

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0539

PHASE II TRIAL OF OBSERVATION FOR LOW-RISK MENINGIOMAS AND OF RADIOTHERAPY FOR INTERMEDIATE- AND HIGH-RISK MENINGIOMAS

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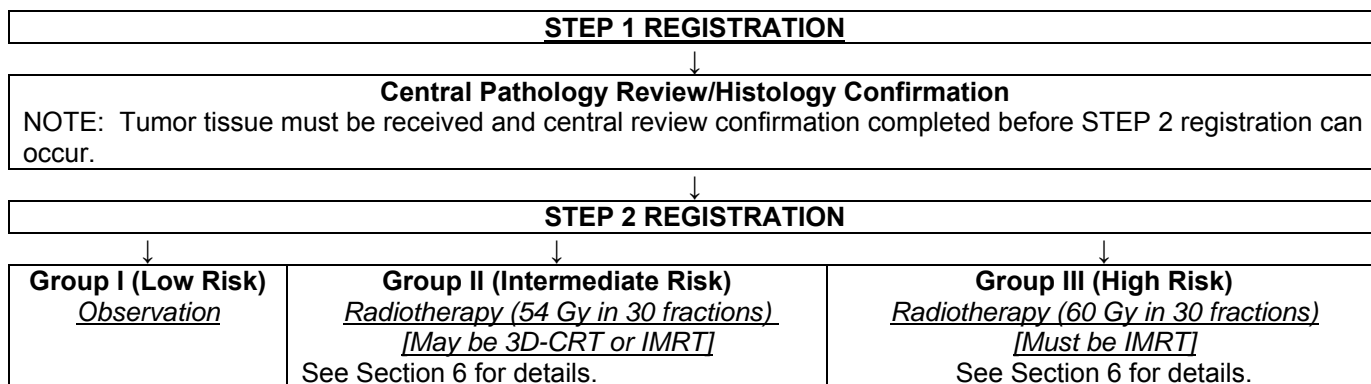
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SCHEMA



INSTITUTION MUST BE CREDENTIALLED PRIOR TO ENROLLMENT (See Section 5.0)

Patient Population: (See Section 3.0 for Eligibility)

Histopathologically confirmed meningioma, **confirmed by central pathology review prior to STEP 2 registration**. Risk categories are defined as follows:

- **Low (Group I):** Patients with a newly diagnosed gross totally resected (Simpson's grade I, II, or III resections with no residual nodular enhancement on postoperative imaging) or subtotally resected (residual nodular enhancement or Simpson grade IV or V excision) World Health Organization (WHO) grade I meningioma. The extent of resection will be based upon the neurosurgeon's assessment and postoperative MR imaging.
- **Intermediate (Group II):** 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 will be assessed according to Simpson's grade on the same basis described above for the low-risk group.
- **High (Group III):** Patients with high-risk features including a newly diagnosed or recurrent WHO grade III meningioma of any resection extent; a recurrent WHO grade II meningioma of any resection extent; or a newly diagnosed subtotally resected WHO grade II meningioma. Resection extent will be recorded on the same basis described above for the low-risk group.

Required Sample Size: 165 (55 Group I, 55 Group II, 55 Group III)
(Based on cases entered on STEP 2 registration)

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ELIGIBILITY CHECKLIST—STEP 1 (6/19/09)

Case # _____

(page 1 of 4)

_____(Y) 1. Is the patient suspected to have WHO grade I, II, or III meningioma?

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

The following questions will be asked at study registration for STEP 1:

- _____ 1. Name of institutional person registering this case
- _____(Y) 2. Has the eligibility checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific consent form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.
- _____(IMRT/3D-CRT) 18. Is the patient going to be treated with IMRT or 3D-CRT?

