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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RTOG 0539

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

SCHEMA (6/9/10)

STEP 1 REGISTRATION

↓

Central Pathology Review/Histology Confirmation
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

↓

STEP 2 REGISTRATION

Group I (Low Risk)	**Group II (Intermediate Risk)**	**Group III (High Risk)**
Observation	*Radiotherapy (54 Gy in 30 fractions) [May be 3D-CRT or IMRT or Proton]* See Section 6 for details.	*Radiotherapy (60 Gy in 30 fractions) [Must be IMRT]* See Section 6 for details.

INSTITUTION MUST BE CREDENTIALED 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)

RTOG Institution # ___

RTOG 0539 **ELIGIBILITY CHECKLIST—STEP 1** (6/9/10)

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/Proton) 18. The patient will be treated with IMRT or 3D-CRT or Proton?

RTOG Institution # ___

RTOG 0539 **ELIGIBILITY CHECKLIST—STEP 2** (6/19/09)

Case # _____ (page 2 of 4)
(assigned in Step 1)

_____(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 ≥ 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 exasperation 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?

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)?

_____(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 at 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; Miramanoff 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 ()

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

(IMRT) [Pirzkall 2003; Uy 2002] or fractionated stereotactic irradiation [Selch 2004]. Meyers and associates [2000] have also argued that the adverse sequelae of 3D-CRT or IMRT appear to be waning because of technical improvements.

Regarding tumor control, recent developments allow more precise critical normal structure and target definition, as well as more accurate dosimetry and dose delivery. Indeed, improvements in local control have been documented when treatment planning was based upon CT or MRI data, rather than on plain films and surgical reports alone. Goldsmith [1994] and Milosevic [1996] each substantiated that improvements in local control have accompanied modern imaging. Goldsmith [1994, 1998] found that appropriate immobilization, along with CT- and/or MRI-based target definition resulted in a 22% improvement in PFS compared with treatment without such techniques ($p = 0.002$).

Fractionated stereotactic and intensity modulated approaches have been employed with excellent intermediate-term local control and survival results [34, 35, 38, 39]. Debus et al [2001] reported 189 patients treated with large skull base meningiomas (median target volume 52.5 cc) to a median total dose of 56.8 Gy in 31 to 32 fractions. With median follow-up of 35 months, actuarial 10-year PFS was 94% for grade I tumors and 78% for grade II meningiomas. Uy and colleagues [2002] used IMRT (median 50.4 Gy) to treat 40 patients and found a 5-year PFS of 93%. Pirzkall and associates [2003] treated 20 skull base meningioma patients to doses of 55.8 to 58.2 Gy. With a median follow-up of 36 months they noted uniform local control. Selch et al [2004] employed fractionated stereotactic radiotherapy (median 50.4 Gy) for 45 cavernous sinus meningioma patients and found 3-year actuarial local control to be 97.4%. These outcomes with modern radiotherapy appear superior to the 5-year PFS rates of 80% to 85% rates from older series [Adegbite 1983; Barbaro 1987; Glaholm 1990; Taylor 1988]. However, there has never been a cooperative group comparison of outcomes between various techniques of radiation therapy for patients with meningioma or any other primary intercranial tumor. We will employ 3D-CRT or IMRT for our intermediate-risk patients and IMRT for high-risk patients, and we will analyze as a secondary endpoint how well IMRT dose constraints for targets and normal tissues are consistently achieved.

The recommended planning target volume (PTV) has ranged from gross tumor volume (GTV) plus a 2-cm margin [Perry 1999], to GTV plus 1 cm [Goldsmith 1998], down to GTV plus 2 mm [Debus 2001]. In the latter report, by Debus and colleagues [2001], a head cast attached to a stereotactic frame was used daily. Interestingly, with a median follow-up of 35 months, they have observed no marginal failures. Recommended doses have generally been 50 to 55 Gy [Condra 1997; Goldsmith 1998; Wara 1997; Uy 2002]. Among 67 patients, Winkler et al [1998] found no clear dose response from 36 to 79.5 Gy (1.5 to 2.0 Gy per day), with 5- and 10-year disease-free survival rates of 82% and 70%, respectively. On the other hand, Goldsmith and associates [1994] found that doses above 52 Gy resulted in improved local control.

1.5 Comparative Outcomes of EBRT and SRS

SRS will not be permitted on the present protocol. However, a brief reference to outcomes with SRS vis a vis EBRT is important as justification. SRS was introduced in the 1950s by Lars Leksell as a single high-dose radiation treatment to an image-defined target. Although this is a much more recent development than EBRT, SRS has been used with increasing frequency over the last two decades and is now an accepted form of treatment for meningiomas [McDermott 2002]. Treatment results with SRS have been impressive, with both linear accelerator–based [Chang 1997; Hakim 1998; Shafron 1999] and Gamma Knife [Duma 1993; Kondziolka 1998a; Kondziolka 1998b; Kondziolka 1999b; Liscak 1999; Roche 2000; Pollock 2000; Stafford 2001; Subach 1998; Vermeulen 1999] systems having similar local control rates. Table 2 lists 24 published series with a total of 2281 patients. Local control at 5 years or greater ranges from 75% to 100%. SRS relies upon a high degree of conformality and a steep dose gradient to enhance local tumor response and to limit side effects, whereas EBRT exploits the radiobiologic advantages of lower dose per fraction, protracted treatment course, and higher total dose.

As emphasized in Table 3, there is apparent equivalence in local control between EBRT and SRS, and either emerges as a treatment option for appropriately selected subtotally resected meningiomas. Combining several retrospective EBRT series reveals 5- to 10-year local control

rates from 79% to 100%, compared with 75% to 100% for SRS. Extracting recent series (published since 2001) yields similar results: 91% to 100% for EBRT and 86% to 100% for SRS. In a publication, Sibtain and Plowman [1999] noted uniform local control from 12 to 83 months in 28 cavernous sinus meningioma patients treated either with EBRT (50 Gy in 30 fractions) or with SRS (12 to 17 Gy at the 90% isodose).

The number of published series with intermediate- and long-term follow-up of SRS has not yet reached that of EBRT. However, the results are impressive enough to have already incorporated SRS into the standard treatment armamentarium for meningiomas. However, there is no suggestion from multiple retrospective series, now with extended follow-up, that SRS results in outcome superior to EBRT. Although we will not incorporate SRS into the present relatively small phase II protocol, once this study is completed, we plan to proceed with a phase III trial incorporating IMRT or SRS.

1.6 Atypical Meningiomas (WHO Grade II)

Atypical features are found in approximately 5% to 20% of meningiomas and are indicative of a more aggressive biologic potential [McDermott 2002; Kuratsu 1996; Wara 1997; Perry 1997, Claus 2005, Pasquier 2008]. In most studies, including recent publications, atypical meningiomas comprise about 5% of patients [Claus 2005, Pasquier 2008]. A higher prevalence of atypical histology of about 20% has been reported by Perry and colleagues [1997, 1999]; corroborating this, a Scottish group recently reclassified approximately 300 meningioma cases with close attention to current WHO standards. They found that 20% of their reclassified meningiomas were atypical (WHO grade II), a 4-fold increase, and that 1.6% were anaplastic (WHO grade III). They commented that 38% of their atypical meningiomas were originally (incorrectly) classified benign. [Willis 2005]. Pearson and colleagues at the University of Alabama Birmingham have also noted a significant change in the percentage of meningiomas designated as atypical in recent years. At their institution 32.7% to 35.5% of meningiomas were categorized as atypical from 2004 through 2006 [Pearson 2008]. Local recurrence rates for patients with atypical meningiomas are higher than those with benign tumors. Perry and colleagues [1997, 1999], in a large series that included 108 atypical meningiomas, found that gross totally resected patients had an estimated 5-year recurrence rate of 40%. The majority of these patients received no treatment beyond surgery. It thus appears that a sizable subset of atypical meningiomas is likely to fail with surgical therapy alone. It is common practice to offer patients with atypical meningiomas adjuvant irradiation.

Studies have indicated that STR for atypical tumors portends more rapid progression than with their benign counterparts. Goyal et al [2000] found 5- and 10-year local control rates of 51% and 17%, respectively, in patients with atypical meningiomas and STR (n = 4) or surgery of unknown extent (n = 3). The majority of the patients did not receive adjuvant therapy. Goldsmith et al [1994] found that with EBRT, patients with subtotally resected atypical tumors achieved a 5-year relapse-free survival rate of 48%, compared with 89% for benign tumors (p = 0.001). Stafford and co-authors [Stafford 2001] found 5-year actuarial local control rates of 100% for benign meningiomas, compared with 83% for atypical meningiomas treated with SRS. Condra et al [1997] commented that patients with atypical meningiomas faired best with either GTR or STR plus radiation therapy, principally EBRT. Others, as well, have recommended postoperative EBRT or SRS for subtotally resected atypical meningiomas [Staffford 1998, Goyal 2000, Hug 2000]. Regarding dose, Hug and associates [2000] reported that local control of atypical meningiomas was significantly enhanced by cumulative doses of ≥ 60 CGE (cobalt Gray equivalent). The majority of their patients had a subtotal resection or recurrent disease.

1.7 Anaplastic/Malignant Meningioma (WHO Grade III)

Malignant meningiomas are relatively rare tumors, comprising less than 5% of all meningiomas [Jaaskelainen 1986, Claus 2005]. In distinction to both benign and atypical meningiomas, malignant meningiomas have a considerably more aggressive clinical course. Whereas the 5-year overall survival rates for low-grade meningiomas are typically between 90% and 100%, those for malignant meningiomas are between 50% and 60% [Coke 1998], prompting broader agreement for aggressive multimodality therapy. In the majority of the published literature, postoperative radiation is recommended regardless of the extent of resection [Hug 2000] and local recurrence is reported to be reduced [Akeyson 1996]. GTR and adjuvant radiation for patients with malignant meningiomas have been shown, in a report by Dziuk et al [1988], to

independently predict improved disease-free and overall survival times. Five-year disease-free survival improved from 15% without radiation to 80% with adjuvant radiation [Dziuk 1988]. Coke and colleagues [1998] reported local disease progression in 65% of patients after surgery alone, versus 18% after surgery plus radiation. Cumulative fractionated doses in the range of 54 Gy, typically used for benign meningiomas, may be insufficient for anaplastic primaries, and many centers employ doses averaging about 60 Gy (with fractions of 1.8 to 2.0 Gy) with 2- to 4-cm margins. A study by Hug et al [2000] from Massachusetts General Hospital included 13 patients treated with surgery and radiation for malignant meningioma. Approximately one third were approached with a combination of photons and protons and two thirds with photons alone. Those with cumulative doses exceeding 60 Gy (expressed as cobalt Gray equivalent) manifested significantly better local control: 5-year actuarial local control was 100% for 6 patients treated with ≥ 60 Gy, versus 0% for 7 patients receiving < 60 Gy ($p = 0.025$). We have thus incorporated a final dose of 60 Gy (in 30 fractions) for patients with WHO grade III (anaplastic/malignant) and other high-risk meningiomas in the present study.

1.8 Recurrent Meningiomas

Meningiomas that have recurred after prior surgery alone appear to pursue a more aggressive clinical course than newly diagnosed meningiomas of the same grade [Miralbell 1992; Taylor 1988; Wara 1975]. Retrospective studies have indicated an improved salvage rate when such patients are treated with combined surgery and radiation or radiation alone as opposed to surgery only [Miralbell 1992; Taylor 1988; Wara 1975]. In the study by Miralbell and associates [1992], 8-year PFS after salvage therapy was 78% in irradiated patients versus 11% with surgery only ($p = 0.03$). Taylor et al [1988] reported respective 10-year figures as 89% versus 30% ($p = 0.01$). Addressing whether radiation can be delayed for the event of further progression, Pourel and colleagues [2001] found numerically improved 5-year relapse-free survival in patients irradiated immediately following STR, as opposed to delaying radiation for progression: 90% versus 73%, but the difference was not statistically significant ($p=0.37$). Although the theses that radiation should be employed in patients with recurrent meningioma and that postponing radiation until further progression may result in less effective tumor control find support in retrospective studies, there have been no cooperative group trials on this issue.

1.9 Histopathologic Evaluation and Prognostic Markers (6/9/10)

Perry and associates [1997, 1999] have proposed criteria for the grading of meningiomas, based upon a large clinicopathologic series showing statistical associations with recurrence-free and overall survival. These criteria have, in large measure, been adopted by the WHO [Kleihues 2000]. Relative to benign (WHO grade I) meningiomas, atypical (WHO grade II) tumors are those with >4 mitoses per 10 high power fields (which may be focal), brain invasion, or at least three of the following: sheeting architecture, small cells, macronucleoli, hypercellularity, and/or necrosis. Exclusionary anaplastic findings are >20 mitoses per 10 high power fields or loss of differentiation under light microscopy (i.e., sarcoma-, carcinoma-, or melanoma-like appearance). Although these criteria are more objective than those used in the past, there is still some interpretive license. A more uniform analysis would be expected by employing central pathology review by a single pathologist with recognized expertise in the field (A. Perry). This is mandated as a secondary analysis in the present protocol.

Evidence is accumulating that immunohistochemical and molecular data may further improve our ability to stratify patients into prognostic subsets [Bostrom 2001; Cai 2001; Perry 1998; Perry 2000; Simon 1995; Weber 1997]. For example, malignant progression has been associated with increased MIB-1 (Ki-67) proliferative indices, decreased progesterone receptor expression, and genetic losses involving chromosomes 1p, 10, and 14q. Whereas most of these have not been validated as independent prognostic markers, preliminary data suggests that 14q deletions detected in paraffin-embedded sections by fluorescence in situ hybridization (FISH) are more common in benign meningiomas that recur despite GTR [Perry 1998]. It is likely that additional markers of interest will become apparent during the course of this study. Therefore, we plan to archive paraffin blocks and blood samples from consenting patients, in order to perform additional immunohistochemical and molecular studies once the enrollment phase is completed. Correlative aims for chromosomal and molecular analyses are found in Section 10.8.

