment. Acute AEs were defined as AEs that occurred ≤ 90 days from the start of RT, and late AEs as those that occurred > 90 days from the start of RT.

We hypothesized that IMRT would minimize treatment-related late toxicities in the dermatological/skin, neurological, and ocular/visual categories compared with 3DCRT. Recognizing that there are no reports of prospectively collected AEs using NCI (National Cancer Institute) Common Toxicity Criteria for meningioma treated with 3DCRT, we tested the hypothesis of reduced toxicities following IMRT by prospectively comparing the late AEs following IMRT in this study with those following 3DCRT in the low-grade glioma patients on NRG Oncology RTOG 0424, which used the same dose and fractionation and similar definitions of treatment volume. Although 3DCRT was allowed for treatment of intermedi-

ate-risk patients in the present study, it was expected that 80% to 90% of the intermediate-risk patients would be treated with IMRT. With 40 IMRT-treated patients, only large differences could be detected with sufficient power. Therefore, a reduction of 10% or more in the worst overall Grade 2+ AEs would be considered as supporting the hypothesis.

Results

Patient Characteristics, Protocol Enrollment, and Treatment Delivery

The study was activated in June 2009, and accrual for the intermediate-risk group was completed in February 2011, 1 year ahead of the projected schedule. Of the 56 patients enrolled, 52 (92.9%) were eligible and treated with protocol-specified RT (Fig. 3). Pretreatment and tumor characteristics for the eligible patients are listed in Table 1. Of these 52 patients, 36 (69.2%) had undergone GTR for newly diagnosed WHO Grade II meningioma, and 16 (30.8%) had a recurrent WHO Grade I tumor. With the RT technologies permitted in this study, 44 patients (84.6%) received IMRT, 8 (15.4%) received 3DCRT, and none were treated with proton therapy. This is the first NRG Oncology RTOG trial of brain cancer treatment with protocol-specific IMRT parameters. The majority of the patients were treated per protocol or with acceptable variations. A PTV_{PRV} was used in 19 patients, principally to limit dose to the optic apparatus. No statistical association was found between protocol adherence or use of the PTV_{PRV} target definition option and progression risk.

PFS, OS, and Local Failure

The median follow-up time for eligible patients still alive was 3.7 years, with a range from 0.4 to 4.9 years. Of the 52 eligible patients who received protocol treatment, 4 (7.7%) withdrew less than 3 years after study entry without disease progression. Based on the 48 patients who were

evaluable for the primary endpoint, the 3-year PFS rate was 93.8% ($p = 0.0003$). There was no significant difference in PFS between the intermediate-risk subgroups of WHO Grade II with GTR and WHO Grade I with recurrent/progressive meningioma ($p = 0.52$, HR 0.56, 95% CI 0.09–3.35). Within 3 years, 3 patients experienced events affecting the PFS: 1 patient with WHO Grade II meningioma died of disease, 1 patient with WHO Grade II meningioma had disease progression and remained alive, and 1 patient with recurrent WHO I meningioma died of undetermined cause without disease progression. Neither median PFS nor median survival time was reached, with a 3-year PFS rate of 93.8% and a 3-year OS rate of 96.0%. The respective Kaplan-Meier PFS and OS curves are shown in Figs. 4 and 5.

Two patients experienced local failure within 3 years; both had WHO Grade II tumors that were treated with GTR. This corresponds to a 3-year local failure rate of 4.1%. After 3 years, 2 additional patients experienced disease progression; one had a recurrent WHO Grade I meningioma, and the other a newly diagnosed WHO Grade II tumor. Both remain alive as of this writing. The cumulative incidence curve for time to local failure is shown in Fig. 6. Of the 4 patients with progression, 3 were treated with re-resection and systemic therapy; for the remaining patient, no off-protocol therapy was reported following progression.

Adverse Events

According to the prespecified analysis of treatment-related AEs (dermatological/skin, neurological, and ocular/visual) definitely, probably, or possibly related to protocol treatment, reported AEs were limited to Grade 1 or 2, and there were no Grade 3 events or higher. In particular, with respect to acute AEs, 5 patients (10.9%) experienced Grade 2 AEs and 10 (21.7%) experienced Grade 1 AEs as the AEs of highest grade. Regarding late AEs with the same reported relationship to protocol treatment, 13 pa-

