Update on Radiation Therapy for Central Nervous System Tumors

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KEYWORDS

• Radiation therapy • Central nervous system tumors • Glioma • Brain metastases • Meningioma

KEY POINTS

- The management of primary brain tumors increasingly is driven by molecular determinants, and older trials must be reinterpreted in this context.
- Multimodality therapy with surgery, radiation, and chemotherapy is critical to achieving the best possible outcomes in high-grade gliomas and low-grade gliomas.
- There is a growing emphasis on neuroprotection in the treatment of brain metastases with increased use of stereotactic radiosurgery and hippocampal avoidance whole-brain radiation therapy.
- Management of meningioma patients increasingly is dictated by large cooperative group trials to select best radiation approach based on extent of resection and tumor grade.

INTRODUCTION

Radiation therapy (RT) plays an important role in the management of patients with central nervous system (CNS) tumors. RT is delivered through external beam RT (x-rays, gamma rays, and protons) or brachytherapy with implanted sources of radioactive activity.[1] RT causes its intended effects through DNA damage.[2] Absorption of ionizing radiation by matter produces charged particles that can ionize DNA directly (direct action) or ionize water molecules to produce reactive hydroxyl radicals that can react with DNA (indirect action) to mediate damage.[3] Complex and severe damage to DNA that cannot be repaired leads to loss of proliferative ability or cell death via mitotic death, necrosis, autophagy, or apoptosis.[4]

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Fractionated Radiation Therapy versus Stereotactic Radiosurgery

For CNS tumors, external beam RT is delivered most commonly with 2 primary techniques: fractionated (conventional) RT and stereotactic radiosurgery (SRS).[5] Conventional fractionated RT treats a patient over several weeks of daily treatment using multiple small fractions (eg, 1.8 Gy or 2 Gy a day over 5–7 weeks). The benefit of fractionation is to give time for normal cells to repair and reduce toxicity while preferentially causing cell death in tumor cells via DNA damage. SRS, a technique pioneered by Lars Leksell in 1951,[6] applies neurosurgical concepts of stereotaxis to precisely deliver high doses of radiation to tumors. In contrast to conventionally fractionated RT, SRS relies on maximal precision, accuracy, and reproducibility to deliver high doses of radiation in 1 treatment.[7] Typical doses to treat brain metastases (BMs), for example, are 18 Gy to 24 Gy in a single treatment session. Stereotactic RT (SRT) refers to a similar stereotactic approach delivered over 2 to 5 treatments.[8]

Types of External Beam Radiation

Photon (x-rays and gamma rays)-based radiation is the most accessible and common form of RT employed for CNS tumors. Generally, a linear accelerator is used to generate ionizing radiation that targets the tumor. In addition to photon-based therapy, proton therapy can be used for purposes of external beam radiation. Proton-based RT delivers a biologic dose to targets similar to photon-based therapy at the Bragg peak, the point at which protons penetrate deepest in tissue followed by a sharp dose falloff. This phenomenon decreases the total integral dose to normal tissue compared with photon-based therapy. Although there can be hypothetical benefits to proton therapy in certain settings,[9] there are only a limited number of facilities in the country due to cost, space, and complexity of this therapy.

Techniques to deliver RT have improved significantly in recent years, including the development of 3-dimensional (3-D)–conformal RT (CRT), intensity-modulated RT (IMRT), and volumetric modulated arc therapy. Proton RT can be delivered with passive scatter and pencil beam scanning, conceptually analogous to 3-D–CRT and IMRT.

This review provides updates on the use of RT in the management of CNS tumors, with a focus on gliomas, BMs, and meningiomas.

GLIOMAS

Gliomas represent primary brain tumors of the CNS that arise from glial cells, and they include astrocytomas and oligodendrogliomas. According to the most recent Central Brain Tumor Registry of the United States update, there are average 24,697 cases of malignant CNS tumors per year.[10]

Although gliomas historically have been classified by histologic findings, molecular classification has revolutionized the field with restructuring and updating of classification of CNS tumors by the World Health Organization (2016) to incorporate molecular changes.[11] In recent years, it has been clear that somatic mutations in isocitrate dehydrogenase 1 gene (*IDH1*) or isocitrate dehydrogenase 2 gene (*IDH2*) are common, particularly in lower-grade gliomas. *IDH1*/*IDH2* mutations were associated with better outcomes relative to *IDH* wild-type glioma patients.[12] Furthermore, among *IDH*-mutant tumors, a subset of patients has whole-arm losses of chromosomes 1p and 19q, findings that now are classified as oligodendrogliomas. Among patients with *IDH* mutation, 1p/19q codeletion is associated with a more favorable prognosis relative to non-codeleted patients.[13]

Although newer and ongoing trials often incorporate molecular findings in tumor classification, clinical trials that have established the role of RT for CNS tumors

were completed in an era prior to understanding of the importance of molecular changes in gliomas. Current practice draws on older literature while incorporating molecular information as possible. Modern studies that contextualize molecular findings and implications for therapy in a prospective manner are awaited.