We also will collect urine samples from consenting patients for a secondary translational analysis of angiogenesis and molecular prognostic factors. Tumor growth depends on angiogenesis, the development and recruitment of new blood vessels. The importance of angiogenesis in oncology was proposed by Folkman [1971], who recognized the importance of targeting cells that support tumor growth rather than the cancer cells themselves. Despite the array of tumor markers currently in use, none serve as general cancer predictors of outcome. In theory, angiogenic factors could identify patients at risk for recurrent disease regardless of tumor type, since the process of angiogenesis is ubiquitous to cancer. Indeed, multiple investigators have explored the use of angiogenic factors as possible general tumor markers [Cai 2002; Gerhards 2001; Kaban 2002; Kausch 2002; Kraft 1999; Kuittinen 2002; Lengyel 2001; Linderholm 1998; Moses 1998; Ondruschka 2002; Poon 2001; Sienel 2003; Smith 2000; Verheul 2000]. While angiogenic proteins such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinases (MMPs), have been shown to have prognostic power in specific tumor types, few studies have individually explored the utility of angiogenic proteins as general tumor markers across different tumor types—both solid tumors and hematologic malignancies. A tumor marker that could consistently identify patients at risk for nonresponsive or recurrent disease would allow selection of these patients for more aggressive or alternate treatment. Furthermore, to our knowledge each of the aforementioned studies has focused on the magnitude of either the VEGF or MMP initial level. No study has explored the dynamic *trend* of these protein levels though a course of therapy, its possible predictive significance, or evaluated which methodology was the most powerful for defining the trend.

VEGF, originally known as vascular permeability factor, is one of the most potent and well-characterized proangiogenic proteins. It is expressed by a variety of human solid tumors, as well as neoplastic myeloid and leukemic cells [Mayerhofer 2002]. VEGF has specific mitogenic activity on endothelial cells and promotes extravasation of proteins from tumor vessels, which creates a fibrin matrix infrastructure allowing for stromal cell invasion and tumor development [Dvorak 1992].

MMPs are a family of zinc-dependent enzymes that enable new vessels to invade the surrounding extracellular matrix. MMPs function during the normal physiologic processes of tissue repair and morphogenesis. Pathologically, MMPs have been implicated in diseases associated with excess degradation of extracellular matrix, such as rheumatoid arthritis, osteoarthritis, periodontitis, autoimmune skin disorders, tumor invasion and metastasis [Vihinen 2002]. Increased MMP expression has been linked to more aggressive metastatic behavior and increased expression of MMPs has been documented in numerous tumor types [Burke 2001].

While clinical prognostic variables have assisted in stratifying patients, many groups are investigating molecular prognostic factors with the hope that these markers might also predict for response to specific therapies. Specific molecular markers in pathology specimens have been found to be prognostic in gliomas and predict responsiveness to chemotherapy [Hashimoto 2003; Pollack 2003; Tchirkov 2003; Thiessen 2003]. Expression of growth factors and the proliferation index have also been found to be prognostic in tumor tissue from patients with high-grade gliomas. However, the majority of studies evaluating molecular prognostic variables with meningioma have focused on the evaluation of tumor tissue obtained at the time of biopsy and/or resection. This approach is well suited to evaluate molecular pretreatment prognostic markers, but the investigation of predictive posttreatment factors in patients with meningioma has been more limited due to the paucity of available tumor tissue after therapy. Evaluating prognostic markers in urine and serum, which can be obtained with minimally invasive procedures, may be more feasible and applicable to this setting.

The NCI Radiation Oncology Branch (ROB) previously evaluated serum and urine markers prior to, during, and following definitive therapy in patients undergoing radiation therapy, including several patients with high-grade gliomas [Chan 2004]. These patients were enrolled in the ROB blood and urine collection protocol, NCI protocol 02-C-0064. Serum and urine were collected from patients with various cancers who were undergoing radiation therapy. The levels of serum and urine angiogenic factors were evaluated to determine if these levels were prognostic of outcome following radiation therapy. Urinary VEGF levels at presentation were different between patients with local-regional cancer and normal controls and between patients with metastatic

prostate cancer and local-regional disease (p = 0.04 and 0.01, respectively). Similar results were found with MMP measurement (p = 0.03 and p <0.0001, respectively). Of those patients subsequently treated with radiation, VEGF levels at presentation between patients with no evidence of disease after radiation (NED) and those who had persistent or recurrent disease following radiotherapy were also different (p = 0.039). The comparison between angiogenic factor levels taken at least 1 month postradiotherapy and the last on-treatment level was the strongest predictor of 1-year PFS (p = 0.004). Overall MMP trending was also significantly associated with 1-year PFS, as was individual MMP-2 trending (p = 0.004 and 0.001, respectively). Step-wise logistic regression revealed that the VEGF trend comparing postradiation levels to last on-treatment levels was an independent predictor of PFS (p = 0.02). Therefore, we plan to expand on these results by prospectively investigating this question in patients with meningioma.

Several growth factors have been implicated in tumors of the central nervous system, and specifically in meningiomas, including EGF, IGF, VEGF, and HGF/SF. We propose to collect serum from our patients at baseline (all groups), at 1 month post-irradiation (Groups II and III), and at the time of recurrence (all groups) if that should occur. Our hypothesis is that HGF/SF may predict for local recurrence after radiotherapy; however, as we have so few patients in each treatment arm, we will collect this data only in a pilot fashion. We will also test our secondary hypothesis that the levels of EGF, IGF, and VEGF cannot independently predict local failures but when combined can create a predictive score for local failure. Again, this will only be done in pilot fashion due to our limited patient numbers.

1.10 Rationale for Study Design

We will evaluate three groups of meningioma patients, based upon WHO grade, extent of resection, and recurrence status. WHO grade will be determined via central pathology review. Resection extent will be determined by operative and imaging findings at the parent institution. Recurrence may be established based upon operative and/or imaging findings. Patients with newly diagnosed gross totally or subtotally resected WHO grade I meningiomas are at relatively low risk for recurrence and will be enrolled in an observation arm (Group I). This will permit better definition of recurrence rates based upon grade and other histopathologic findings from centrally reviewed and banked tissue. Group II patients will receive postoperative radiation therapy. Group II patients have a several-fold increased rate of recurrence over newly diagnosed grade I meningiomas. As iterated in Section 1.6 above, Perry and colleagues [1997, 1999] found that gross totally resected atypical meningiomas exhibited a 40% 5-year local recurrence risk. As outlined in Section 1.8, recurrent grade I patients have yet poorer progression-free survival in the absence of radiation therapy. With this rationale, it is common practice to offer these patients postoperative irradiation. There is yet broader agreement upon the use of radiation therapy for high-risk patients and, as reviewed in Section 1.6, the total radiation doses employed are commonly higher than in other settings. Thus our Group II and Group III patients will receive IMRT.

Regarding the use of IMRT in the present trial, although RTOG has an unparalleled track record for completing important brain tumor studies, all RTOG brain tumor trials to date have specified that IMRT is <u>not</u> permitted. No brain tumor trial has addressed whether specific dose constraints for target and normal tissues can be met in the multi-institutional setting across academic, community hospital, and private practice group settings. Numerous IMRT techniques have developed largely independent of one another. The present protocol will be the first RTOG brain tumor trial to use and measure adherence to carefully specified parameters using IMRT and other highly conformal radiotherapy techniques. It will thus serve as the basis for the rational and methodical use of these approaches for future RTOG brain tumor trials.

Group II patients will receive 54 Gy in 30 fractions, and Group III patients will receive 60 Gy in 30 fractions. As has been the case with many prior large cooperative group studies, submission of pathology slides for central pathology review will be mandatory and will provide tissue for secondary analysis. In addition, paraffin-embedded tumor specimens, serum, and urine are strongly encouraged to be submitted and will be stored in the RTOG Biospecimen Resource for future molecular, epidemiological, and other correlative studies as described in Section 10.8. Urine collection will be used to determine whether urinary VEGF and MMP levels are predictive of

clinical outcome in patients being observed or receiving radiotherapy for meningioma. Centralized neuroradiology review will be utilized to perform a more uniform secondary assessment of recurrence and of imaging correlates but will not be requisite prior to protocol enrollment.

With the hope that we might identify a reliable surrogate marker for the outcome of meningioma patients, and perhaps in the future circumvent the lengthy time intervals required to identify recurrence rates and survival via the traditional measures, we encourage smaller cohort studies of metabolic imaging. These will not be included in the present larger multi-institutional study but may be run in parallel with it. Surrogate outcome markers will also be sought in all enrolled patients via analysis of centrally reviewed and banked tissue as described above. Conditional to the results of the present phase II protocol, we plan to follow with a phase III randomized study comparing observation to radiation therapy (conformal standard fractionated techniques or stereotactic radiosurgery) in selected low- and intermediate-risk patients. The phase III undertaking should be greatly enhanced by the current phase II approach, which will document our ability to accrue meningioma patients within the RTOG framework, to assess histopathologic and imaging correlated centrally, to adhere to highly conformal EBRT guidelines (as yet undocumented in multi-institutional brain tumor trials), and to report outcomes within the prognostic groups we have herein defined.

Table 1
External Beam Radiation Therapy Progression-Free Survival

			≥ 5-year PFS		
Author (yr)	**N**	**f/u (mo)**	**GTR**	**STR**	**STR+ EBRT**
Adegbite (1983)	114	10-276 (range)	90%	45%	82%
Mirimanoff (1985)	225	65% >60	93%	63%	
Barbaro (1987)	135	78	96%	60%	80%
Taylor (1988)	132	60% >60	96%	43%	85%
Glaholm (1990)	117	80			84%
Miralbell (1992)	115	57		48%	88% (8y PFS)
Mahmood (1994)	254	61	98%	54%	
Goldsmith (1994)	117	40			89% (98% after 1980)
Peele (1996)	86	46		52%	100%
Condra (1997)	246	98	95%	53%	86%
Stafford (1998)	581	55	88%	61%	
Nutting (1999)	82	108			92%
Vendrely (1999)	156	40			79%
Maguire (1999)	28	41			92% (4y PFS)
Wenkle (2000)	46	53			100%
Pourel (2001)	26	30			95%
Dufour (2001)	31	73			93% (10y PFS)
Debus (2001)	189	35			98% (FSRT)
Jalali (2002)	41	21			100% (3y PFS)
Uy (2002)	40	30			93%
Pirzkall (2003)	20	36			100%
Soyuer (2004)	92	92	77%	38%	91%
Selch (2004)	45	36			98% (3y PFS)
Milker-Zabel (2005)	317	68			93%
Henzel (2006)	224	36			97%
Milker-Zabel (2007)	94	53			94%
Total:	**3544**	**21, 108 (mean, median)**	**77-98%**	**38-63%**	**79-100%**

Table 1. Compiled series allowing for comparison in the rates of progression-free survival (PFS) for patients treated with gross total resection (GTR), subtotal resection (STR), or with STR + external beam radiation therapy (EBRT). Actuarial intervals other than 5 years are given in parenthesis. Patients in the above reports typically, but not exclusively, had either known or presumed low-grade meningiomas. yr: year published, n: number of patients, f/u: length of follow-up (mean or median unless otherwise indicated), FSRT: fractionated stereotactic radiosurgery. The STR + EBRT column includes some patients treated with primary EBRT.

Table 2
Stereotactic Radiosurgery Progression-Free Survival

Author (yr)	n	f/u (mo)	No Histology	Dose	≥ 5 yr-PFS
Chang (1997)	55	48	-	18 Gy	98%
Hakim (1998)	127	31	54%	15 Gy	89%
Chang (1998) [1]	24	46	-	17.7 Gy	100%
Liscak (1999)	53	19	64%	12 Gy	100%
Kondziolka (1999b)	99		43%	16 Gy	93%
Morita (1999) `	88	35	44%	16 Gy	95%
Shafron (1999)	70	23	NR	12.7 Gy	100%
Roche (2000)	80	31	63%	14 Gy	93%
Aichholzer (2000)	46	48	33%	15.9 Gy	96%
Stafford (2001)	168		41%	16 Gy	93%
Shin (2001)	15	42	30%	10-12 Gy	75% (5&10y PFS)
	22		”	14-18 Gy	100% (5&10y PFS)
Nicolato (2002)	111	48	50%	15 Gy	96%
Lee (2002) [1]	159	35	52%	13 Gy	93% (97% if SRS sole tx)
Spiegelmann (2002)	42	36	-	14 Gy	97.5%
Pollock (2003)	62	64	46%	17.7 Gy	95% (7y PFS)
Roche (2003)	32	56	75%	13 Gy	100%
Iwai (2003)	42	49	48%	11 Gy	92%
Flickinger (2003)	219	29	100%	14 Gy	93% (5&10y PFS)
Chuang (2004)	43	75	48%	16 Gy	90% (7y PFS) (100% if SRS sole tx)
DiBiase (2004)	137	54	62%	14 Gy	86.2% (91.9% if <10cc)
Kim (2005)	26	33	91%	16 Gy	95%
Kreil (2005)	200	95	51%	12 Gy	98.5% (97.2% at 10 y)
Zachenhofer (2006)	36	103	31%	16.8 Gy	94% (5 & 8 y PFS)
Kollova (2007)	325	60	70%	12.6 Gy	97.9%
Total:	**2281**	**19-103**	**30-100% (mean 54%)**	**10-18Gy**	**75-100%**

Table 2. Compiled stereotactic radiosurgery with reported 5-year progression-free survival (PFS) rates. Actuarial intervals other than 5 years are given in parenthesis. The “no histology” column refers to the percentage of patients diagnosed with meningioma on the basis of neuroimaging. Patients in the above reports typically, but not exclusively, had either known or presumed low-grade meningiomas. The follow-up and dose columns list the mean or median figures. f/u: follow-up, y: year; mo: month; Gy: Gray; SRS: stereotactic radiosurgery; tx: treatment

Table 3
EBRT vs SRS Progression-Free Survival

	n	Follow-Up (Mean or Median)	PFS (5 to 10 year)
SRS Combined	2281	19-103 mo	75-100%
EBRT Combined	3544	21-108 mo	79-100%
SRS Recent	1639	29-103 mo	86-100%
EBRT Recent	1110	30-92 mo	91-100%

Table 3. Compiled series allowing comparison of fractionated external beam radiation therapy (EBRT) with stereotactic radiosurgery (SRS), with 5- to 10-year progression-free survival (PFS) as the endpoint. Patients in the above reports typically, but not exclusively, had either known or presumed low-grade meningiomas. "Recent" refers to those reports published 2001-2007 with appropriate data available. n: number of patients, mo: months.