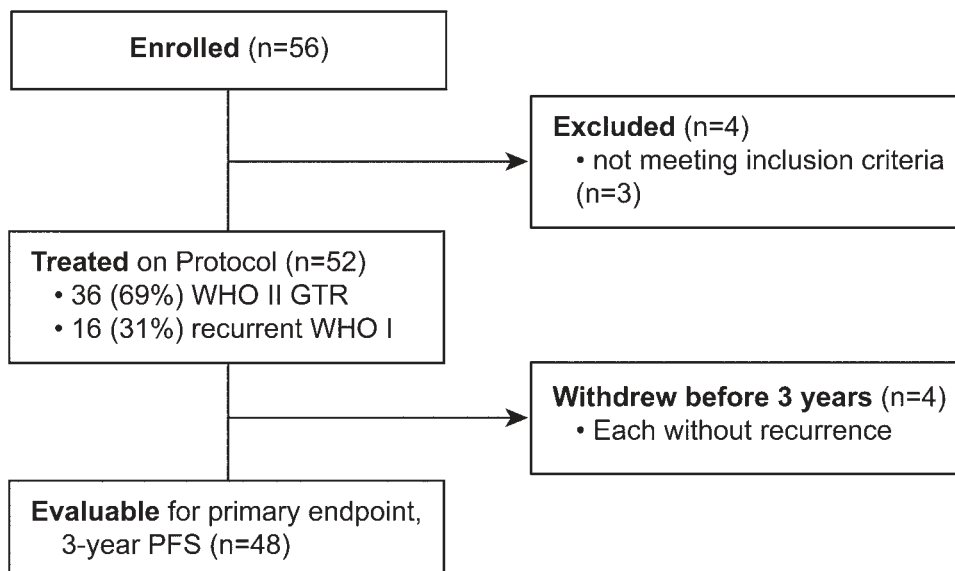


FIG. 3. CONSORT diagram for the intermediate-risk group (Group 2).

TABLE 1. Patient and tumor characteristics in 52 cases in which patients received the protocol treatment

| Characteristic | Group 2 |
|---|-----------|
| Age (years) | |
| <50 | 20 (38.5) |
| ≥50 | 32 (61.5) |
| Sex | |
| Male | 20 (38.5) |
| Female | 32 (61.5) |
| Race | |
| American Indian/Alaska Native | 1 (1.9) |
| Asian | 1 (1.9) |
| Black or African American | 4 (7.7) |
| Native Hawaiian or other Pacific Islander | 0 (0.0) |
| White | 44 (84.6) |
| Unknown or not reported | 2 (3.8) |
| Ethnicity | |
| Hispanic or Latino | 4 (7.7) |
| Not Hispanic or Latino | 45 (86.5) |
| Unknown (individuals not reporting ethnicity) | 3 (5.8) |
| Pretreatment Zubrod Performance Status | |
| 0 | 39 (75.0) |
| 1 | 13 (25.0) |
| Pretreatment neurological function | |
| No symptoms | 27 (51.9) |
| Minor symptoms | 21 (40.4) |
| Moderate symptoms | 4 (7.7) |
| Status of tumor | |
| Initial diagnosis | 36 (69.2) |
| Recurrent | 16 (30.8) |
| Extent of resection (Simpson grade)* | |
| At initial surgery | |
| Grade I | 7 (13.5) |
| Grade II | 17 (32.7) |
| Grade III | 8 (15.4) |
| Grade IV | 2 (3.8) |
| Unknown | 2 (3.8) |
| At recurrence | |
| Grade I | 0 (0.0) |
| Grade II | 0 (0.0) |
| Grade III | 0 (0.0) |
| Grade IV | 3 (5.8) |
| Diagnosis by imaging only | 13 (25.0) |
| Histology† | |
| At initial surgery | |
| WHO Grade I | 2 (3.8) |
| WHO Grade II | 32 (61.5) |
| WHO Grade III | 1 (1.9) |
| Unknown | 1 (1.9) |
| At recurrence | |
| WHO Grade I | 2 (3.8) |

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TABLE 1. Patient and tumor characteristics in 52 cases in which patients received the protocol treatment

| Characteristic | Group 2 |
|------------------------------------|-----------|
| Histology† (<i>continued</i>) | |
| At recurrence (<i>continued</i>) | |
| WHO Grade II | 1 (1.9) |
| WHO Grade III | 0 (0.0) |
| Identified by imaging only | 13 (25.0) |
| Lateralization of tumor | |
| Right | 20 (38.5) |
| Left | 25 (48.1) |
| Bilateral | 7 (13.5) |
| Unknown | 0 (0.0) |

Data are numbers of cases or patients (%) unless otherwise indicated.

* Simpson resection grades are per enrolling institution.

† WHO grades are per central review.

tients (25.5%) and 7 patients (13.7%) experienced Grade 2 and Grade 1 AEs, respectively, as the AEs of highest grade. Of the 13 patients with late Grade 2 AEs, 1 was dermatological and 12 were neurological. Some patients with Grade 2 neurological AEs experienced more than 1 AE. The most commonly reported late Grade 2 neurological events were seizure ($n = 6$), speech disorder ($n = 3$), depression ($n = 3$), trigeminal nerve disorder ($n = 2$), olfactory nerve disorder ($n = 2$), peripheral sensory neuropathy ($n = 2$), memory impairment ($n = 2$), and dizziness ($n = 2$). Some patients with Grade 1 late AEs experienced more than 1 AE as well. Seven patients had Grade 1 late AEs, but the total number of AEs they experienced was 15: 2 dermatological, 6 ocular/visual, and 7 neurological. The most common Grade 1 neurological events, in descending order of likelihood, were dizziness, memory impairment, peripheral sensory neuropathy, and peripheral motor neuropathy. The most common ocular/visual events were blurred vision, flashing vision, dry eye, and diplopia.