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ELIGIBILITY CHECKLIST—STEP 2 (6/19/09)

Case # _____
(assigned in Step 1)

(page 2 of 4)

- _____ (Y) 1. Does the patient have histologically confirmed WHO grade I, II, or III meningioma, confirmed by central pathology review?
- _____ (Y/N) 2. Does the patient have newly diagnosed meningioma?
____ (Y) If yes, was a histologic diagnosis reached within 24 weeks of Step 2 registration?
- _____ (Y/N) 3. Does the patient have newly diagnosed or surgically treated recurrent disease?
____ (Y) If yes, did the neurosurgeon provide a Simpson grade for degree of resection?
- _____ (Y) 4. Were a history and physical, including neurologic examination, done within 8 weeks prior to Step 2 registration?
- _____ (Y) 5. Is the patient's Zubrod performance status 0-1?
- _____ (Y) 6. Is the patient's age \geq 18?
- _____ (Y) 7. Were diagnostic MRIs done per Section 3.1.5 through 3.1.5.3 of the protocol based on group/subgroup?
- _____ (Y/N) 8. Does the patient fall into Groups II or III?
____ (Y/NA) If yes and if the patient is a woman is of childbearing potential, was a negative serum pregnancy test obtained within 14 days prior to Step 2 registration?
____ (N/NA) If yes, is there evidence of active connective tissue disorders such as lupus and/or scleroderma?
- _____ (N) 9. Are extracranial, multiple, and/or hemangiopericytoma present?
- _____ (N) 10. Is there evidence of major medical or psychiatric illness that would interfere with treatment and/or follow-up or preclude informed consent?
- _____ (N) 11. Has the patient had previous radiation to the scalp, brain, and/or skull base?
- _____ (N) 12. Has the patient had a prior malignancy except for those specified in Section 3.2. of the protocol?
- _____ (N) 13. Does the patient have unstable angina or congestive heart failure requiring hospitalization at the time of registration?
- _____ (N) 14. Has the patient had a transmural myocardial infarction within the last 6 months?
- _____ (N) 15. Does the patient have acute bacterial and/or fungal infection requiring antibiotics at the time of registration?
- _____ (N) 16. Does the patient have chronic obstructive pulmonary disease exacerbation or respiratory illness requiring hospitalization at the time of registration?
- _____ (N) 17. Does the patient have hepatic insufficiency as described in Section 3.2 of the protocol?
- _____ (N) 18. Does the patient have AIDS based upon the current CDC definition at the time of Step 2 registration?

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ELIGIBILITY CHECKLIST—STEP 2 (6/19/09)

Case # _____
(assigned in Step 1)

(page 3 of 4)

The following questions will be asked at study registration for STEP 2:

- _____ 1. Name of institutional person registering this case
- _____ (Y/N) 2. Is the patient going to receive protocol treatment?
_____ If no, provide the reason the patient cannot continue to Step 2:
1) progression of disease
2) patient refusal
3) physician preference
4) death
5) other complicating disease
6) other, specify: _____
- _____ 3. Patient's Initials (First Middle Last) [If no middle initial, use hyphen]
- _____ 4. Verifying Physician
- _____ 5. Patient's ID Number
- _____ 6. Calendar Base Date
- _____ 7. Registration/randomization date: This date will be populated automatically (for Step 2).
- _____ (Y) 8. Has the Eligibility Checklist (in Step 2 above) been completed?
- _____ 9. Neurosurgeon
- _____ (Y/N) 10. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?
- _____ (Y/N) 11. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?
- _____ (Y/N) 12. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?
- _____ (Y/N) 13. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?
- _____ (Y/N) 14. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?
- _____ (Y/N) 15. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

RTOG Institution # _____

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ELIGIBILITY CHECKLIST—STEP 2 (6/19/09)

Case # _____
(assigned in Step 1)

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_____(Y/N) 16. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ 17. Risk group (low, intermediate, high)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Background and Epidemiology