2.0 OBJECTIVES

2.1 Primary

2.1.1 To estimate the rates of progression-free survival (PFS) at 3 years in each of the patient risk groups.

2.2 Secondary

2.2.1 To study the concordance, or lack thereof, between central and parent institution histopathologic diagnosis, grading, and subtyping.

2.2.2 To estimate the incidence rates of grade 2+ acute and late adverse events for Group II (intermediate-risk) and Group III (high-risk) patients. These rates will be analyzed separately owing to treatment and dosing differences between the groups.

2.2.3 To appraise histopathologic correlates of PFS including light microscopy, immunohistochemical analysis and microarray analysis.

2.2.4 To evaluate, via central neuroradiology review, imaging (MRI) predictors at diagnosis, at any failure, and at 3 years.

2.2.5 Molecular correlative studies as described in Section 10.8.

2.2.6 To evaluate adherence to protocol-specific target and normal tissue radiation therapy parameters.

2.2.7 To estimate the rates of overall survival at 3 years in each of the patient risk groups.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (6/9/10)

3.1.1 A histologically documented WHO grade I, II, or III meningioma, newly diagnosed or recurrent, and of any resection extent, **confirmed by central pathology review (See Section 10.0).** Patients are partitioned according to three groupings: Group I (low risk), Group II (intermediate risk), and Group III (high risk) as defined below:

- Group I (low risk): Patients with a newly diagnosed WHO grade I meningioma that has been 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). The extent of resection will be based upon the neurosurgeons' assessment and postoperative MR imaging.
- Group II (intermediate risk): Patients with a newly diagnosed gross totally resected WHO grade II meningioma or patients with a recurrent WHO grade I meningioma irrespective of the resection extent. Resection extent will be recorded on the same basis described above for the low-risk group.
- Group III (high risk): Patients with a newly diagnosed or a recurrent WHO grade III meningioma of any resection extent; patients with a recurrent WHO grade II meningioma of any resection extent; or patients with a newly diagnosed subtotally resected WHO

grade II meningioma. In the setting of a newly diagnosed meningioma, the histologic diagnosis must have been reached within 6 months of Step 2 registration. Resection extent will be recorded on the same basis described above for the low-risk group.

3.1.1.1 In the setting of a newly diagnosed meningioma, the histologic diagnosis must have been reached within 24 weeks prior to Step 2 registration. In the setting of a recurrent meningioma, there are no such time constraints. Additional resection or biopsy is encouraged for patients with recurrence but is not requisite. If further biopsy or resection is performed at recurrence, these specimens must be submitted; submission of the original pathology specimens is encouraged but not required. The diagnosis of recurrence solely on the basis of imaging findings is permitted, but if no additional resection is performed, specimens from prior resection must be submitted.

3.1.1.2 In cases of newly diagnosed or surgically treated recurrent meningioma, the operating neurosurgeon must provide a Simpson grade for the degree of resection (Appendix V).

3.1.2 History/physical examination, including neurologic examination, within 8 weeks prior to Step 2 registration

3.1.3 Zubrod Performance Status 0-1

3.1.4 Age ≥ 18

3.1.5 All patients must have an MRI within 12 weeks prior to Step 2 registration. Both preoperative and postoperative MRIs are required for all newly diagnosed patients in groups I, II, or III. In the setting of group II or III patients with recurrent/progressive meningioma and without recent surgery, a pre-operative study may not apply, although MRI documentation of recurrence or progression is required. MRIs must include precontrast T1, T2, and flair images and multiplanar (axial, sagittal, and coronal) postcontrast T1. The postoperative study must be completed within 12 weeks of surgery.

3.1.5.1 Group I: All group I patients will have surgery. Preoperative and postoperative MRIs are thus required in order to assess resection extent.

3.1.5.2 Group II: Surgery will be undertaken for the subgroup with a gross totally resected WHO grade II meningioma. For these patients preoperative and postoperative MRIs are necessitated. For the other subgroup with recurrent WHO grade I meningioma, preoperative and postoperative MRIs are required if surgery is undertaken for the recurrent/progressive tumor. However, only the follow-up imaging documenting recurrence or progression will apply if further surgery is not completed.

3.1.5.3 Group III: Surgery will be undertaken for the subgroup with a newly diagnosed WHO grade III meningioma. For these patients preoperative and postoperative MRIs are obligatory. For the subgroups with recurrent WHO grade II or III meningioma, preoperative and postoperative MRIs are required if surgery is undertaken for the recurrent/progressive tumor. However, only the follow-up imaging documenting recurrence or progression will apply if further surgery is not completed.

3.1.6 For woman of childbearing potential who are intermediate or high risk:

3.1.6.1 Negative serum pregnancy test within 14 days prior to Step 2 registration

3.1.6.2 The patient must agree to practice adequate contraception from the time of the negative serum pregnancy test throughout the entire course of EBRT**.**

3.1.7 Patient must sign study-specific informed consent prior to study entry

3.2 Conditions for Patient Ineligibility (6/9/10)

3.2.1 Extracranial meningioma

3.2.2 Multiple meningiomas

3.2.3 Hemangiopericytoma

3.2.4 Major medical illnesses or psychiatric impairments which, in the investigators opinion, will prevent administration or completion of the protocol therapy or preclude informed consent

3.2.5 Previous radiation therapy to the scalp, cranium, brain, or skull base

3.2.6 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.7 Patients with severe, active comorbidity including, but not restricted to:

3.2.7.1 Unstable angina and/or congestive heart failure requiring hospitalization at the time of Step 2 registration

3.2.7.2 Transmural myocardial infarction within the last 6 months

3.2.7.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of Step 2 registration

3.2.7.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of Step 2 registration

3.2.7.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects. Note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.7.6 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.7.7 Active connective tissue disorders such as lupus or scleroderma if the patient is intermediate or high risk

3.2.8 Inability to receive gadolinium

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 Documentation of steroid doses within 8 weeks prior to Step 2 registration

4.1.2 Documentation of other hormonal agents (e.g., estrogens, progesterones, contraceptives) within 8 weeks prior to Step 2 registration

4.1.3 CBC with differential, ANC, and platelets within 8 weeks prior to Step 2 registration

5.0 REGISTRATION PROCEDURES

5.1 Preregistration Requirements for 3D-CRT or IMRT Treatment Approaches and the Use of IGRT (6/9/10, 7/1/10)

5.1.1 In order to utilize either 3D-CRT or IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the Radiological Physics Center (RPC) web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG." To determine if these requirements have already been met, select "Credentialing Status Inquiry."

In order to utilize IMRT for this protocol, a phantom study with the RPC must be successfully completed (if the institution has not previously met this credentialing requirement on a RTOG IMRT Head and Neck or Prostate study). Instructions for requesting and irradiating the phantom are available on the RPC web site.

5.1.1.1 The PTV margins for this protocol are 5.0 mm. The margins can be reduced to 3.0 mm when daily IGRT is used. The RTOG has a strict definition of IGRT. This definition can be found on the ATC website at http://atc.wustl.edu. Institutions must be credentialed to use daily IGRT with reduced margins. The credentialing process is designed to demonstrate that the institution can accurately position the patient each day to stay within the reduced margins. The procedure for demonstrating that the institution can stay within the 3.0 mm margin is described on the ATC website.

5.1.1.2 The institution or investigator must complete a new facility questionnaire and set up an SFTP account for digital data submission, both of which are available on the ATC web site at http://atc.wustl.edu. It is necessary to declare on the facility questionnaire if 3D-CRT, IMRT or both are to be used for the protocol. Credentialing for IMRT allows the institution to treat with either 3D-CRT or IMRT. Both types of treatment require a "Dry-Run QA" test. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.1.1.3 Institutions can elect to treat Group II patients only and restrict treatments to 3D-CRT. In this case, the phantom irradiation is not required.

5.1.1.4 For Proton Credentialing contact the RPC at rpc@mdanderson.org

5.2 Regulatory Preregistration Requirements

5.2.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.2.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.2.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

5.2.3.1 **For institutions that do not have an approved LOI for this protocol:**

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.2.3.2 **For institutions that have an approved LOI for this protocol:**

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3 Summary of Registration Procedures

Once the site has met pre-registration requirements, this study incorporates a 2-step registration process.

Step 1 of registration entails an initial registration for central pathology review.

- The site will register the patient and will then submit tissue to the RTOG Biospecimen Resource (see Section 10). A pathology screening form (P4), pathology materials, and pathology report must be submitted per Section 10.
  - The RTOG Biospecimen Resource will forward these materials to Dr. Arie Perry to confirm that the histology is meningioma. If the histology is meningioma, the site may proceed to Step 2 registration.
- See Section 5.4 for online registration procedures.

Step 2 of registration entails a second web registration, at which time protocol treatment can start.

- A treatment assignment (Group 1, 2, or 3) will then be provided along with a data submission calendar.
- See Section 5.4 for online registration procedures.

5.4 Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the

checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (Groups II and III only) (6/9/10)

Note: Intensity Modulated RT (IMRT) is allowed for both patient groups. The use of 3D-CRT is allowed for Group II patients but is not permitted for Group III patients. The RBE for photons is 1.0. Thus for photons, the D [Gy (RBE)] = D (Gy), i.e. the biological dose is equal to the physical dose.

Note: Protons are allowed for Group II patients only. Proton facilities must be approved by the RTOG, after successfully completing a site visit by the Radiological Physics Center and successfully transferring proton treatment plans in a digital format to the ITC, before any patients can be entered onto this protocol. For protons, the doses to be delivered are in terms of dose equivalent, i.e. Gy (RBE). The physical dose is the dose equivalent divided by the RBE, which is defined as 1.1. Gy = Gy (RBE)/1.1.

6.1 Treatment/Dose Specifications (6/9/10)

6.1.1 Protocol treatment will require highly conformal external beam radiation therapy (EBRT) for Groups II and III. Group I patients will not receive radiation therapy. Patients in either Group II or Group III will receive EBRT, although the target volume definitions (see Section 6.4) and dosing guidelines (see below) will differ by group.

6.1.1.1 Group I patients will not receive radiation therapy.

6.1.1.2 Group II patients will receive EBRT to a total dose of 54 Gy (RBE) in 30 fractions. Fractions will be 1.8 Gy (RBE) daily, 5 fractions per week, excluding weekends. Radiation therapy must begin within 1 month of Step 2 registration. Either 3D-CRT photons, 3D-CRT protons, or IMRT (photons) can be used for this patient group.6.1.1.3Group III patients will receive EBRT using IMRT only. The number of fractions will be 30, however, the total dose and dose per fraction will vary among 2 defined planning target volumes (PTV). Target volume definitions are clarified in Section 6.4. The smaller planning target volume (PTV_{60}) will receive 60 Gy in 30 fractions, while the larger (PTV_{54}) receives 54 Gy during the same 30 fractions. Five fractions will be given per week, excluding weekends. Radiation therapy must begin within 1 month of Step 2 registration.

6.2 Technical Factors (6/9/10)

Treatment will be highly conformal external beam radiation therapy (EBRT) delivered with megavoltage radiation therapy machines of energy ≥ 6 MV or proton delivery machines. Either

3D-CRT or IMRT can be used for Group II patients. Group III patients must be treated with IMRT. Group II patients will be treated with photon 3D-CRT, IMRT, or 3D-CRT protons.

6.3 Localization, Simulation, and Immobilization (7/1/10)

6.3.1 Localization of the tumor, target, and critical normal structures will be on the basis of preoperative and postoperative MRIs.

6.3.2 A non-invasive, stereotactic, relocatable immobilization is recommended for simulation and treatment delivery. These systems may include head cast immobilization, a modified stereotactic frame, a camera-based localization system, etc. The immobilization/relocalization system should be capable of reproducing the patient setup to within 5.0 mm. As a minimum requirement, treatment verification and documentation must be carried out for the first treatment fraction, with weekly portal imaging thereafter. Orthogonal images should be used to document isocenter setup accuracy for the first treatment fraction. These orthogonal images can be obtained with film or EPID. Alternatively, daily imaging techniques can be used. One example of an alternative imaging method is the BrainLab ExacTrac system that uses two orthogonal imaging panels irradiated with KV x-rays. Another example is the volume images obtained with cone-beam CT or any other CT capability that is integrated with the treatment unit. A complete list of IGRT technologies is given on the ATC website at http://atc.wust.edu. Institutions can reduce margins when daily imaging is used. In order to reduce the PTV margins from 5 mm to as little as 3 mm, the institution must be credentialed for the use of IGRT (See section 5.1. and section below).

6.3.2.1 It is acceptable for institutions to reduce margins to less than 5.0 mm without going below 3.0 mm. If reduced margins are to be used, the institution must demonstrate its ability to stay within these limits. The accepted method for reducing margins is to use integrated image guidance on a daily basis. The RTOG definition of IGRT can be found on the ATC website at http://atc.wust.edu. The credentialing procedure for the use of IGRT in RTOG protocols can also be found on this website. The procedure involves sending IGRT verification information to RTOG Headquarters. The Physics Study Chair of this protocol is responsible for reviewing this information. RTOG Headquarters will inform the institution when this credentialing step has been successfully completed.