For AEs with any relationship to protocol treatment, the reported highest-grade AE was Grade 1 in 4 patients (7.7%), Grade 2 in 35 (67.3%), and Grade 3 in 8 (15.4%). There were no reported Grade 4 or 5 events. Among the reported Grade 3 AEs, 3 patients had auditory complaints without categorical evidence of audiometric loss, 2 had neurological complaints, 1 had pain, 1 developed infection, 1 reported skin complaints, and 1 had gastrointestinal symptoms.

Functional outcomes were measured by Zubrod Performance Status, Mini-Mental State Examination (MMSE), and neurological function score. The distributions of these outcomes at baseline, end of RT, and Year 3 are shown in Table 2. For each of these measures, the majority of the patients had either stable or improved status at the end of RT and Year 3.

Intensity-Modulated Radiation Therapy

We hypothesized that IMRT would minimize late toxicity compared with 3DCRT. Recognizing that there are

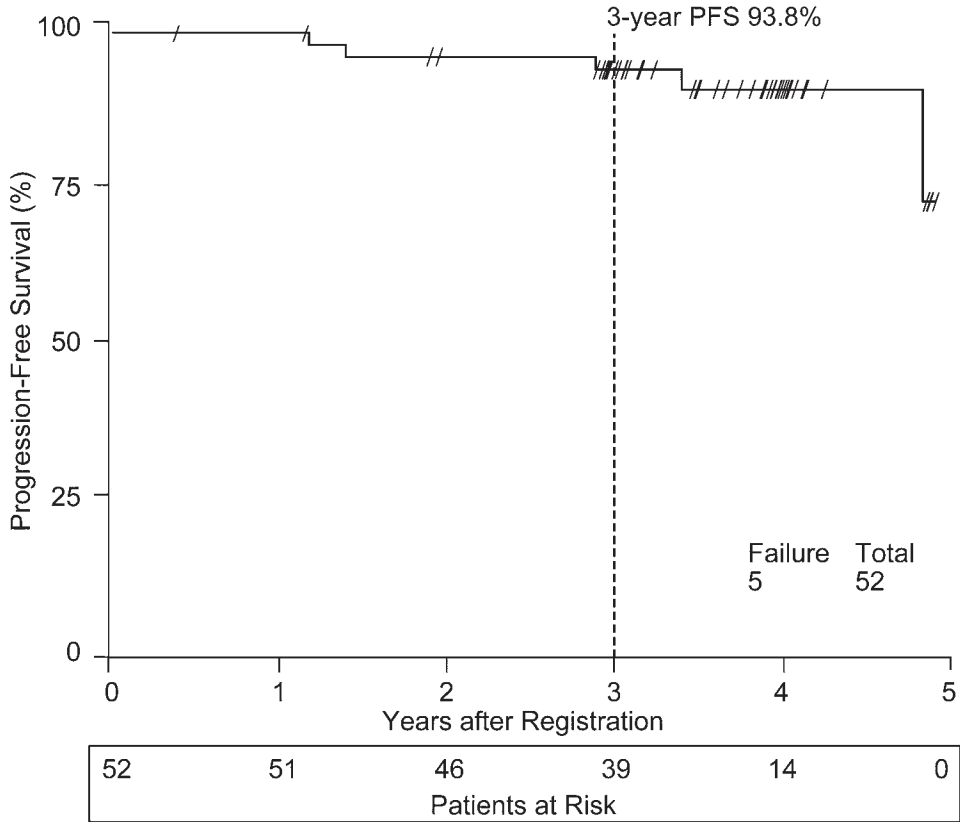


FIG. 4. Progression-free survival, determined with progression and/or death as events. The 3-year PFS rate was 93.8% (95% CI 87.2%–100%).

