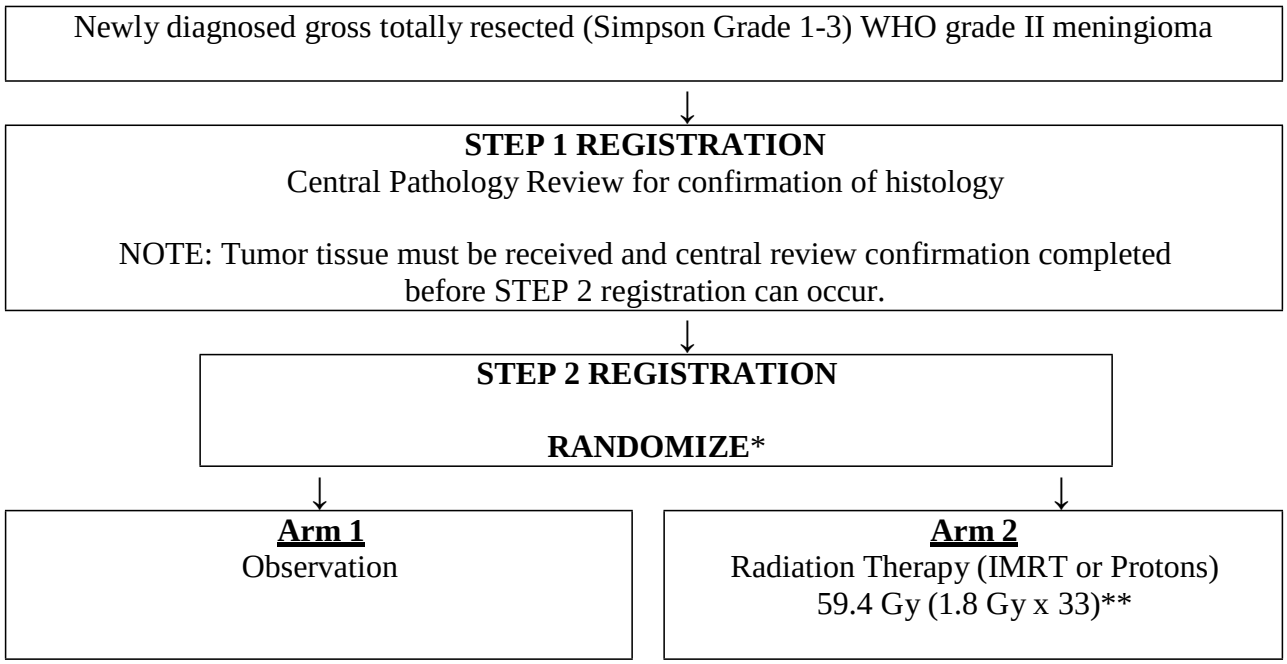
NRG ONCOLOGY NRG-BN003 *(ClinicalTrials.gov NCT #)*

PHASE III TRIAL OF OBSERVATION VERSUS IRRADIATION FOR A GROSS TOTALLY RESECTED GRADE II MENINGIOMA

SCHEMA



*Randomization is 1:1.
**See Section 5 for radiation therapy details and Section 8 for radiation therapy credentialing requirements.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential randomized to receive radiation therapy must use medically acceptable forms of contraception, hormonal or non-hormonal, throughout the entire course of radiation therapy.

3.1.3 Submission of tumor tissue is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (Left-over tissue will be returned to the submitting institution or, for consenting patients, banked for future research. See details for tissue submission requirements in Sections 3.2 and 10.)

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

PRIOR TO STEP 1 REGISTRATION

3.2.1 The patient must have a newly diagnosed unifocal intracranial meningioma, gross totally resected, and histologically confirmed as WHO grade II based upon pathology findings at the enrolling institution. WHO grade will be assigned according to WHO 2016 criteria.

3.2.2 Gross total resection (GTR) will be interpreted as modified Simpson grade 1-3 (see table below) without gross residual dural-based or extradural tumor. GTR must be confirmed both by modified Simpson grade and by post-operative MRI findings. For the protocol definition of GTR and the amended definitions of Simpson resection grade 1-3, see Section 3.2.1, and the first two paragraphs of Section 2 and the table below.