6.4 Treatment Planning/Target Volumes (6/9/10)

6.4.1 Any of the methods of conformal EBRT (including IMRT, IGRT, tomotherapy, protons, etc.), may be used, each subject to protocol localization and dosimetry constraints.

6.4.2 Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. A single planning target volume (PTV) will be defined for Group II patients, whereas two target volumes will be defined for Group III patients. For both patient groups, the option of creating an accessory PTV is provided below. This is only to be used if it is necessary to limit dose to organs at risk (OAR) as detailed in the table under Section 6.5.

6.4.2.1 **Group II:** The gross tumor volume (GTV) will be defined by the tumor bed on the postoperative-enhanced MRI and is to include any residual nodular enhancement. Neither cerebral edema nor the "dural tail" are to be specifically included within the GTV. (Note: "dural tail" is defined below in Section 6.5). The Group II clinical target volume (CTV_{54}) will be the GTV plus a margin of 1.0 cm. The CTV_{54} margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull. The planning target volume (PTV_{54}) is an additional margin of 3.0 to 5.0 mm, depending upon localization method and reproducibility. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined (see Section 6.5), along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3.0 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTV_{PRV}), defined as the overlap between the PTV_{54} and the particular PRV of concern, may be created. Dose to the PTV_{PRV} must be as close as permissible to 54 Gy (RBE) while not exceeding the OAR dose limit.

6.4.2.1.1 **Group II Proton-Specific Requirements:** In addition to the specifications listed in 6.4.2.1, the following are proton-specific requirements. In addition to the PTV_{54} defined above, an adjustment will be made during the treatment planning process to take into

account the uncertainties along the beam direction, i.e. the range uncertainties, to insure both distal and proximal coverage.

6.4.2.2 **Group III:** The gross tumor volume (GTV) will be defined by the tumor bed on the postoperative-enhanced MRI and is to include any residual nodular enhancement. Neither cerebral edema nor the "dural tail" are to be specifically included within the GTV. (Note: "dural tail" is defined below in Section 6.5). Based upon the GTV, two clinical target volumes (CTVs) will be defined for Group III patients. CTV_{60} will be the GTV plus a margin of 1.0 cm and will receive 60 Gy in 30 fractions. CTV_{54} will be the GTV with a margin of 2.0 cm and will receive 54 Gy in the same 30 fractions. CTV_{54} margins may be reduced to 1 cm (thus corresponding to the PTV_{60}) around natural barriers to tumor growth such as the skull. Planning target volume (PTV) margins of 3.0 to 5.0 mm will be added to the CTVs to account for uncertainties of daily set-up and localization. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, organs at risk (OAR) must be defined (see Section 6.5), along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3.0 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTV_{PRV}), defined as the overlap between the PTV_{54} and the particular PRV of concern, may be created. Dose to the PTV_{PRV} must be as close as permissible to the respective PTV dose (i.e. 60 Gy for PTV_{60}, 54 Gy for PTV_{54}) while not exceeding the OAR dose limit.

6.4.3 Prescription isodose coverage (Groups II and III only)

6.4.3.1 **Group II:** The 54 Gy prescription isodose must cover ≥ 95% of the PTV_{54}. The minimum dose within PTV_{54} must not fall below 51 Gy. The maximum dose to any point (defined as 0.03 cc) must not exceed 62 Gy.

6.4.3.2 **Group III:** Group III patients will have two defined PTVs (see below). The PTV_{60} will be given a dose of 60 Gy in 30 fractions of 2 Gy each. The prescription isodose must cover at least 95% of PTV_{60}. The minimum dose to PTV_{60} must not fall below 57 Gy. The maximum dose within this PTV must not exceed 69 Gy. The second target region (PTV_{54}) will receive a dose of 54 Gy, and this dose must cover at least 95% of the volume. The maximum dose to any point (larger than 0.03 cc) within PTV_{54} should not exceed 62 Gy.

6.5 Critical Structures

In addition to the above defined GTVs, CTVs and PTVs the lenses of both eyes, both retinae, both optic nerves, the optic chiasm, and the brainstem must be defined. The maximum point (defined as a volume greater than 0.03 cc) doses permissible to the structures vary somewhat between Groups II and III and are listed in the table below.

Critical Structure	Group II	Group III
Lenses	5 Gy	7 Gy
Retinae	45 Gy	50 Gy
Optic Nerves	50 Gy	55 Gy
Optic Chiasm	54 Gy	56 Gy
Brainstem	55 Gy	60 Gy

6.5.1 Dural tail definition

The vast majority of meningiomas are durally based. Dura adjacent to the region of dural attachment may enhance in linear fashion, trailing off from the gross tumor. The linear trailing enhancement is referred to as the "dural tail," and is typically composed entirely or almost entirely of hypervascular dura. Microscopic clusters of meningioma are occasionally observed in addition to the hypervascular tissue, but these are as well occasionally encountered in randomly selected dural strips away from the dural tail. There is no evidence to suggest that recurrences are more likely to occur within the dural tail than any other portion of dura next to the main tumor mass [Rogers 2005]. In this protocol dural tail is defined as any linearly enhanced dura trailing off from the primary meningioma mass for several millimeters to centimeters. The GTV should not be modified with respect to the dural tail. However, nodular dural enhancement will be considered as target, and will be included within the GTV.

6.6 Compliance Criteria

6.6.1 For **Group II** patients, as mentioned in Section 6.4, the PTV prescription isodose is to be 54 Gy and must cover >95% of the PTV_{54} volume. The minimum dose will be 51 Gy. If the minimum

dose falls below 51 Gy but remains at or above 48 Gy, an acceptable variation will be assigned. If the minimum dose falls below 48 Gy, an unacceptable deviation will be assigned. The maximum dose for the PTV_{54} should not go above 60 Gy for any volume that is greater than 0.03 cc. If the maximum dose exceeds 60 Gy but does not exceed 63 Gy, an acceptable variation will be assigned. If the maximum dose exceeds 63 Gy, an unacceptable deviation will be assigned.

6.6.2 For **Group III** patients (see Section 6.4), the PTV_{60} prescription dose is 60 Gy and must cover >95% of the PTV_{60} volume. The minimum dose is 57 Gy. If the minimum dose falls below 57 Gy but remains at or above 53 Gy, an acceptable variation will be assigned. If the prescription dose falls below 53 Gy an unacceptable deviation will be assigned. The maximum dose within this PTV (PTV_{60}) should not exceed 66 Gy to any volume that exceeds 0.03 cc. If the maximum dose exceeds 66 Gy but does not exceed 70 Gy, an acceptable variation will be assigned. If the maximum dose exceeds 70 Gy, an unacceptable deviation will be assigned. With reference to the PTV_{54} for Group III patients, the prescription dose is 54 Gy (to 95% volume). The minimum dose for this PTV is 51 Gy. If the minimum dose within PTV_{54} falls below 51 Gy but remains at or above 48 Gy, an acceptable variation would be assigned. If the minimum dose within PTV_{54} falls below 48 Gy, an unacceptable deviation will be assigned. The maximum dose for the PTV_{54} should not go above 60 Gy for any volume that is greater than 0.03 cc. If the maximum dose exceeds 60 Gy but does not exceed 63 Gy, an acceptable variation will be assigned. If the maximum dose exceeds 63 Gy, an unacceptable deviation will be assigned.

6.6.3 As mentioned in Section 6.1, up to 3 days of treatment interruption are permitted for any reason. Interruptions of 4 to 5 treatment days will be considered an acceptable protocol violation. For interruptions of 6 days or greater, an unacceptable deviation will be assigned.

6.7 R.T. Quality Assurance Reviews

The Principle Investigator, Leland Rogers, MD, will perform an RT Quality Assurance Review. These reviews will be ongoing. The final cases will be reviewed within 6 months after the study has reached the target accrual. The primary endpoint is 3-year progression-free survival (PFS). By RTOG quality assurance review criteria, this endpoint requires a full review of diagnostic imaging. The Neuroradiology/Imaging co-chair, Bruce Dean, MD, will perform this review.

6.8 Radiation Adverse Events

Events that may be expected from some, but not all, target locations and beam arrangements include: scalp redness and soreness; hair loss, which may be temporary or permanent; ear/ear canal reactions (irritation or other skin reaction, fluid build-up), possibly resulting in short-term hearing loss; fatigue; lethargy; temporary aggravation of symptoms such as headaches, nausea, seizures, or weakness.

Events that are expected to be uncommon but that may occur include: mental slowing/cognitive defects; decreased memory; permanent hearing loss; cataracts, dry eye(s); decreased sense of smell; decreased sense of taste; dry mouth; behavioral changes; flattened affect; decreased vision; visual field deficits; blindness; motor and/or sensory deficits; decreased balance; unstable gait; seizures; brain edema, possibly with steroid dependency and/or the need for further cranial surgery; necrosis, possibly with steroid dependency and/or the need for further cranial surgery; brainstem or spinal cord damage; and death.

6.9 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

AdEERS REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Use the patient's case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS **must also be reported to RTOG on the AE case report form (see Section 12.1).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons. Sites must bypass the "NOT Required" assessment and complete and submit

the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

	3		**3**		**4 & 5**	**4 & 5**
	Unexpected		**Expected**		**Unexpected**	**Expected**
	With Hospitalization	**Without Hospitalization**	**With Hospitalization**	**Without Hospitalization**		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

	3		**3**		**4 & 5**	**4 & 5**
	Unexpected		**Expected**		**Unexpected**	**Expected**
	With Hospitalization	**Without Hospitalization**	**With Hospitalization**	**Without Hospitalization**		
Unrelated Unlikely	Not required	Not required	Not required	Not Required	Not required	Not required
Possible Probable Definite	10 Calendar Days	Not required	Not required	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA, version 10.0, for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded

from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

6.9.1 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

8.1 Definitions of extent of surgical resection

8.1.1 Simpson's Classification (Appendix V)

The extent of resection is to be defined by the operating neurosurgeon using the Simpson classification of the extent of resection of intracranial meningiomas (Appendix V). Simpson's grade I-III will be defined as gross total resection (GTR), and grades IV and V as subtotal resections (STR). The operative report must be submitted for Quality Assurance Review.

8.1.2 Postoperative Neuroimaging

All patients must have an MRI within 3 months prior to protocol enrollment. Newly diagnosed patients must have MRIs preoperatively and postoperatively. The postoperative study must be completed within 3 month of surgery. The extent of resection will also be defined by postoperative imaging, which will be reviewed centrally. A separate analysis of the surgeon's versus the neuroradiologist's determination of resection extent will be performed.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on

each site's source documents as concomitant medication. The following supportive care measures are permitted:

- Anticonvulsants
- Steroids
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic growth factors
- Herbal products
- Nutritional supplementation

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, including tissue/specimen submission.

- If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note**: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 General Information

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high-quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for central review of pathology. Central review of tissue can be for eligibility and/or analysis.

In this study, meningioma grade will be determined by central pathology review in conjunction with Step 1 registration (mandatory for eligibility for treatment).

In addition, tissue, plasma, serum, buffy coat, and urine will be collected for the purpose of tissue banking and translational research questions (strongly encouraged) as outlined below.

10.2 Specimen Collection for Central Pathology Review for Eligibility (Step 1 Registration)

(6/9/10)

Central pathology review will be performed by Dr. Arie Perry and is required for every case in conjunction with Step 1 registration. Central review will be completed within 4 weeks of receipt. Once the review has been performed and the patient has been deemed eligible, the submitting institution will be sent back the Pre-Registration Pathology Form (P4). The institution will then register the patient according to the Step 2 registration instructions in Section 5.4.

The following material must be supplied for central pathology review:

- One H&E stained slide per paraffin block. Given the heterogeneity that is commonly encountered in meningiomas, just one representative H&E is insufficient for central review. This can be accomplished most efficiently and expeditiously by simply requesting that the histology lab cut 2 sets of slides up front (one for routine diagnosis and the other for central review).
- A paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the RTOG Biospecimen Resource. The block or core must be clearly labeled with the pathology identification number that corresponds to the pathology report. (See Appendix VI for details on obtaining a core/plug sample.)
- A Pathology Report documenting that the submitted block, core, or slides contain a meningioma meeting protocol constraints. The report must include the RTOG protocol number and the patient's case number. The patient's name and/or identifying information should be removed from the report. However, the surgical pathology numbers and

information must NOT be removed from the report. The pathology identification number for the specimen must concur with applicable number on the pathology report.
- A Specimen Transmittal Form and a Pre-Registration Central Pathology Review Form (P4). These forms must include the RTOG protocol number and the patient's case number.
- Submit all materials to the RTOG Biospecimen Resource as described in Section 10.4.

After tissue specimens have been received and logged in at the RTOG Biospecimen Resource, the Biospecimen Resource will forward stained slides to Dr. Arie Perry, where Dr. Perry will perform central review for every case. Once Dr. Perry has completed central pathology review, he will return the slides to the RTOG Biospecimen Resource, where it will be banked for patients who consent to the banking component of the study (See Section 10.3) or returned to the institution that submitted it for non-consenting patients.

10.3 Specimen Collection for Tissue Banking and Translational Research(strongly encouraged)
For patients who have consented to the tissue component of this study (See "About Using Tissue for Research" portion of Appendix I)

See Section 10.8 for translational research study details.

The following material must be provided to the RTOG Biospecimen Resource:

10.3.1 For tissue blocks or fresh, frozen tissue (see Appendix VII for detailed collection instructions):
- A Pathology Report documenting that the submitted tissue specimen contains tumor. The report must include the RTOG protocol number and the patient's case number. The patients' name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource. The form must include the RTOG protocol number and patient's case number.
- Collection kits and instructions for obtaining fresh, frozen specimens are available by contacting the RTOG Biospecimen Resource (See Section 10.4)
  - Kits are available free of charge
  - The RTOG Biospecimen Resource will pay for the shipping of frozen tissue samples (contact the Biospecimen Resource for more information)
- Submit all materials to the RTOG Biospecimen Resource as described in Section 10.4.