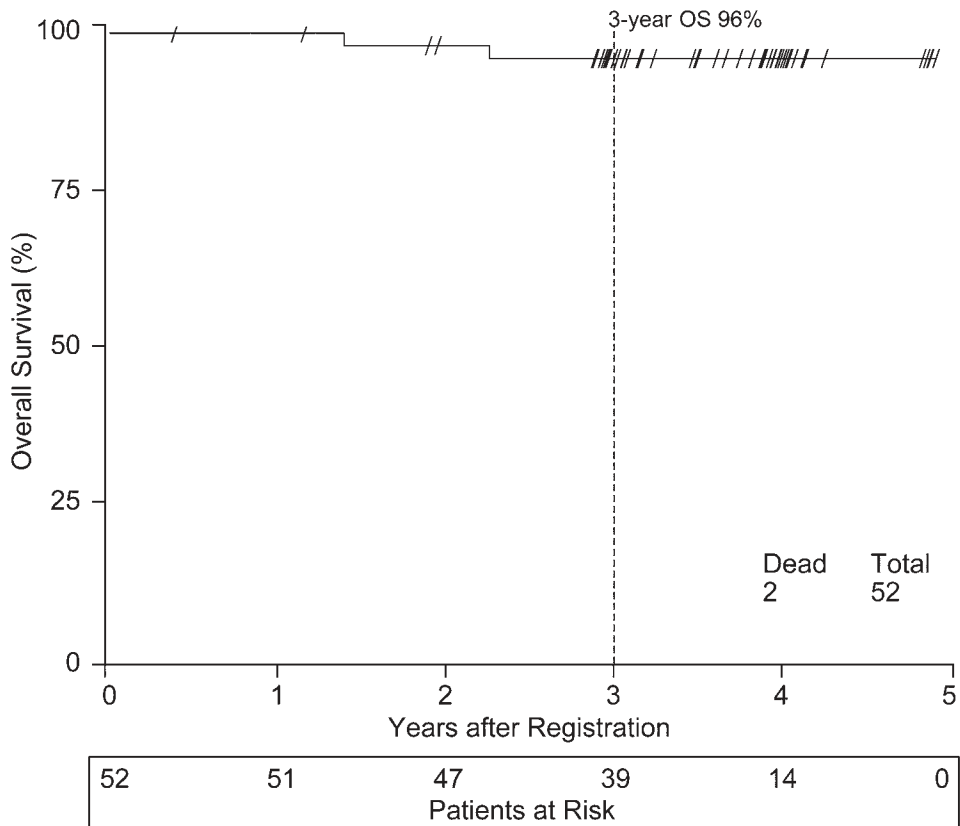


FIG. 5. Overall survival. The 3-year OS rate was 96% (95% CI 90.4%–100%).

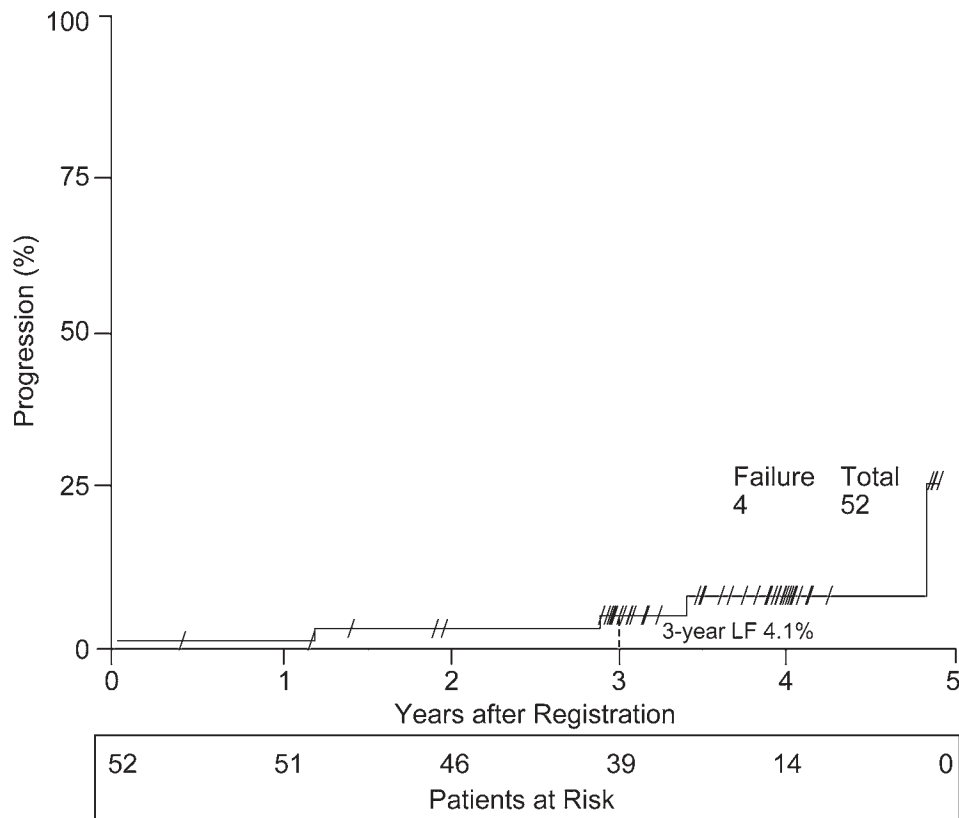


FIG. 6. Local failure. The 3-year local failure (LF) rate was 4.1% (95% CI 0.7%–12.5%).

no reports of prospectively collected AEs using NCI Common Toxicity Criteria for 3DCRT for meningioma, we determined to prospectively test the hypothesis of reduced IMRT toxicity by prospectively comparing late AEs following IMRT on NRG Oncology RTOG 0539 to 3DCRT on NRG Oncology RTOG 0424, a high-risk low-grade glioma study that used the same dose and fractionation and similar definitions of treatment volume. A reduction of 10% or more in worst overall Grade 2+ AEs was considered supportive. Initial results of the NRG Oncology RTOG 0424 trial have been published,¹¹ with additional data supplied by NRG Oncology.

Of the 44 intermediate-risk patients who received IMRT, 43 were evaluable for late AEs. Eleven (25.6%) of these 43 patients developed Grade 2+ late AEs in the dermatological/skin, neurological, or ocular/visual realms that were deemed definitely, probably, or possibly related to protocol treatment, with 1 patient (2.3%) who experienced a Grade 2 AE in the dermatological/skin realm and 10 patients (23.3%) who had Grade 2 AEs in the neurological realm. This showed a 17.4% reduction in the rate of treatment-related Grade 2+ late AEs in those categories with IMRT (Table 3). According to the statistical design described above, these results are considered supportive of the hypothesis that IMRT minimizes late toxicity.