Meningiomas are tumors of arachnoidal cap cell origin, arising principally from the dura mater, although occasionally they occur intraventricularly. Meningiomas account for approximately 15% to 30% of primary brain tumors; they are thus ranked as either the most common [Claus 2005] or, if gliomas are considered collectively, the second most common primary intracranial tumor [Central Brain Tumor Registry in the United States (CBTRUS) 2000; Kuratsu 1996; Kuratsu 2000; McDermott 2002]. The reported incidence varies from <1 to >6 per 100,000 depending upon the method of identification and the population studied [Central Brain Tumor Registry in the United States (CBTRUS) 2000; Jaaskelainen 1986; Kuratsu 1996; Kuratsu 2000; Longstreth 1993; McCarthy 1998]. Overall, an incidence of 2.6 per 100,000 has been calculated, with a greater relative incidence among Africans and Americans of African descent [8]. Except in the setting of neurofibromatosis type 2 (NF2) [Perry 2001], meningiomas occur infrequently in the pediatric population. The peak incidence is during the sixth and seventh decades of life; however, the range is broad, with a 5% or greater incidence in all age brackets from the second to ninth decades [Adegbite 1983; Stafford 1998]. A female preponderance is evident, with a female:male ratio of about 2:1 [Goldsmith 1998; McDermott 2002; Mirimanoff 1985; Wara 1997]. Most meningiomas are well differentiated, with low proliferative capacity. In older series up to 90% were reportedly benign [World Health Organization (WHO) grade I]; 5% to 10% were atypical (WHO grade II); and less than 5% were anaplastic or malignant (WHO grades III or IV) [Jaaskelainen 1986]. However, recent analyses by Perry and colleagues [1997, 1999], using updated grading criteria adopted by the WHO, have indicated that as many as 15% to 20% of meningiomas should be classified as atypical.

1.2 Surgery

Surgery is the mainstay in the diagnosis and treatment of meningiomas, and the completeness of surgical removal is an important prognostic factor [Condra 1997; DeMonte 1995; Stafford 1998]. Resection of the tumor, its involved dura, and any involved soft tissue and bone is accepted procedure [Perry 2001], and high local control rates can be achieved by thorough resection. Kinjo and colleagues [1993] reported the outcome of 37 patients with convexity meningiomas who underwent gross total resection (GTR) of the tumor, any hyperostotic bone, and all involved dura with a 2-cm dural margin. They observed no local recurrences, with over half the patients followed beyond 5 years. Resection to this extent is, however, often unfeasible within the constraints of acceptable morbidity, and the likelihood of GTR varies substantially among intracranial primary sites [DeMonte 1995; Goldsmith 1998; Mirimanoff 1985; Pollock 2000]. The most likely sites for complete removal are the convexity and tentorium, and the least likely are in the skull base [Pollock 2000]. Overall, about one third of meningiomas are not fully resectable [Mirimanoff 1985].

The extent of surgical resection was classically defined by Donald Simpson [1957]. As portrayed in Appendix V, the degree to which the tumor, its dural attachments, and hyperostotic bone were removed surgically related to the local recurrence risk. Many series have corroborated this correlation; however, with the possible exception of the extensive excisions of convexity meningiomas reported by Kinjo and colleagues [1993], the recurrence rates after GTR have not been trivial. Mirimanoff and associates [1985] reported 5-, 10- and 15-year recurrence rates of 7%, 20%, and 32% and second operation rates of 6%, 15% and 20%, respectively, among 145 patients with GTR. These rates were confirmed in a Mayo Clinic series, in which recurrence rates after GTR were 12% at 5 years and 25% at 10 years [Stafford 1998]. Condra et al [1997] confirmed the importance of the total excision but found no association between Simpson grade and local control or cause-specific survival, as long as the resection was gross total (Simpson grades I-III). For patients treated with surgery alone, GTR resulted in 5-, 10-, and 15-year actuarial recurrence rates of 7%, 20%, and 24%, respectively.

Recurrence rates following subtotal resection (STR) are substantially higher. Wara and colleagues [Wara 1975] reported on 58 patients treated with STR alone. Forty-seven percent developed a local recurrence within 5 years, as did an additional 16% between 5 and 10 years and a further 12% (n = 7) from 10 to 20 years. Among 116 patients with STR, Stafford and associates [1998] found recurrences in 39% at 5 years and 61% at 10 years. Condra et al [1997]

detailed local recurrences in 47%, 60%, and 70% of patients with STR at 5, 10, and 15 years, respectively. Overall, approximately 40% to 50% of patients with STR develop local progression within 5 years, 60% within 10 years, and at least 70% within 15 years [Condra 1997; Pollock 2000].