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

Simpson Grade	Definition of Resection Extent
1	Gross total resection of tumor, dural attachments and abnormal bone
2	Gross total resection of tumor and gross extradural extensions (e.g. venous sinus or invaded or hyperostotic bone), coagulation of dural attachments
3	Gross total resection of tumor without resection or coagulation of dural attachments, but including resection of all gross extradural extensions (e.g. venous sinus or invaded or hyperostotic bone)

3.2.3 Step 1 registration must occur within 180 days of the initial surgery. This will provide sufficient time for post-operative imaging confirmation of resection extent after resolution of operative changes. Moreover, it will permit additional surgery if needed to achieve a GTR. Within this 180 day interval, a second surgery is permitted in order to achieve GTR, but even with a second surgery, Step 1 registration must occur within 180 days of the initial resection.

3.2.4 For step 1 registration the operating neurosurgeon must provide the modified Simpson grade (see table above).

3.2.5 GTR must be confirmed on post-operative imaging following the most recent surgery. For protocol enrollment, the assessment of GTR will be made at each site. However, submission of both pre-operative and post-operative MRIs is required for patients. If a second surgery is performed, submission of post-operative MRI is required and pre-operative MRI is required only if obtained. All sequences obtained in the pre- and post-operative MR imaging are to be submitted to NRG Oncology for study registration. Imaging subsequent to enrollment must include pre and post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan and an axial T2 FLAIR sequence. To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE axial MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. The post-operative MRI must be completed within sufficient time to permit Step 1 registration within 180 days of the initial resection. These same conditions apply in the setting of a second surgical procedure, although if a second surgery is completed, Step 1 registration must still occur with 180 days of initial surgery (see Section 3.2.3). CT imaging is not required, but may be obtained if desired clinically, for instance to assess calcifications or hyperostosis.

3.2.6 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

NOTE: Central pathology review must occur between Steps 1 and 2 of registration. Once appropriate pathology specimens are received, central pathology review will occur within 15 days, and must confirm WHO grade II meningioma before the patient can proceed to Step 2 registration and randomization. See Section 10 for details of central pathology review.

PRIOR TO STEP 2 REGISTRATION

3.2.8 Histologically confirmed diagnosis of WHO grade II meningioma confirmed by central pathology review prior to Step 2 registration

3.2.9 Age ≥ 18;

3.2.10 History/physical examination, including neurologic examination within 60 days prior to Step 2 registration

3.2.11 Post-operative Zubrod Performance Status 0-1 within 60 days prior to Step 2 registration;

3.2.12 If the patient is a woman is of childbearing potential, a serum pregnancy test, obtained within 14 days prior to Step 2 registration, must be negative, and, if randomized to receive radiation therapy, the woman must agree to use contraception as defined in Section 3.1.2.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Optic nerve sheath meningioma, spinal or other extracranial meningioma, multiple meningiomas, hemangiopericytoma;

3.3.2 Definitive evidence of metastatic meningioma (metastasis, although rare, can occur and is exclusionary);

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

3.3.4 Previous radiotherapy to the scalp, cranium, brain, or skull base and radiation-induced meningiomas;

3.3.5 Major medical illnesses or psychiatric impairments, which in the investigators opinion, will prevent administration or completion of the protocol therapy and/or preclude informed consent. These include, but are not restricted to:

- Unstable angina and/or congestive heart failure requiring hospitalization at the time of Step 2 registration;
- Transmural myocardial infarction within the last 6 months prior to Step 2 registration;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of Step 2 registration;
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of Step 2 registration;
- Type II neurofibromatosis (NF2);
- Ailments entailing substantial increases in sensitivity and side effect risk from radiation therapy (ataxia telangiectasia, Nijmegen breakage syndrome, and HIV with CD4 count < 200 cells/microliter); HIV testing is not required for eligibility for this protocol, and known HIV positive patients are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to Step 2 registration.
- Inability to undergo MRI with and without contrast (e.g. claustrophobia, non-MRI compatible implant or foreign body, gadolinium allergy or renal dysfunction preventing the patient from receiving gadolinium- institutional guidelines should be used to determine if patients are at risk for renal dysfunction). Note that patients with severe claustrophobia are permitted on this study if they are willing and able to undergo MRI with adequate sedation or anesthesia.