Discussion

Meningiomas are the most frequently reported primary intracranial neoplasms, accounting for 36.1% of intracra-

nial tumors, compared with 15.4% for glioblastomas and 28.4% for all gliomas.³³ The identification of meningiomas has been increasing over the last several decades, likely related to improved imaging and an aging population rather than actual changes in incidence.⁷

In older series, approximately 90% of meningiomas were classified as benign, 5%–10% atypical, and less than 5% anaplastic or malignant.²⁰ Even in a recent CBTRUS (Central Brain Tumor Registry of the United States) report, WHO Grade II tumors accounted for only 4.2% of all newly diagnosed meningiomas.²⁴ That report, however, was based on a database query and did not include regrading of pathology specimens. Nevertheless, over its study period of 2004–2010, it did document an annual increase in WHO Grade II meningioma of 3.6%. With improved adoption of modern WHO standards, an increased incidence of WHO Grade II histology and improved correlations between histopathology and clinical outcomes have been documented. Perry and colleagues updated grading criteria and found that approximately 20%–25% of meningiomas fall into the intermediate prognostic group.^{38,39} These grading parameters were adopted by the WHO for their 2000 criteria.

The 2007 and most recent 2016 WHO criteria have added brain invasion as a criterion for Grade II. With these new criteria, the proportion of meningiomas that are classified as WHO Grade II tumors has increased to approximately 25%,^{37,47} even reaching 35% in a single-institution report by Pearson et al.³⁵ and 30% per Backer-Grøndahl and colleagues.³

TABLE 2. Functional outcome scores

| Measure | Time Point | | |
|----------------------------------|------------|------------|------------|
| | Baseline | End of RT | Year 3 |
| Neurological function | | | |
| No. of cases w/ data available | 52 | 52 | 42 |
| No symptoms | 27 (51.9%) | 21 (40.4%) | 22 (52.4%) |
| Minor symptoms | 21 (40.4%) | 26 (50.0%) | 9 (21.4%) |
| Moderate symptoms | 4 (7.7%) | 3 (5.8%) | 2 (4.8%) |
| Unknown | 0 | 2 (3.8%) | 9 (21.4%) |
| MMSE total score | | | |
| No. of cases w/ data available | 52 | 48 | 27 |
| Median | 30 | 29 | 30 |
| Range (min–max) | 24–30 | 23–30 | 26–30 |
| IQR | 28–30 | 28–30 | 29–30 |
| Zubrod Performance Status | | | |
| No. of cases w/ data available | 52 | 52 | 42 |
| 0 | 39 (75.0%) | 35 (67.3%) | 26 (61.9%) |
| 1 | 13 (25.0%) | 12 (23.1%) | 4 (9.5%) |
| 2 | 0 | 1 (1.9%) | 0 |
| Unknown | 0 | 4 (7.7%) | 12 (28.6%) |

IQR = interquartile range.

Histopathological grading is a critical element guiding management decisions for patients with meningioma. Large series have independently confirmed tight associations between WHO 2000/2007 histopathological grade and patient outcomes.^{8,9,17,31,37} A secondary analysis from NRG Oncology RTOG 0539, a comparison of histopathological concordance between the enrolling institution and central review, was recently published.⁴⁰ We found a concordance rate of 87.8% for WHO Grade II, statistically inferior to the concordance for WHO Grades I and III, for which the rates were, respectively, 93.0% and 93.6% ($p < 0.0001$). Twenty-two cases were reclassified after central review. The most common reclassification was from WHO Grade I at the enrolling institution to WHO Grade II after central review (9 cases), although 8 WHO Grade II cases were reclassified as WHO Grade III, and 2 WHO Grade II cases were reclassified as WHO Grade I. Additionally, 2 cases graded as WHO Grade III by the enrolling institution were reclassified as WHO Grade II. In only 1 case did the reclassification not involve WHO Grade II: a tumor diagnosed as WHO Grade I at the enrolling hospital was identified as WHO Grade III on central review.

These findings indicate that the current meningioma classification system is largely interpretable and congruous among pathologists at typically large institutions such as those accruing to this protocol. This was found to be the case with respect to overall meningioma grade, but subjectivities remain in component elements of grading. For instance, there was only slight agreement on focal papillary and focal clear cell; fair agreement for focal rhabdoid, chordoid, and small cells; and moderate agreement on hypercellularity, macronucleoli, sheeting, diffuse papillary, anaplasia, and mitoses ≥ 4 per 10 high-power fields.⁴⁰ The number of mitoses is a critical element, as it is the most

TABLE 3. Comparison of CTCAE version 3 Grade 2+ late AEs from IMRT in RTOG 0539 (meningioma) versus 3DCRT in RTOG 0424 (low-grade glioma)

| Variable | RTOG 0539 (IMRT) | RTOG 0424 (3DCRT) |
|----------------------------|------------------|-------------------|
| No. of patients | 43 | 52 |
| AEs (% of patients) | | |
| Grade 2+ | 25.6 | 43 |
| Grade 2 | 25.6 | 33 |
| Grade 3 | 0 | 8 |
| Grade 4 | 0 | 2 |

CTCAE = Common Terminology Criteria for Adverse Events.

common differentiating factor for meningioma grade. Improvements in concordance may require clarifications of the criteria exhibiting lower rates of interobserver concordance and the development of biomarkers predictive of clinical outcome. These are secondary goals of the present trial, awaiting further data maturity and recurrence events.