GTR, whether for benign [Condra 1997; Mirimanoff 1985; Pollock 2000; Stafford 1998] or atypical [Goyal 2000] meningiomas, is the preferred treatment and is generally considered definitive. However, surgery may be insufficient as a sole modality in certain groups of patients, including those with subtotally resected, high-grade or recurrent tumors [Condra 1997; Mirimanoff 1985; Stafford 1998]. There is no uniform consensus as to the optimal approach for patients who have undergone STR or for those who are considered inoperable due to tumor location, poor medical status, or patient refusal [Akeyson 1996; Goyal 2000; Jung 2000; Mirimanoff 1985]. An article by Jung et al [2000] described a very low rate of recurrence in 38 patients following STR with or without adjuvant radiation therapy. Jung et al deemed incomplete resection an appropriate option for patients with STR, given a slow rate of growth, with a mean tumor doubling time of 8 years.

Historically, due to infrequent tumor regression following external beam radiation therapy (EBRT), meningiomas were considered resistant to irradiation, which itself was felt to carry considerable side effects [King 1996; Mirimanoff 1985]. Confounding concerns have been voiced regarding the rare circumstance of malignant degeneration as well as the more common relationship between irradiation and the development of meningiomas [Hug 2000; Ron 1988a; Ron 1988b; Strojan 2000]. In a review of the literature by Strojan and colleagues [2000], the actuarial risk of developing a meningioma after radiation therapy was 0.53% at 5 years and 8.18% at 25 years. Although Kondziolka and colleagues [1999a] have found that surgical resection is not rendered more or less problematic by radiosurgery, there remains apprehension among surgeons about arachnoid scarring from irradiation. These concerns continue to lead to many subtotally resected meningioma patients being observed postoperatively, rather than receiving adjuvant therapy [Akeyson 1996; Jung 2000].

1.3 External Beam Radiation Therapy (EBRT)

Due to the fact that GTR is often not feasible, alternative treatment strategies have been employed. The only currently accepted non-surgical treatment is radiation therapy, either as fractionated external beam radiation therapy (EBRT) or stereotactic radiosurgery (SRS). Chemotherapeutic, immunotherapeutic, and hormonal agents have been the subject of investigation but have not yet been validated. Several well-executed retrospective reviews have indicated that postoperative radiation therapy results in significant improvements in local control [Barbaro 1987; Condra 1997; Goldsmith 1994; Taylor 1988; Wara 1975], and even possibly improved cause-specific and overall survival [8,17], in patients with STR, thus supporting a role for postoperative EBRT after incomplete surgery and, on occasion, as primary treatment [Condra 1997; Debus 2001; Goldsmith 1994; Selch 2004; Stafford 1998; Wara 1975].

Table 1 reviews 26 series contrasting outcomes following GTR, STR, and/or STR plus EBRT. The findings of these studies are consistent: progression-free survival (PFS) following STR is improved by the addition of EBRT. However, these studies are retrospective. The thesis that radiation therapy improves outcome has not been subjected to the rigors of a prospective or cooperative group trial. Many patients with STR are not referred for EBRT or SRS, and the role for radiation therapy after STR remains controversial [Akeyson 1996].

1.4 3D-Conformal Radiation Therapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT)

Technical advancements have favorably impacted both the outcome and the side effect profile of postoperative EBRT. As to the latter issue, the risk of radiation-related side effects appears to be improved with modern approaches, as demonstrated by Goldsmith [1994] and Debus [2001]. Debus et al [Debus 2001] found a 2.2% rate of clinically significant toxicity, but no grade IV complications, with fractionated SRS. This rate is substantially superior to the 38% reported by Al-Mefty et al [1990] with older methods of radiation delivery. Goldsmith et al [1994] found a 3.6% rate of complications attributable to EBRT. These complications most often involved the anterior visual pathway; however, they are uncommon with doses per fraction < 2.0 Gy and with total doses < 54 Gy [Goldsmith 1992], as well as in series using intensity modulated radiation therapy