10.3.2 For serum, plasma, or buffy coat cells (See Appendix VIII for detailed collection instructions):
- Serum and plasma samples will be collected from patients at baseline (all groups), , at 1 month post-radiation (Groups II and III), and at the time of recurrence if that should occur (all groups).
- Buffy coat cells will be collected from patients at baseline (all groups)
- A Specimen Transmittal Form documenting the date of collection of each specimen, the RTOG protocol number, the patient's case number, and method of storage (for example, stored at –-80º C).
- Collection kits and instructions for obtaining fresh, frozen specimens are available by contacting the RTOG Biospecimen Resource (See Section 10.4)
  - Kits are available free of charge
  - The RTOG Biospecimen Resource will pay for the shipping of frozen peripheral blood samples (contact the Biospecimen Resource for more information)
- Submit all materials to the RTOG Biospecimen Resource as described in Section 10.4.

10.4 Submit all materials (except for urine as described in Section 10.5) to:

US Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Send frozen specimens via overnight courier to the address below. Specimens should be only shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples can be stored at –80ºC until ready to ship.

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.5 Urine Collection for Translational Research (strongly encouraged)

See Section 10.8 for translational research study details.

- Urine samples will be collected at the following times:
  - At baseline (Groups I, II, and III)
  - On the last day of EBRT (Groups II and III)
  - 1 month after the completion of EBRT (Groups II and III)
- Submit the following items to the address listed below:
  - At least 5 cc in a sterile collection cup labeled with patient ID, date and time, and placed in a freezer (range -20˚c to 4˚c).
  - A Specimen Transmittal Form documenting the date of collection of each urine specimen, the RTOG protocol number, the patient's case number, and method of storage (for example, stored at -20º C).
- Send urine samples to Dr. Camphausen's laboratory for appropriate processing and storage in an overnight FEDEX box covered with dry ice. Please call 301-496-5457 and ask for the clinic nurse or email camphauk@mail.nih.gov to obtain a FEDEX shipping code. All shipping charges will be paid by Dr. Camphausen. Please ship to:

Kevin Camphausen
Attn: Clinic Nurse
National Cancer Institute
10 Center Drive
Building 10, CRC Rm B2-3561
Bethesda, MD 20892-1682

Dr. Camphausen will test urine samples using a commercial Elisa system for VEGF, (R&D systems). Urine samples will also have creatinine levels measured by the clinical pathology department for standardization of the VEGF levels in the urine.

As needed, urine aliquots will be shipped to the laboratory of Marsha Moses for MMP activity using gel zymography. These results will be evaluated by two observers blinded to the clinical profile of the patient who supplied the sample. A binary evaluation of low-MW MMP, MMP-2, MMP-9 and high MW-MMP will be made. Each of the five MMPs will be scored as absent (0) or present (1). The five values for each MMP will be cumulated for each patient to create an MMP score from 0-5.

Urine samples collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document. No germline mutation testing will be performed on any of the samples collected unless the patient gives separate informed consent.

10.6 Reimbursement

RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue; $200 per case for a block or core of material; $100 per case for serum or plasma; and $50 for urine. After confirmation from the RTOG Biospecimen Resource and/or Dr. Camphausen's laboratory

that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.7.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.7.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.8 Molecular Correlative Studies

Perry and associates [1997, 1999] have proposed criteria for the grading of meningiomas, based upon a large clinicopathologic series showing statistical associations with recurrence-free and overall survival. These criteria have, in large measure, been adopted by the WHO [Kleihues 2000]. Relative to benign (WHO grade I) meningiomas, atypical (WHO grade II) tumors are those with $\geq$4 mitoses per 10 high power fields (which may be focal), brain invasion, or at least three of the following: sheeting architecture, small cells, macronucleoli, hypercellularity, and/or necrosis. Exclusionary anaplastic findings are $\geq$20 mitoses per 10 high power fields or loss of differentiation under light microscopy (i.e., sarcoma-, carcinoma-, or melanoma-like appearance). Although these criteria are more objective than those used in the past, there is still some interpretive license.

However, evidence is accumulating that immunohistochemical and molecular data may further improve our ability to stratify patients into prognostic subsets [Cai 2001; Bostrom 2001; Perry 1998; Simon 1995; Weber 1997]. For example, malignant progression has been associated with increased MIB-1 (Ki-67) proliferative indices, decreased progesterone receptor expression, and genetic losses involving chromosomes 1p, 10, and 14q. Whereas most of these have not been validated as independent prognostic markers, preliminary data suggests that 14q deletions detected in paraffin-embedded sections by fluorescence in situ hybridization (FISH) are more common in benign meningiomas that recur despite GTR [Perry 1998]. Additionally, loss of expression of a candidate tumor suppressor gene on chromosome 14q termed NDRG2 has recently been identified specifically in the anaplastic and clinically aggressive atypical meningiomas. [Lusis 2005] Whether this represents a truly independent meningioma biomarker requires further testing, but an immunohistochemical assay for this marker is now available at Washington University. Lastly, the finding of p16 (CDKN2A) deletions has been statistically associated with decreased survival times in patients with anaplastic meningiomas, suggesting that this may be a useful prognostic biomarker in this subset of patients. [Perry 2002]

However, the majority of studies evaluating molecular prognostic variables with meningioma have focused on the evaluation of tumor tissue obtained at the time of biopsy and/or resection. This approach is well suited to evaluate molecular pretreatment prognostic markers, but the investigation of predictive post-treatment factors in patients with meningioma has been more limited due to the paucity of available tumor tissue after therapy. Evaluating prognostic markers in urine and serum, which can be obtained with minimally invasive procedures, may be more feasible and applicable to this setting. Therefore, we will also collect both blood products and urine samples from consenting patients for a secondary translational analysis of angiogenesis and molecular prognostic factors. In theory, angiogenic factors could identify patients at risk for recurrent disease, regardless of tumor type since the process of angiogenesis is ubiquitous to cancer. Indeed, multiple investigators have explored the use of angiogenic factors as possible general tumor markers [Cai 2002; Gerhards 2001; Kaban 2002; Kausch 2002; Kraft 1999;

Kuittinen 2002; Lengyel 2001; Linderholm 1998; Moses 1998; Ondruschka 2002; Poon 2001; Sienel 2003; Smith 2000; Verheul 2000]. While angiogenic proteins such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and matrix metalloproteinases (MMPs), have been shown to have prognostic power in specific tumor types, few studies have individually explored the utility of angiogenic proteins as general tumor markers across different tumor types—both solid tumors and hematologic malignancies. A tumor marker that could consistently identify patients at risk for nonresponsive or recurrent disease would allow selection of these patients for more aggressive or alternate treatment. Furthermore, to our knowledge each of the aforementioned studies has focused on the magnitude of either the VEGF or MMP initial level. No study has explored the dynamic *trend* of these protein levels though a course of therapy, its possible predictive significance, or evaluated which methodology was the most powerful for defining the trend.

10.8.1 Specific Aim 1: Do the molecular correlates derived from immunohistochemical evaluation of the pre-therapy surgical specimens add to the standard clinicopathological staging of patients with meningiomas?

Currently, fluorescence in situ hybridization (FISH) testing for deletions of chromosomes 1p, 14q, and the p16 (CDKN2A) region on 9p21 are among the most promising genetic biomarkers for predicting biologic behavior in meningiomas of various grade using routine formalin fixed paraffin material. Additionally, studies have suggested that MIB-1, progesterone receptor, and NDRG2 immunohistochemistry (IHC) may each provide ancillary prognostic information independent of routine histology. We therefore plan to perform both FISH and IHC using these 6 markers on submitted specimens with available paraffin embedded tissue, subsequently correlating disease-free and overall survival times with biomarker data, both on univariate analyses and multivariate analyses incorporating known clinicopathologic prognostic variables such as extent of resection and histologic grade. Given the current rate of scientific discovery, it is further anticipated that additional biomarkers of interest will be identified before the close of this study. If so, the most promising of those additional markers would be added to this panel.

10.8.2 Specific Aim 2: Do the molecular correlates derived from serum evaluation add to the standard clinicopathological staging of patients with meningiomas, and do the initial levels of serum HGF/SF add to the standard clinicopathological staging of patients with meningiomas?

Serum samples provided to the laboratory of Dr. Camphausen will have HGF/SF levels measured using an ELISA system from R&D systems. As the collection of serum from every patient is not mandatory, we will use this data in a hypothesis-generating fashion only. In those patients for whom HGF/SF levels are known, we will stratify the patients by known clinicopathological measures and then within each strata we will divide the patients into two groups: those above and those below the mean HGF/SF for that strata. If HGF/SF adds to the clinicopathological measures the two groups will diverge; if HGF/SF does not add to the clinicopathological measures the groups will admix. We will also test a minor secondary hypothesis that the serum levels of EGF, IGF, and VEGF cannot independently predict local failures better than the standard clinicopathological staging but when combined can create a predictive score for local failure. Serum samples provided to the laboratory of Dr. Camphausen will have EGF, IGF, and VEGF levels measured using ELISA systems from R&D systems. A binary score for each growth factor will be computed with a value of 0 if the growth factor is below the mean and 1 if it is above the mean. Each growth factor score will be combined to create a composite growth factor score from 0-3. In those patients for whom growth factor levels are known, we will stratify the patients by known clinicopathological measures and then within each strata we will divide the patients into two groups: those with a composite score of 0-1 and those with a composite score of 2-3. If composite score adds to the clinicopathological measures the two groups will diverge; if the composite score does not add to the clinicopathological measures the groups will admix.

10.8.3 Specific Aim 3: Do the initial levels of urinary VEGF or MMP add to the standard clinicopathological staging of patients with meningiomas?

Urine samples provided to the laboratory of Dr. Camphausen will have VEGF levels measured using an ELISA system from R&D systems and normalized for kidney function with a spot urinary creatinine level. As the collection of urine from every patient is not mandatory, we will use this data in a hypothesis-generating fashion only. In those patients for whom VEGF levels are known we will stratify the patients by known clinicopathological measures and then within each strata we will divide the patients into two groups: those above and those below the mean

VEGF for that strata. If VEGF adds to the clinicopathological measures the two groups will diverge; if VEGF does not add to the clinicopathological measures the groups will admix. An aliquot of urine will be sent to Marsha Moses, Children's Hospital, Harvard Medical School for MMP analysis by gel zymography. Evaluation of MMP as disease markers will parallel the VEGF analysis as stated above.

10.8.4 Specific Aim 4: Does the dynamic trend of VEGF or MMP level on the last day of radiotherapy compared to the level at the 1-month follow-up predict for disease-free survival at 1-year?

The NCI Radiation Oncology Branch (ROB) previously evaluated urine markers prior to, during, and following definitive therapy in patients undergoing radiation therapy, including several patients with central nervous system tumors [Lusis 2005]. The comparison between angiogenic factor levels taken at least 1 month post-radiotherapy and the last on-treatment level was the strongest predictor of 1-year progression-free survival ($p = 0.004$). Overall MMP trending was also significantly associated with 1-year progression-free survival, as was individual MMP-2 trending ($p = 0.004$ and 0.001, respectively). Step-wise logistic regression revealed that the VEGF trend comparing post-radiation levels to last on-treatment levels was an independent predictor of progression-free survival ($p = 0.02$). Therefore, we plan to expand on these results by prospectively investigating this question in patients with meningioma. Urine samples will be processed and evaluated as in 10.8.1. However for this analysis the change in VEGF level or MMP level from the last day of treatment versus the one-month follow-up value will be compared to the patient's disease status at 1 year. As the collection of urine from every patient is not mandatory, we will use this data in a hypothesis-generating fashion only.

10.9 Specimen Collection Summary

Required Specimens for Central Pathology Review
(send to RTOG Biospecimen Resource, see Section 10.4)

Specimens taken from patient:	Submitted as:	Shipped:
One H&E stained slide of the primary tumor	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2-mm diameter core of tissue, punched from the tissue block with a skin punch	Paraffin-embedded tissue block or punch biopsy	Block or punch shipped ambient

Optional Specimens for Tissue Banking (send to RTOG Biospecimen Resource, see Section 10.4)

Specimens taken from patient:	Submitted as:	Shipped:
A 5-mm^3 surgical sample from tumor	1 sample of fresh, flash frozen tumor taken at surgery	Frozen on dry ice via overnight courier Monday-Wednesday.
5-10 mL of whole blood (red-top) centrifuge for serum	Serum samples into four (4) 1-mL cryovials	Frozen on dry ice via overnight courier Monday-Wednesday.
5-10 mL of anticoagulated blood (EDTA) centrifuge for plasma	Plasma samples into three (3) 1-mL cryovials	Frozen on dry ice via overnight courier Monday-Wednesday.
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat	Frozen buffy coat samples in 1 mL cryovials	Frozen on dry ice via overnight courier Monday-Wednesday

Optional Specimens for Urine Translational Research (send to Dr. Camphausen, see Section 10.5)

Specimens taken from patient:	Submitted as:	Shipped:
At least 5 cc urine	Urine sample in sterile collection cup	Overnight via FEDEX covered with dry ice

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II

11.2 Evaluation During Study

11.2.1 For Group I patients, a neurologic examination and a general examination evaluating potential toxicities will be performed at least once every 6 months for 3 years after protocol enrollment, then yearly for at least 10 years. Group II and III will be examined at least once every 3 months for 3 years. After 3 years, clinical follow-up will be at least yearly for 10 years.

11.2.2 Group I patients will have MRIs prior to study entry and at 6-month intervals for at least 3 years, more frequently if indicated by neurologic symptomology. Patients in Groups II and III will have a pre- and a postoperative MRI, an MRI obtained 3 months post-EBRT, and an MRI obtained at least every 6 months for 3 years. Thereafter, protocol imaging will be at least yearly for 10 years.

11.3 MRI Review

NOTE: A central radiology review form (SR) must be completed by a radiologist and submitted along with each submitted scan.

Serial MRIs will be examined at the institution by an independent reviewer, a radiologist or neuroradiologist. Evaluation of the scans will be compared to and correlated with the patient's clinical course.