For patients with WHO Grade I tumors, a Simpson Grade I resection is often curative. Control rates drop somewhat for Simpson Grades II and III, although resections of Simpson Grades I–III are often considered gross total and definitive. With sufficient follow-up, however, recurrence many years following a GTR is common. Retrospective studies with prolonged follow-up have shown progression rates of 15%–40% at 10 years^{44,45} and up to 60% at 15 years.⁴⁴ Rates in this range have been confirmed in more recently published series as well.^{13,28}

Recurrent meningiomas of any grade behave more aggressively than initially diagnosed tumors. After first salvage treatment for a WHO Grade I meningioma, considerably higher rates of subsequent progression have been reported, particularly after surgery alone.^{29,30,36,45,46} For recurrent Grade I meningiomas treated with re-resection, a 3-year local progression risk of 55%–60% is reported.^{30,46} Stafford et al. identified a 25% 10-year local progression risk after initial diagnosis and essentially the same risk at 2 years (24%) after first recurrence.⁴⁵ With specific reference to sphenoid wing meningiomas involving the optic apparatus, often treated with subtotal resection (STR), Peele et al. found a mean interval to first recurrence/progression of 4.4 years, but a considerably shorter mean interval of 14 months from first recurrence to subsequent recurrence or progression.³⁶ Mehdorn published an experience with 463 patients, noting that first recurrences were found at a mean of 65 months after surgery, whereas second recurrences developed at a mean of 34 months after the first occurrence.²⁹ This approximates the rates of first recurrence following gross-total resection of a WHO Grade II meningioma.

With such background data, we formulated an intermediate-risk group composed of patients with a newly diagnosed gross-totally resected WHO Grade II meningioma or with a recurrent WHO Grade I tumor irrespective of resection extent. These patients formed Group 2 in the trial and are the subjects of this report. The results we have observed to date support our decision to include patients with WHO Grade II tumors that have been gross-totally resected as well as patients with recurrent WHO Grade I