For patients in Group I, the following MRIs will be collected: MRI performed pre- and postoperatively, at progression, and at 3 years after registration (irrespective of progression status).

For patients in Groups II and III, the following MRIs will be collected:

- *Subgroups with subtotally resected or newly diagnosed disease*: MRI performed pre- and postoperatively, at progression, and at 3 years after registration (irrespective of progression status.).
- *Subgroups with recurrent or progressive disease*: If surgery was performed, MRI performed pre- and postoperatively; if surgery was not performed: follow-up imaging of progression.

Scans for all groups must be submitted on a CD in DICOM format to RTOG HQ. Central neuroradiology review will be completed as an important outcome measure in this protocol.

11.4 Measurement of Response

Response will be evaluated in this study, where appropriate, incorporating the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See http://ctep.info.nih.gov/guidelines/recist.html for further details. These criteria have been modified as listed below to better apply to meningiomas.

11.4.1 Continual No Evidence of Disease (CNED): will be identified as the circumstance in which a patient with no measurable residual meningioma (gross totally resected, or surgeon's assessed subtotally resected without measurable nodularity on postoperative imaging) has not recurred on follow-up neuroimaging.

11.4.2 Complete Response (CR)*:* will be defined as the circumstance in which there is disappearance of any residual, measurable meningioma.

11.4.3 Partial Response (PR): will be defined as the circumstance in which measurable tumor decreased by ≥20% in any diameter, but does not meet the criteria for CR.

11.4.4 Minor Response (MR): will be defined as the circumstance in which measurable meningioma decreases in any diameter by less than 20%.

11.4.5 Stable Disease (SD): will be defined as the circumstance in which measurable tumor remains unchanged, or increases in any diameter by less than 20%.

11.4.6 Progressive Disease (PD): will be defined as an increase in measurable tumor of greater than 20% in any diameter, or as new nodular enhancement in patients with no measurable tumor on initial postoperative imaging. In the absence of neurologic progression (see below for definition of neurologic progression), suspected imaging progression of less than 5 mm (maximum diameter) must be confirmed on two successive follow-up MRI studies, a minimum of 3 months apart.

11.4.7 Neurologic Progression (NP): will be defined as a new or progressive neurologic deficit attributed to the meningioma, with or without measurable meningioma growth. NP would include, for instance, new diplopia with a cavernous sinus meningioma. In the setting of NP, the designation NP is to be used in conjunction with its appropriate measured response criterion above.

11.5 Central Neuroradiology Review

Central neuroradiology review will be performed by the Neuroradiology Co-Chair, Bruce Dean, MD.

The contrast-enhanced MRI taken before surgery and postoperatively must be submitted per Section 12.1. The follow-up MRI images at the time of any progression and at 3 years after registration (irrespective of progression status) must be submitted on a CD in DICOM format to RTOG Headquarters (no hard films allowed) and must include precontrast axial T1, T2, and FLAIR and postcontrast multiplanar (axial, coronal, and sagittal) T1 images.

For all groups: An MRI must be completed in the event of any neurologic deterioration suggestive of tumor recurrence, unless the last MRI has been done within one month and was compatible with recurrence. Other possible causes of neurologic deterioration, such as metabolic imbalance, increased levels of anticonvulsants, or increased use of other medications, should be considered and properly investigated.

The Central Radiology Review Form (SR) will be used to measure disease and response for each protocol patient. The form is to be completed by the parent institution radiologist. For patients in Groups II and III, a completed form must be submitted for the preoperative and postoperative MRIs, for the protocol-mandated imaging at the time of progression, and at 3 years from registration irrespective of failure status. For patients in Group I, a completed form must be submitted for the prestudy MRI, at the time of progression, and at 3 years from registration. The form should also be completed for any other MRI that may be obtained and from which measurements and other tumor characteristics can be ascertained. The form is to be completed by the institution radiologist. A copy of the form must be kept at the institution.

11.6 Criteria for Evaluation of Therapy Effectiveness

11.6.1 Tumor response and re-growth can frequently be difficult to measure directly and accurately. Serial neurological examinations and MRI may provide a guide. A case will be considered to have experienced progression if MRI scans confirm a case as progressive or if a patient needing neurosurgical intervention/re-resection has a pathologic specimen proving persistent/recurrent viable meningioma.

11.6.1.1 In the event of a discrepancy in progression assessment between the central reviewer and the institutional review, the case will be further reviewed by the neuroradiology co-chair and the RTOG CNS committee chair.

11.6.1.2 The time interval to progression will be measured from the date of study entry until the date of progression.

11.6.2 Overall survival will be measured from the date of study entry until the date of death (or date of last follow-up for patients alive at the time of analysis)

11.6.3 Progression-free survival (PFS) will be measured from the date of study entry until the date of progression or death (or date of last follow-up for patients alive and progression-free at the time of analysis).

11.6.4 Postmortem evaluation of cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on the meningioma and on normal tissue.

12.0 DATA COLLECTION

Data should be submitted to:
RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (6/19/09, 6/9/10)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)** Surgical Report **(S2)** Surgical Pathology Report **(S5)**	Within 2 weeks of registration
Central Pathology Review Form **(P4)**	Within 4 weeks of Step 1 registration
MMSE Mini Mental Status Exam	Within 2 weeks of registration
Follow-up Form **(F1)** MMSE Mini Mental Status Exam	Group I: At least every 6 months for 3 years from registration, then yearly for at least 10 years. Groups II and III: At least every 3 months for 3 years from registration, then yearly for at least 10 years.
Scan data to be collected at RTOG HQ: Groups II & III	
Subgroups of totally resected or newly diagnosed disease, or of recurrent disease treated with surgery	
▪ Pre- and postoperative MRIs and reports **(MR, ME)**, on CD only (no Hard Film)	Within 2 weeks of Step 2 registration
▪ Central Radiology Review Form **(SR)**	
▪ 3 year follow-up, progression, and 2 confirmation of progression MRIs and reports **(MR,ME)** on CD only	Within 2 weeks of scan date
▪ Central Radiology Review Form completed for each scan **(SR)**	
Subgroup of recurrent disease without further surgery for recurrence	Within 2 weeks of scan date
▪ Pre-study MRI scan & report showing progression	
▪ 3 year follow-up, progression, and 2 confirmation of progression MRIs and report **(MR,ME)** on CD only	
▪ Central Radiology Review Form completed for each scan **(SR)**	

Scan data to be collected at RTOG HQ: Group I

▪ Pre- and postoperative MRIs and reports **(MR, ME)** on CD only (no hard film)	Within 2 weeks of Step 2 registration
▪ Central Radiology Review Form **(SR)**	
▪ 3-year follow-up, progression, an MRIs and reports **(MR, ME)** on CD only	Within 2 weeks of scan date
▪ Central Radiology Review Form **(SR)** completed for each scan	

12.2 Summary of Dosimetry Data Submission (6/9/10)

Submit to ITC; see Section 12.2.1

Item	Due
Preliminary Dosimetry Information (DD) †Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • Planning MRI SCAN (The scan used to delineate the target volumes for planning. If more than 1 series is submitted digitally, specify on the DDSI form which one was used for planning. For submission on CD, please also include information regarding the series used for planning with the submission of the CD.) Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html) Hard copy isodose distributions for total dose plan as described in QA guidelines† **NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".**	Within 1 week of RT start
Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	Within 1 week of RT end

†Available on the ATC web site, http://atc.wustl.edu/

For proton submission; information available on the ATC website.

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints (6/19/09)

13.1.1 Primary Endpoint: The progression-free survival (PFS) rate at 3 years (Failure: Local progression or death)

13.1.2 Secondary Endpoints

13.1.2.1 Grade 2-5 neurology category - acute (≤ 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.2 Grade 2-5 ocular/visual category - acute (≤ 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.3 Grade 2-5 dermatology/skin category - acute (≤ 90 days from start of radiation) adverse events [CTCAE, v3.0] excluding alopecia where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.4 Any grade 2-5 - acute (≤ 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.5 Grade 2-5 neurology category - late (> 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.6 Grade 2-5 ocular/visual category - late (> 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.7 Grade 2-5 dermatology/skin category - late (> 90 days from start of radiation) adverse events [CTCAE, v3.0] excluding alopecia where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.8 Any grade 2-5 - late (> 90 days from start of radiation) adverse events [CTCAE, v3.0] where the attribution is related to treatment as definite, probable, possible, or unknown;

13.1.2.9 The survival rate at 3 years;

13.1.2.10 The concordance between central and parent institution histopathologic grading and subtyping;

13.1.2.11 Histopathologic correlates of PFS including light microscopy, immunohistochemical analysis, and microarray analysis;

13.1.2.12 Central neuroradiology review of imaging (MRI) predictors at diagnosis, any failure, and at 3 years from patient registration;

13.1.2.13 Molecular correlative studies as described in Section 10.8;

13.1.2.14 Adherence to protocol-specific target and normal tissue EBRT parameters.

13.2 Background and Sample Size Calculations

The primary endpoint of the study is to estimate the 3-year PFS rate for the three defined patient risk groups, since there are no prospectively collected data available from cooperative group or multi-center clinical trials. The intermediate- and the high-risk groups will receive EBRT, while the low-risk group will be observed following surgery. This trial will generate these estimates based

upon multi-institution experience. They can be subsequently used to design a future trial in the intermediate- and/or high-risk setting. The targeted sample size was arbitrarily set at 50 patients in each risk group for the following reasons:

- The 95% confidence interval around the estimated 3-year PFS rate for each risk group would be no greater than +/- 14% using a binomial distribution;
- A possible estimation of this PFS rate will be obtained separately in patients with new disease and in patients with recurrent disease for the intermediate- and the high-risk groups;
- This will also provide a greater number of patients for histopathologic and molecular correlative studies. These studies will be considered as exploratory analyses to generate hypotheses to be tested in a subsequent study.

Adjusting by approximately 10% to allow for ineligibility and lack of data, the total sample size required will be 55 patients per risk group.

The 3-year failure rate for each risk group was estimated by the study team from reviewing the literature to serve as a guideline in evaluating protocol treatment efficacy. The estimate for the low-risk group is 10% [Adegbite 1983; Condra 1997; Glaholm 1990; Jung 2000; Miralbell 1992; Mirimanoff 1985; Wara 1975]; 10% for the intermediate-risk group [Hug 2000; Miralbell 1992; Taylor 1988]; and 50% for the high-risk group [Dziuk 1998]. If the observed failure rate from this trial is greater than the 95% upper boundary of this literature based–estimate for a risk group assuming binomial distribution, it is of concern that the failure rate may be unacceptably high. Since the intermediate- and high-risk groups both contain patients with newly diagnosed and recurrent disease, failures will be examined relative to the patient's disease status at protocol entry. If the vast majority of failures are seen in patients with recurrent disease, then the definition for that risk group may be changed in addition to considering more intensified treatment for them. If there is no striking difference in failure rates between the newly diagnosed and the recurrent patients within that risk group, then more intensified treatment should be considered for future trials. The frequency of failures will be evaluated twice in each of the intermediate- and high-risk groups. The first time will be after the first 25 eligible patients have been potentially followed for 3 years; the second will be after all patients entered on each of these two risks groups have been potentially followed for 3 years.

A secondary endpoint is to determine the compliance rate of delivering EBRT in the intermediate- and high-risk groups of patients who will be treated with EBRT. In the immediate-risk group, EBRT can be delivered either by 3D CRT or by IMRT; however, in the high-risk group, only IMRT is allowed. The definition of compliance is included in Section 6.6 of the protocol for both groups. If patients treated with EBRT will be reviewed for compliance by the study principle investigator. A case will be considered compliant with protocol treatment prescription if it is scored either per protocol or with acceptable variation. Initially, compliance will be tested using patients separately in the intermediate- and high-risk groups. In each group we will test a compliance rate of 85% against a hypothesized null rate of 65% with type I and II errors of 0.10. In each group the first 30 analyzable patients will be required. The compliance rate will then be tested in each risk group after 30 patients are analyzable. If the significance level with this test is less than 0.10, the protocol may be modified.

It is hypothesized that IMRT will minimize late toxicity in the treatment of meningiomas. There are no randomized studies available that have definitively tested this hypothesis. In fact, there are no reports of prospectively collected adverse events using NCI common toxicity criteria for the treatment of meningiomas with 3D-CRT. The low grade glioma patients treated with 3D-CRT on RTOG 0424 received 54 Gy/30 fractions, as will the intermediate-risk patients on this protocol. Their treated volumes will be similar. Therefore, RTOG 0424 patients will serve as a reference group in evaluating the hypothesis of reduced toxicity with IMRT-treated patients in the immediate-risk group. The rates of adverse events for the neurology, ocular/visual, dermatology/skin (excluding alopecia) categories, individually and combined, were calculated for the 52 patients on RTOG 0424 who potentially had 2 years of follow-up. These calculations appear in the table below:

RTOG 0424 Patients
Treatment Adverse Events
Reported as Definitely, Probably, or Possibly Related to Treatment
(n=52)

	Grade			
Category	1	2	3	4
Dermatology/skin	17	7	2	0
Dermatitis exfoliative NOS	2	1	0	0
Dermatitis radiation NOS	13	3	0	0
Dermatology/skin – Other	4	1	1	0
Erythema multiforme	0	1	1	0
Nail disorder NOS	1	0	0	0
Photosensitivity reaction NOS	2	1	0	0
Pruritus	1	0	0	0
Radiation recall syndrome	1	0	0	0
Neurology	12	12	2	1
Anxiety	3	1	0	0
Cerebral ischaemia	0	0	0	1
Cognitive disorder	2	0	0	0
Confusion state	1	0	0	0
Convulsions NOS	1	1	0	0
Depressed level of consciousness	0	1	0	0
Depression	1	2	0	0
Dizziness	7	1	0	0
Encephalopathy	0	0	1	0
Memory impairment	7	6	2	0
Neurology – Other	3	1	0	0
Olfactory nerve disorder	0	1	0	0
Peripheral sensory neuropathy	4	3	0	0
Tremor	4	0	0	0
Ocular/Visual	5	3	0	0
Dry eye NOS	0	1	0	0
Lacrimation increased	3	0	0	0
Nystagmus NOS	1	0	0	0
Ocular/visual – Other	1	1	0	0
Scleral disorder NOS	1	0	0	0
Vision blurred	1	1	0	0
Worst overall	18 (35%)	17 (33%)	4 (8%)	1 (2%)

Although 3D-CRT is allowed for treatment of intermediate-risk patients, it is expected that 80% to 90% of intermediate-risk patients will be treated with IMRT. With 40 to 45 IMRT-treated patients, only large differences can be detected. For example, an 18% absolute decrease (from 43% to 25%) in the rate of patients with worst overall grade 2+ can be detected with 80% statistical power with a one-sided test at significance level 0.05 assuming binomial distribution. Therefore, reduction of 10% or greater in the rate of patients with worst overall grade 2+ will be considered as supporting the hypothesis. Only a randomized trial between the two treatment deliveries (3D-CRT vs. IMRT) can definitively test that hypothesis.

13.3 Patient Accrual

It is anticipated that the total accrual to this study will be an average of 7 cases per month (3 cases in the low-risk group, 2 cases in the intermediate-risk group, and 2 cases in the high-risk

group). As the first 6 months of the study will see an accrual rate of near zero while the protocol is being approved by member IRBs, it is expected that the accrual period will last approximately 24 months for the low-risk group and 30 months for the intermediate- and high-risk groups. If the observed monthly accrual rate is 1 patient or less during study months 13 to 18 for any of the patient risk group, the feasibility of completing this study in that group will be reviewed by the RTOG CNS Committee and the RTOG Data Safety Monitoring Board (DSMB). Once a risk group meets its target accrual, no further patient registrations will be allowed to that group.

13.4 Analysis Plans (7/1/10)

13.4.1 Interim Reports

Interim reports are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- Monthly patient accrual rate with a projected completion date for the accrual phase;
- Patient accrual by institution;
- Listing of all excluded cases with reasons for exclusion;
- Frequency of baseline patient characteristics; and
- Frequency and severity of adverse events.

All the above items except for institutional accrual will be reported separately by patient risk group. No information regarding efficacy (i.e., progression, survival) will be reported in these interim analyses. Through examining the above items, the statistician and study chairs can identify problems with the execution of the study. These problems will be reported to the RTOG CNS Committee and, if necessary, the RTOG DSMB, so that corrective action can be taken.

13.4.2 Interim Analysis of Treatment Delivery

When the first 30 eligible patients have completed their protocol treatment in each of the intermediate- and high-risk groups, the analysis will be undertaken as soon as their treatment delivery has been reviewed and scored by the study chair. Decisions regarding compliance of EBRT will be calculated separately in each of the risk groups based on the following rules.

13.4.2.1 If at least 23 of the 30 cases are scored as per protocol or with acceptable variation (23/30=76.7%), we will reject the hypothesis that the true compliance rate is no better than 65%.

13.4.2.2 If no more than 22 of the 30 cases are scored as per protocol or with acceptable variation (22/30=73.3%), we will reject the hypothesis that the true compliance rate is at least 85%.

13.4.2.3 If more than 30 cases are available in either group at the time of the analysis, the boundaries for decision making will be adjusted accordingly.

13.4.2.4 The results from each analysis will be reported to the RTOG CNS Committee and the RTOG DSMB so that corrective action can be taken if patients are still being accrued to a patient risk group.

13.4.3 Interim Analysis of Efficacy

When the first 25 eligible patients have been potentially followed for a minimum of 3 years in each of the intermediate- and high-risk groups, the analysis will be undertaken to ascertain the number of failures. In the intermediate-risk group with estimated failure rate of 10%, if the number of failures is greater than 5, it is of concern. In the high-risk group with estimated failure rate of 50%, if the number of failures is greater than 17, it is of concern. If either boundary is crossed, the rate of failures will be calculated with respect to disease status (newly diagnosed vs. recurrent disease). The results from each analysis will be reported to the RTOG CNS Committee and the RTOG DSMB so that corrective action can be taken if patients are still being accrued to a patient risk group.

13.4.4 Analysis for Reporting the Initial Treatment Results for Each Patient Risk Group

This analysis will be undertaken, as described in Section 13.2, when each patient in a risk group has been potentially followed for a minimum of 3 years and after a central review of progression status has been completed. All information reported in the interim analyses (see above) will be included in the final report. All eligible patients receiving any protocol treatment will be included in the analyses of the primary and secondary endpoints as described in Section 13.1.

PFS (as defined in Section 11.5) will be estimated separately using the Kaplan-Meier method for each risk group. The frequency of observed failures within 3 years will be also generated separately. From reviewing the literature, 10% is the estimate for the low-risk patient group;

10% for the intermediate-risk group; and 50% for the high-risk group. If the observed failure rate from this trial is greater than the 95% upper boundary of this literature based–estimate for a risk group assuming binomial distribution, it will reported that the failure rate may be unacceptably high and that more intensified treatment should be considered. If the observed failure rate is unacceptably high, the rate will be examined further by disease status (newly diagnosed vs. recurrent disease). If the vast majority of failures are seen in patients with recurrent disease, we will recommend that the definition for that risk group be revised.

The incidence rates of grade 2+ acute and late adverse events for the neurology, ocular/visual, dermatology/skin (excluding alopecia) categories, individually and combined, will be reported separately for the intermediate- and the high-risk groups because of treatment differences. In addition, incidence rates for intermediate-risk patients treated with IMRT will be compared to those for RTOG 0424 low grade glioma patients treated with 3D-CRT. Lower incidence rates for RTOG 0539 patients will be interpreted as supporting the hypothesis that IMRT delivery reduces toxicity compared to 3D-CRT delivery.

13.4.5 Analysis for Reporting the Results with Combined Patient Risk Groups

This analysis will be undertaken after the initial treatment results have been reported for the three patient risk groups. All eligible patients receiving any protocol treatment will be included in these analyses.

13.4.5.1 All patients will undergo central pathology review of meningioma WHO grade and histology by the study neuropathologist. The rate of concordance between the reviewer from the submitting institution and the central reviewer will be tested using a kappa statistic with a significance level of 0.05. This test will be performed when the review data are available in all three risk groups.

13.4.5.2 All patients will undergo central neuroradiology review to assess tumor size and other features such as edema, homogeneous enhancement, calcification, hyperostosis, and brain invasion. An association between these factors and PFS will be done employing a Cox proportional hazards model (stratified by risk group) using stepwise selection and a significance level of 0.05.

13.4.5.3 Given the projected rates of 3-year PFS for each of the three groups of patients, we would expect that approximately 30% to 60% of patients among the 150 analyzable patients will have experienced progression at the time of this combined analysis. For each of the molecular correlative studies, we would expect 50% to 75% of cases on the study to be available for tissue, serum, and urine analysis. Using Schoenfeld's formula [Schoenfeld 1981], the following table shows statistical powers to detect hazard ratios for PFS of 2.0, 2.25, and 2.5 with prevalence of 30%, 40% and 50%, respectively.

Percentage of patients with tissue analysis	Percentage of events among 150 analyzable patients	Number of events	Prevalence of biomarker	Hazard Ratio		
				2.0	2.25	2.5
50%	30%	23				
			30%	0.33	0.42	0.52
			40%	0.37	0.47	0.57
			50%	0.38	0.49	0.59
	40%	30				
			30%	0.41	0.53	0.63
			40%	0.46	0.58	0.69
			50%	0.47	0.60	0.70
	50%	37				
			30%	0.48	0.61	0.72
			40%	0.54	0.67	0.77
			50%	0.55	0.69	0.79
	60%	45				
			30%	0.56	0.70	0.80
			40%	0.62	0.75	0.85
			50%	0.64	0.77	0.86
75%	30%	34				
			30%	0.45	0.58	0.68
			40%	0.50	0.63	0.74
			50%	0.64	0.65	0.76
	40%	45				
			30%	0.56	0.70	0.80
			40%	0.62	0.75	0.85
			50%	0.64	0.77	0.86
	50%	56				
			30%	0.66	0.79	0.88
			40%	0.71	0.84	0.91
			50%	0.73	0.85	0.92
	60%	67				
			30%	0.73	0.86	0.93
			40%	0.79	0.90	0.95
			50%	0.80	0.91	0.96

13.4.6 CDUS Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5 Gender and Minorities

No publications have reported a survival difference between gender or race in this patient population. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, a statistical analysis will be performed to examine such possible differences if accrual across classes of race and gender permits. The projected gender and minority accruals below are based on reported incidence from the 2004-2005 Central Brain Tumor Registry of the United States (CBTRUS) report, which does not report racial categories of other than white and black:

Projected Distribution of Gender and Minorities

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	11	5	16
Not Hispanic or Latino	99	50	149
Ethnic Category: Total	110	55	**165**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	16	8	24
Native Hawaiian or other Pacific Islander	0	0	0
White	94	47	141
Racial Category: Total	110	55	**165**

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APPENDIX I

SAMPLE CONSENT FOR RESEARCH STUDY

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

RTOG 0539

Informed Consent Template for Cancer Treatment Trials
(English Language)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a meningioma. Meningiomas are tumors that usually arise from the lining of the brain or spinal cord, an area that is known as the meninges. Patients enrolled in this trial will have meningiomas that occur within the skull, around the brain. Meningiomas come in different types and grades, factors that can affect the rate of growth. Meningiomas also can occur in different locations. The location where the meningioma occurs affects how safely and completely a neurosurgeon can remove it. Patients enrolled in this trial can have meningiomas of any type and grade, and the meningioma can have been either completely or partially removed at surgery.

Why is this study being done?
For patients with a newly diagnosed, low-grade meningioma, this study will find out whether surgery alone results in a good outcome. For patients with a recurrent low-grade meningioma or a newly diagnosed higher-grade meningioma, this study will find out what effects, good and/or bad, radiation therapy has on you and on your tumor.

In addition, the researchers will try to see if they can identify through the collection of tissue and MRI scans ways to tell which meningiomas should be treated and which can be watched. Since tissue specimens from every participant will be reviewed by one central pathologist, the study will compare the pathology results of your hospital's pathologist and the study's central pathologist.

How many people will take part in the study?
About 165 people will take part in this study (number of people who participate in this study once their tumors are determined to be meningiomas by the study's central pathology reviewer).

What will happen if I take part in this research study?

Before you begin the study…

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical and neurological exams and history
- Blood work for blood counts
- MRI scan of your brain (an image of your brain produced by magnetic rays). If this is the first time you have had surgery you will need to have had an MRI scan before and after surgery
- Pregnancy test if relevant

You will need to have the following exams, tests, or procedures done because you are in the study.

- Documentation of any steroids, antiseizure medications, or hormones (such as estrogen, progesterone replacements or contraceptives) you are taking
- Documentation of how much of your normal activities you are able to do

During the study…

When you enter the study, your study doctor will need to send the block of tumor tissue obtained at the time of your brain tumor surgery to a central pathology site. There, a pathologist will confirm that the tumor is a meningioma. If the tumor is not a meningioma, you will not be able to continue to participate on this study.

If all exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will need to do the following. They are part of regular cancer care:

- Documentation of any side effects you are experiencing
- Documentation of how much of your normal activities you are able to do
- Documentation of any change in your medications

Study Plan

Based on the grade of your tumor and how much of the tumor was removed at surgery, you will be placed in one of three groups.

- Group I (Low Risk): Patients with a newly diagnosed meningioma that has been completely or partially removed by a neurosurgeon, confirmed by an MRI scan, and found to be World Health Organization (WHO) grade I* when examined by a pathologist.

- Group II (Intermediate Risk): Either
  - Patients with a newly diagnosed meningioma that has been completely removed by a neurosurgeon, confirmed by an MRI scan, and found to be WHO grade II** when examined by a pathologist, or
  - Patients who had a low-risk, WHO grade I* meningioma when first diagnosed but whose tumor has now returned regardless of how much tumor was removed at their surgery.

- Group III (High Risk): Patients with high-risk features including a newly diagnosed or recurrent WHO grade III*** meningioma when examined by a pathologist regardless of how much tumor was removed at their surgery; a recurrent WHO grade II** meningioma

when examined by a pathologist regardless of how much tumor was removed at their surgery; or a newly diagnosed meningioma that has been partially removed by a neurosurgeon, confirmed by a MRI scan, and was found to be WHO grade II** when examined by a pathologist.

*WHO grade I means that you have a benign meningioma. Meningiomas are benign if, under a microscope, they look similar to the cells that they came from and if they do not have features that suggest that they will grow quickly. This is the most common type of meningioma. It has the best prognosis of all the meningioma grades, tends to grow slowly, and is usually cured or well controlled with appropriate treatment and follow-up.

**WHO grade II means that you have an atypical meningioma. Meningiomas are atypical if, under a microscope, they have features that suggest that they will grow at an intermediate rate. This is the second most common meningioma grade, but atypical meningiomas are more likely to come back than grade I tumors are. These meningiomas therefore require more aggressive treatment.

***WHO grade III means that you have the highest grade of meningioma. These tumors are called either anaplastic or malignant meningiomas, which means that they look the least like the cells that they came from and that they usually grow more quickly than meningiomas of other grades. These meningiomas have the highest risk of coming back and therefore require the most aggressive treatment.

A total of 55 patients will have low-risk meningiomas (Group I), 55 will have intermediate-risk meningiomas (Group II), and 55 will have high-risk meningiomas (Group III).

If you are in Group I: You will follow the common practice of being observed without further treatment. You will be observed closely by your study doctor at least every 6 months for at least 3 years, so your study doctor can see if and when your tumor comes back

If you are in Group II: You will receive radiation therapy daily, Monday through Friday, for 30 treatments. The dose will be 54 Gy. You will be seen in follow-up at least every 3 months for at least 3 years.