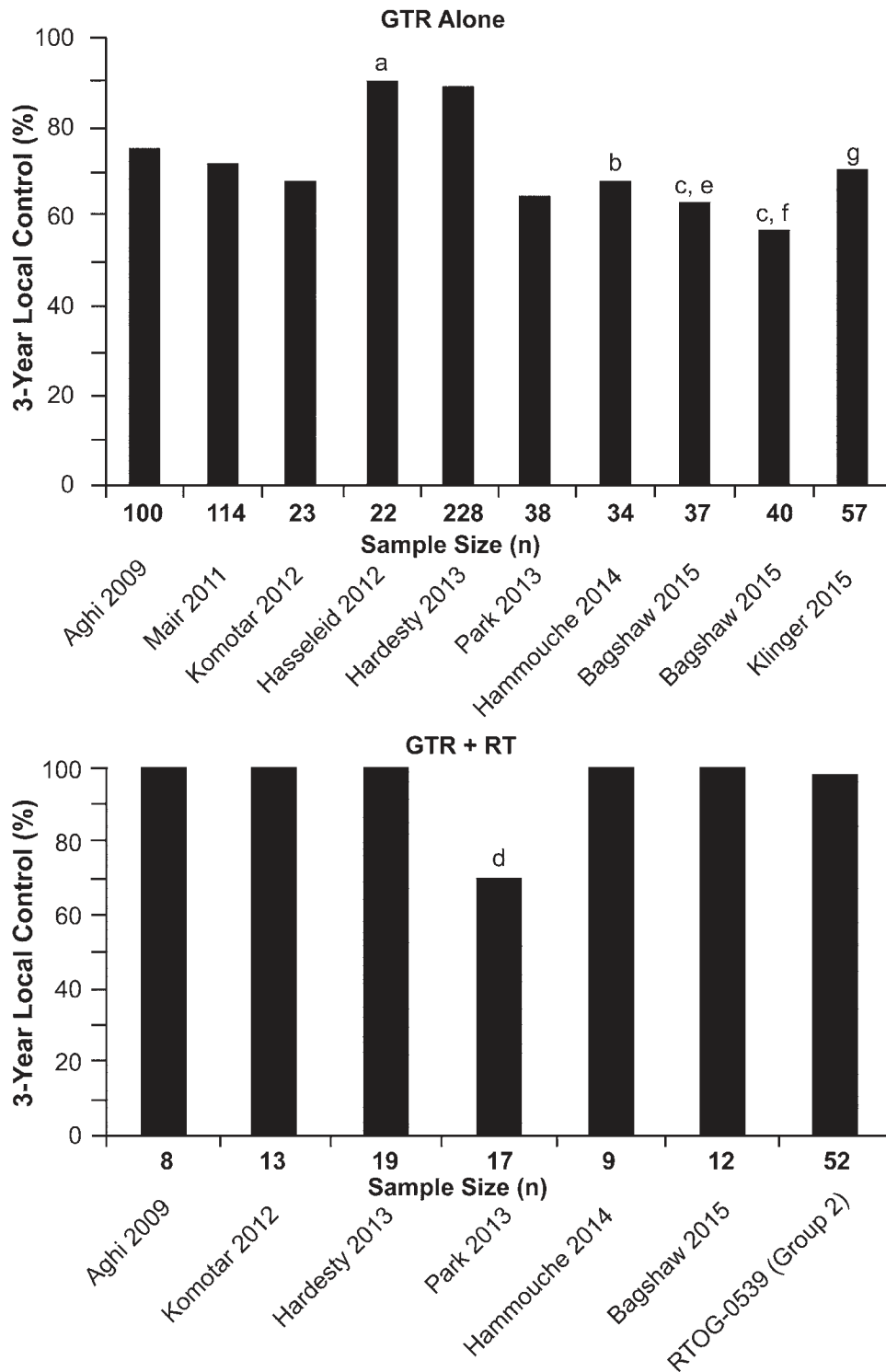


FIG. 7. Three-year local control after GTR alone (**upper**) versus GTR plus RT (**lower**). ^aConvexity meningioma only, 90% 3-year retreatment-free survival. ^bCrude 4-year local control after GTR. ^c63% for Simpson Grade I resection, 57% for Simpson Grades I–III. ^dPre-3DCRT methods used in 18 (67%) of 27 patients who received RT from 1997 to 2011. ^eSimpson Grade I. ^fSimpson Grades I–III. ^gSimpson Grades I and II; 3 of 57 patients received early adjuvant therapy.

tumors in the intermediate-risk group, albeit with recognition that few recurrent events have occurred in this combined population to date. Moreover, the results of this prospective study corroborate retrospective analyses, which

suggest that RT should play a role in the management of intermediate-risk meningioma. Three-year PFS rates from retrospective reports using WHO 2000–2007 grading criteria are shown in Fig. 7;^{1,4,14–16,22,23,26,34} included are 10 re-

ports in which patients were treated with GTR alone and 7 in which they were treated with GTR + RT.

Aghi et al. described 108 patients with atypical meningioma who underwent Simpson Grade I resection, 100 of whom underwent surgery alone and 8 of whom had surgery and EBRT to a mean RT dose of 60.2 Gy. The 5-year recurrence with GTR alone was 45%, but 0% with surgery and RT ($p = 0.1$).¹ Komotar et al.²³ reported 45 patients with atypical meningioma and a Simpson Grade I to II resection: 32 (71%) had a GTR alone, and 13 (29%) had a GTR and RT, median RT dose 59.4 Gy. After GTR alone, 13 patients (41%) had a recurrence at a median of 19 months. After GTR plus RT, 1 patient (8%) had a recurrence at 52.5 months, for respective 6-year actuarial recurrence risks of 65% versus 20% ($p = 0.085$).²³

Park and colleagues³⁴ analyzed the role of RT following resection of atypical meningioma in 82 patients. Fifty-six were treated with initial surgery alone and 27 with surgery followed by RT. The median dose of RT was 61.2 Gy. Defining GTR as Simpson Grade I to II, they found that postoperative RT significantly improved PFS for the entire cohort, although not for patients with GTR ($p = 0.858$). Three-year PFS was 65% after GTR alone and 71% following GTR + RT, but at 5 years PFS remained 65% with GTR alone and fell to 53% after GTR + RT.³⁴ This differs from the other recent reports, perhaps owing in part to patient selection, in part to the determination of GTR in their analysis based on the surgeon's report without the requirement for corroborating postoperative imaging, and in part to the fact that many of their patients (18 [67%] of 27) received RT prior to the incorporation of 3D image-based treatment planning. Goldsmith and colleagues reported that CT- and MRI-based treatment planning resulted in significantly superior tumor control.¹²

Reports using protons further illuminate outcomes with larger field RT following STR, and provide information that may be important for dose-response assessment for WHO Grade II meningioma. Boskos et al. detailed 24 patients with high-grade meningioma (79% WHO Grade II), typically following STR. Cause-specific survival at 5 years was 80% with > 60 Gy versus 24% with ≤ 60 Gy ($p = 0.01$), with a trend toward further improvement with doses > 65 Gy ($p = 0.06$).⁵ Hug et al. reported on 15 patients treated with 40 to 72 Cobalt Gray Equivalent (CGE). The 5-year local control rate was 90% with > 60 CGE and 0% with ≤ 60 CGE.¹⁹

Stereotactic radiosurgery (SRS) has become standard in the management of meningioma, and has resulted in favorable outcomes in the primary or adjuvant treatment of WHO Grade I or presumed Grade I tumors.⁴¹ We did not include SRS as an option with this trial on 4 accounts: 1) patients with newly diagnosed WHO Grade I meningioma were observed even following STR; 2) there was no impetus to include SRS as an option for gross-totally resected WHO Grade II meningioma because no traditional SRS target would be available; 3) recurrent WHO Grade I and newly diagnosed gross-totally resected Grade II meningiomas display similar recurrence rates and patterns of progression;³² and 4) SRS for WHO Grade II meningioma has met with high rates of recurrence outside the SRS volume, although in or near (e.g., within 2 cm of) the resection bed.^{2,41}

Huffmann et al. reviewed 15 patients treated with SRS, median dose 16 Gy. At 18 to 36 months, crude local control was 60%. Six (40%) progressed, 1 in field, but all within the resection bed.¹⁸ Choi et al. reviewed 25 patients with atypical meningioma, median SRS dose 22 Gy in 1–4 fractions. Recurrence occurred in 9: 3 within the targeted region, 5 elsewhere in the resection bed, and 1 regionally.⁶ These findings suggest that the appropriate target volume for atypical meningioma extends beyond the enhancing tumor, and includes the entire resection bed. Future patterns of failure analyses are needed before definitive guidelines can be developed.