If you are in Group III: You will receive radiation therapy daily, Monday through Friday, for 30 treatments. The dose will be 60 Gy. You will be seen in follow-up at least every 3 months for at least 3 years.

When I am finished receiving radiation therapy (Groups II and III) …. ***OR***
When I have reached the follow-up stage (Group I) ….

The following tests and procedures will be repeated regularly when you are seen in follow-up as part of your normal care:

- Physical and neurological exams
  - Group I: At least every 6 months for 3 years, then at least yearly for 10 years
  - Groups II and III: At least every 3 months for 3 years, then at least yearly for 10 years

- MRI scan of your brain
    - Group I: Every 6 months for 3 years, then yearly for 10 years
    - Groups II and III: 3 months after you stop receiving radiation therapy, then at least every 6 months for 3 years, then at least yearly for 10 years

As a result of your being in the study, the following tests and procedures will be repeated regularly when you are seen in follow-up:

- You will be asked about any side effects of treatment you are experiencing.
- You will be asked to document your ability to perform your normal activities.
- You will be asked about any steroids, antiseizure medications or hormones (such as estrogen, progesterone replacements or contraceptives) you are taking.

How long will I be in the study?
If you are in Groups II or III, you will receive radiation therapy for about 6 weeks. Patients in all groups will be followed closely for 3 years and will be seen at least yearly for 10 years from then on.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your study doctor if you are thinking about stopping, so he or she can evaluate any risks from the radiation therapy (Groups II and III). Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving treatment. In some cases, side effects can be serious, long lasting, or may never go away. In rare situations, a severe side effect may be life threatening.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the radiation therapy include those that are:

Likely
- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions (irritation or other skin reaction, fluid buildup), possibly resulting in short-term hearing loss
- Fatigue

- Tiredness/sluggishness
- Temporary worsening of symptoms such as headaches, seizures, or weakness

Less Likely

- Mental slowing
- Decreased memory
- Permanent hearing loss
- Cataract(s)
- Dry eye(s)
- Decreased sense of smell
- Decreased sense of taste
- Dry mouth
- Behavioral change
- Decreased vision

Rare but Serious

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration) which can cause swelling. Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment. Short- or long-term steroid use may be needed.
- Injury to the eyes with the possibility of loss of part of your vision or blindness
- Worsening of neurologic problems such as muscle weakness, loss of sensation, decreased balance, trouble walking, decrease in motor function, difficulty speaking, and seizures.
- Development of other tumors (either benign or malignant)
- Edema (swelling of the brain), possibly requiring short- or long-term steroid use and surgery, and very rarely leading to death
- Brainstem or spinal cord damage

Reproductive risks (6/9/10):

You should not become pregnant while receiving radiation on this study because the radiation can affect an unborn baby. If you are a woman of childbearing potential, it is important you understand that you need to use birth control while receiving radiation on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before receiving radiation on this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. If you are in Group I, you may benefit from surgery alone, without radiation therapy. If you are in Groups II or III. you may benefit from the addition of radiation therapy through improved control of your

meningioma. We do know that the information from this study will help doctors learn more about meningiomas. This information could help future patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:

- Receiving treatment or care for your meningioma without being in a study
- Participating in another study
- Receiving no treatment other than close observation and follow-up
- Having surgery alone or surgery in combination with radiation treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- Local institutional research boards
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?
You and/or your health plan/insurance company will pay for the costs of your treatment in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting other treatment for your meningioma.

You will not receive payment for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor_____*[investigators/ name(s)],* if you feel that you have been injured because of taking part in this study. You can tell your study doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor_____ *[name(s)]* at_____ *[telephone number].*

For questions about your rights while taking part in this study, call the_____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *[telephone number].*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

Consent Form for Use of Samples for Research

About Using Tissue/Blood/Urine for Research

Tissue: You have had surgery to see if you have a meningioma. During surgery, your doctor removed some or all of your meningioma. A portion of this tissue will be sent to a central study pathologist who will review tissue from all patients enrolled in the study. The pathologist will examine the tumor tissue to confirm that the tumor is a meningioma and to confirm the tumor grade. This review is an essential part of the clinical trial; therefore, permission to let the pathologist review the tissue is mandatory to your participation in the main part of this study.

In addition, we would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about meningiomas and other diseases. You will not be charged for the processing of your tissue for any of this research. Please read the information sheet called "How is Tissue Used for Research" to learn

more about tissue research. This information sheet is available to all at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

Blood: As a result of your participation in the trial, you also will have a blood test performed before you enter the study. We would like to collect for future research about three tablespoons of blood during this time (all Groups). We would also like to collect for future research about three tablespoons of blood taken at the following additional times: 1 month after you have finished receiving radiation (Groups II and III) and if your disease gets worse while you are on the study (all Groups). If you agree, this blood will be kept and may be used in research to learn more about meningiomas and other diseases. You will not be charged for the processing of your blood for any of this research.

Urine: In addition, we would like to keep some of your urine for future research. We would collect your urine at the following times: at the beginning of the study (all Groups), on the day you finish receiving radiation therapy (Groups II and III), and 1 month after you have finished receiving radiation (Groups II and III). If you agree, the urine will be kept and may be used in research to learn more about meningiomas and other diseases. You will not be charged for the processing of your urine for any of this research.

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have meningiomas and other diseases in the future.

Reports about research done with your tissue, blood, and urine will not be given to you or your study doctor. These reports will not be put in your health record. This research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will be returned to the institution that submitted it, and any blood or urine that remains will be destroyed.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research (about diseases that are passed on in families). Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new products in the future.

Benefits

The benefits of research using tissue, blood, and urine include learning more about what causes meningiomas and other diseases, how to prevent them, and how to treat them.

Risks
The greatest risk to you is the release of information from your health record. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence circle "Yes" or "No". If you have any questions, please talk to your study doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer as follows:

- *Tissue ☐Yes ☐No*
- *Blood ☐Yes ☐No*
- *Urine ☐Yes ☐No*

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease) as follows:

- *Tissue ☐Yes ☐No*
- *Blood ☐Yes ☐No*
- *Urine ☐Yes ☐No*

3. Someone may contact me in the future to ask me to take part in more research.
☐Yes ☐No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov.cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all__*[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant

Date

APPENDIX II

STUDY PARAMETER TABLE

(see Sections 11.2, 11.3, & 11.5 for details) (6/19/09, 6/9/10)

	Pre-Treatment				**During RT (Groups II & III)**		**Follow-Up**					
	Prior to Step 2 Regis-tration	Within 12 weeks prior to Step 2 Regis-tration	Within 8 weeks prior to Step 2 Regis-tration	Within 14 days prior Step 2 Regis-tration	Weekly	On the last day of RT	1 month after the comple-tion of RT (Groups II & III)	3 months after the comple-tion of RT (Groups II & III)	At least every 6 months for 3 years, then at least yearly for 10 years	At least every 3 months for 3 years, then at least yearly for 10 years	At 3 months post-RT, then at least every 6 months for 3 years, then at least yearly for 10 years	At failure if appli-cable
Neurologic exam/history/physical			X				X		Group I	Groups II & III		
MMSE Mini Mental Status Exam				X			X		Group I	Groups II & III		
Steroid dose documentation			X		X	X	X		Group I	Groups II & III		
Documentation of other hormonal agents (e.g., estrogens, progesterones, contraceptives)			X				X		Group I	Groups II & III		
Performance status			X									
CBC w/ diff & ANC, platelets			X									
Brain MRI*		X						X	Group I		Groups II & III	X
Serum pregnancy test (if applicable)				Groups II & III								
Adverse event evaluation					X					Groups II & III		
Tissue block (central pathology review)	X											

APPENDIX II (CONT'D)

	Pre-Treatment				During RT (Groups II & III)		Follow-Up					
	Prior to Step 2 Regis-tration	Within 12 weeks prior to Step 2 Regis-tration	Within 8 weeks prior to Step 2 Regis-tration	Within 14 days prior Step 2 Regis-tration	Weekly	On the last day of RT	1 month after the comple-tion of RT (Groups II & III)	3 months after the comple-tion of RT (Groups II & III)	At least every 6 months for 3 years, then at least yearly for 10 years	At least every 3 months for 3 years, then at least yearly for 10 years	At 3 months post-RT, then at least every 6 months for 3 years, then at least yearly for 10 years	At failure if appli-cable
Specimen Banking for Consenting Patients (encouraged but not mandatory)												
Tissue block or fresh frozen tissue		X										
Serum or plasma		X					X					X
Buffy coat		X										
Urine		X				X	X					

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed (Karnofsky 10-20).**
5	**Death (Karnofsky 0).**

APPENDIX IV

NEUROLOGIC FUNCTION (NF) STATUS

NF	
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX V

Simpson's Classification of the Extent of Resection of Intracranial Meningiomas

GRADE	DEFINITION OF EXTENT OF RESECTION
I	Gross total resection of tumor, dural attachments and abnormal bone
II	Gross total resection of tumor, coagulation of dural attachments
III	Gross total resection of tumor without resection or coagulation of dural attachments, or extradural extensions (e.g. invaded or hyperostotic bone)
IV	Partial resection of tumor
V	Simple decompression (biopsy)

APPENDIX VI

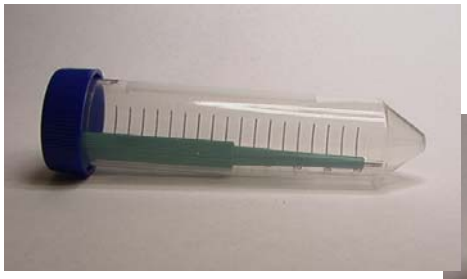
SPECIMEN PLUG KIT*

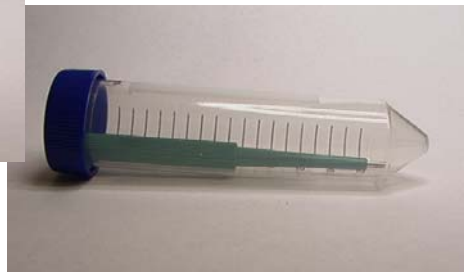
The specimen plug kit contains a shipping tube and a dermal needle.

Step 1
Place the dermal needle on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the needle into the paraffin block. Twist the needle once around to separate the plug from the block. Then pull the needle out of the block. The needle should be filled with tissue sample.

Step 2
Label dermal needle with proper specimen ID. DON'T try to remove specimen from needle.

Use a separate derma needle for every specimen. Please do not mix specimens. Call or email us if you have any questions or need additional specimen plug kits.





Step 3
Once specimen needle is labeled, place in shipping tube and mail to address below.

We will remove specimen from the needle and embed in a cassette and label with specimen ID.

***NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.**

Ship: Specimen plug kit, specimen in derma needle, and all paperwork to the address below:

US Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VII

FROZEN TISSUE KIT INSTRUCTIONS

Instructions for use of frozen tissue kit:

This kit includes:

- Biohazard pads/wipes 4" x 4" (orange)
- Five (5) 5-mL cryovials
- Disposable scalpel blades
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label

Preparation of **Fresh Frozen Tissue**:

- ❑ On sterile cutting board, lay out the underpads.
- ❑ Keep biohazard wipes nearby to keep area clean throughout process.
- ❑ Label cryovials with RTOG study and case numbers

Process:

- ❑ Using provided disposable scalpel, evenly cut tissue into 5 separate pieces (Note: if a frozen core was obtained, do not cut but send it whole).
- ❑ Use forceps to place each piece of tissue into individual 5-mL cryovials.
- ❑ Snap freeze tissue samples.
- ❑ Once frozen, place all of the cryovials into biohazard bag
- ❑ Use RTOG labels* to label bag.
- ❑ Store at –80° Celsius until ready to ship.

*RTOG labels are obtained at the time of patient registration. **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Shipping/Mailing:

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (if appropriate; double-check temperature sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.*
- ❑ Send frozen specimens via overnight courier to the address below. Specimens should be only shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples can be stored at –80ºC until ready to ship.
- ❑ For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource:

Courier Address (FedEx, UPS, etc.): <u>For Frozen Specimens</u>
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: RTOG@ucsf.edu; 415-476-RTOG (7864)/FAX 415-476-5271

APPENDIX VIII

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit:

This kit includes:

- Ten (10) 1-mL cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label(s)

Preparation of **Serum:**

- ❑ Using four (4) or more 1-mL cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one 5-mL red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
3. Aliquot a minimum of 0.5 mL serum into each of the four 1-mL cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as "serum".
4. Place cryovials into biohazard bag.
5. Store serum at –80° Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Preparation of **Plasma:**

- ❑ Using three (3) or more 1-mL cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

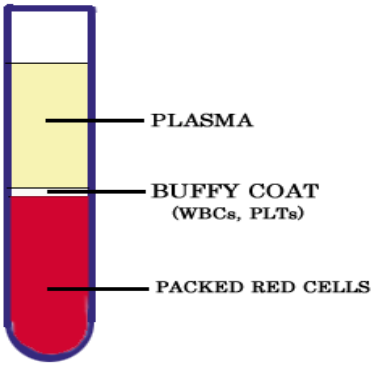
Process:

1. Centrifuge specimen within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully pipette and aliquot a minimum of 0.5-mL plasma into each of the 1-mL cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as "plasma".
4. Place cryovials into biohazard bag.
5. Store plasma at a minimum –80° Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Preparation of **Buffy coat:**

For a visual explanation of Buffy coat, please refer to diagram below.



- ❑ Using three (3) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "buffy coat".

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into the 1ml cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date and time of collection.
5. Place cryovials into biohazard bag.
6. Store buffy coat samples frozen until ready to ship.

Shipping/Mailing:

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*
- ❑ Send frozen specimens via overnight courier to the address below. Specimens should be only shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples can be stored at –80ºC until ready to ship.
- ❑ Notify the Biospecimen Resource before you send specimens
- ❑ For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource:

Courier Address (FedEx, UPS, etc.): <u>For Frozen Specimens</u>
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
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