NRG Oncology RTOG 0539 employed a fractionated external beam RT (EBRT) dose of 54 Gy in 30 fractions and found that this was well tolerated, with a favorable AE profile and no serious AEs. This RT dose was chosen over a decade ago, at which time arguments against the use of RT for an intermediate-risk meningioma patient were even more vociferous than at present. However, we now have a larger volume of literature to draw from, suggesting, as described in the aforementioned reports, that higher doses may provide improved PFS.

EORTC 22042–26042 (accrual completed, pending publication), a Phase II trial of postoperative RT for patients with atypical or malignant meningioma, employed 60 Gy following a GTR and added a 10-Gy boost after STR. The definition of GTR as well as target volumes were very similar to those used in the present trial (NRG Oncology RTOG 0539). GTR was defined as Simpson Grade I–III. RT targets included the resection bed with any remaining enhancing tumor, with a 10-mm margin added for subclinical extension, and a planning margin of 5 mm with conformal or intensity-modulated RT, permitting smaller margins (1–5 mm) if stereotactic methods were employed. This trial will provide further guidance regarding dosing for atypical meningioma, especially once long-term follow-up data are available from both the EORTC and NRG Oncology RTOG trials and comparative outcomes can be assessed.

Conclusions

NRG Oncology RTOG 0539 has demonstrated that meningioma patients can be successfully enrolled in large cooperative group trials. Indeed, accrual was ahead of schedule. It also shows that patients with intermediate-risk meningioma have limited risk of local failure (4.1%) and excellent rates of PFS (93.8%) and OS (96%) at 3 years when treated with RT. Comparison with historical control data suggests that 3-year PFS for intermediate-risk patients is better with RT than with observation. The results of this single-arm study support enrollment to a definitive, Phase III trial evaluating RT versus observation following GTR of WHO Grade II meningioma. In this respect, 2 Phase III trials are presently open to enrollment internationally, NRG BN-003 (<http://clinicaltrials.gov/ct2/show/NCT03180268>) and the ROAM trial (<http://roam-trial.org.uk>).

Acknowledgments

The late Dr. Bruce Dean, Barrow Neurological Institute, was

the neuroradiologist instrumental in the trial design. He reviewed all images at protocol inception. It is with gratitude that we acknowledge his contributions.

This project was supported by grants U10CA21661, U10CA180868, and U10CA180822 from the National Cancer Institute to RTOG (now NRG Oncology). In addition, NRG Oncology RTOG 0539 was supported by an ARRA (American Recovery and Reinvestment Act) grant obtained from the NIH by Dr. Rogers.

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Disclosures

Dr. Vogelbaum reports patent and royalty interests in Infuseon Therapeutics, Inc., and receiving personal fees from Neuralstem and from Pharmaco-Kinesis, outside the submitted work. Dr. De Groot reports receiving personal fees from Genentech, VBL Therapeutics, Deciphera Therapeutics, Celldex Therapeutics, Foundation Medicine, Monteris Medical, Omniox, and Oxigene, outside the submitted work; grants from Deciphera Therapeutics, Novartis, and Eli Lilly; and stock ownership in Ziopharm Oncology (also spouse's employer). Dr. Knisely reports receiving support for attending scientific meetings from Brainlab AG, Elekta AB, and Cyber Medical Corporation and an honorarium from Brainlab AG. Dr. Mehta reports receiving personal fees from AbbVie, Novelos, Phillips, BMS, Celldex, Roche, Elekta, Novartis, Cavion, Novocure, Pharmacyclics, and Monteris; and grants from Novelos and Novocure, outside the submitted work.

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Conception and design: Rogers, Vogelbaum, Alleman, Brachman, Mehta. Acquisition of data: Rogers, Vogelbaum, Ashby, Modi, Galvin, Brachman, Jenrette, De Groot, Bovi, Werner-Wasik, Knisely, Mehta. Analysis and interpretation of data: Rogers, Zhang, Vogelbaum, Perry, Alleman, Brachman, Jenrette, De Groot, Bovi, Werner-Wasik, Knisely, Mehta. Drafting the article: Rogers, Zhang, Vogelbaum, Perry, Galvin, Brachman, Knisely, Mehta. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rogers. Statistical analysis: Zhang.

Supplemental Information

Previous Presentations

Portions of this work were previously presented at the 57th Annual Meeting of the American Society of Therapeutic Radiology and Oncology, San Antonio, Texas, October 2015.

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