Glioblastoma

Historical perspective

Glioblastoma (GBM) is the most common primary malignant CNS brain tumor, representing 48.6% of all malignant CNS tumors.[10] The role of RT in high-grade gliomas has been long established, including in studies from the 1970s showing a survival benefit associated with RT compared with supportive care or chemotherapy alone.[14–16] Initial studies used whole-brain RT (WBRT) for treatment, but data eventually emerged to show that more localized approaches to treatment with involved-field RT resulted in survival outcomes similar to those from WBRT.[17] These early studies also established a dose of 60 Gy for GBM, with a dose response and improved survival associated with 60-Gy treatment relative to lower doses.[18]

Standard treatment paradigm

The standard treatment of GBM involves RT with concurrent and adjuvant temozolomide, as evaluated by the European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981 National Cancer Institute of Canada trial.[19,20] In this trial, patients were randomized to RT alone versus RT with concurrent and adjuvant temozolomide. There was a survival benefit with temozolomide therapy (median survival 14.6 months vs 12.1 months, respectively) and 5-year survival advantage (10% vs 2%, respectively).[20] The use of tumor-treating fields after chemoradiation also has shown a survival benefit in a phase 3 randomized trial in patients with newly diagnosed GBM,[21] although adoption of this treatment remains variable.

Radiation dose

Given poor outcomes associated with GBM and a dose response with RT,[18] there have been many attempts to dose escalate in GBM. Unfortunately, these attempts generally have not been successful. Radiation Therapy Oncology Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) 1374 evaluated a total dose of 70 Gy without a survival benefit.[22] Subsequent studies using doses higher than 60 Gy,[23] accelerated fractionation,[24] hyperfractionation,[25] brachytherapy boost,[26] and SRS boost (RTOG 9305)[27] have been investigated but failed to show a clear benefit.

Radiation volumes

A vast majority of GBM patients have recurrence within the high-dose radiation field.[28,29] There is significant heterogeneity in radiation fields, and European and North American cooperative groups have adopted different approaches for target delineation. Consensus EORTC–Advisory Committee for Radiation Oncology Practice guidelines generally recommend a single clinical target volume (CTV), with a focus on the resection cavity and residual enhancing regions on T1-weighted sequences (gross tumor volume [GTV]) and the addition of a 2-cm margin.[30] In contrast, NRG protocols favor a 2-phase approach, with CTV covering T2/fluid-attenuated inversion recovery abnormality (FLAIR) and 2-cm expansion in an initial phase (46 Gy) and cone-down CTV of enhancing disease and cavity with 2-cm expansion to full dose (60 Gy).[31] Although standard RT involves generous margins, there is emerging retrospective literature supporting the use of more limited fields for RT with comparable outcomes.[32–34]

Management in elderly patients

GBM has a median age of 65 years old, and several trials have evaluated shorter courses or omission of RT for elderly patients.[35] The most important trials are summarized in **Table 1**. The Roa and colleagues[36] trial demonstrated that comparable outcomes can be achieved with hypofractionated radiation over 3 weeks (40 Gy over 15 fractions) relative to standard fractionation over 6 weeks. Although this trial was done prior to the temozolomide era, a subsequent Canadian Cancer Trials Group/EORTC trial has shown the superiority of hypofractionated radiation with concurrent and adjuvant temozolomide, compared with hypofractionated radiation alone; this has become a standard-of-care option for elderly patients with newly diagnosed GBM with good performance status.[37]

For elderly patients who may tolerate only single-modality treatment, *MGMT* promoter methylation status can help guide treatment decisions per the NOA-08 and Nordic trials.[38,39] Temozolomide monotherapy could be considered for MGMT methylated patients, whereas RT appears to provide a similar benefit regardless of MGMT methylation status. For frail and/or elderly patients, a randomized IEAE trial demonstrated that a hypofractionated RT regimen over 1 week (25 Gy) was associated with outcomes similar to those from hypofractionated RT over 3 weeks.[40]

Future directions

Given poor outcomes in GBM patients with standard therapy, there are tremendous research efforts to improve outcomes. An example from an RT perspective is NRG-BN001, which is an ongoing phase II randomized trial evaluating the use of IMRT and proton therapy to evaluate hypofractionated dose-escalated radiation treatment (75 Gy in 30 fractions) with temozolomide compared with chemoradiation with standard fractionation.

Anaplastic Gliomas

Historical perspective

Anaplastic gliomas generally refer to grade 3 gliomas (astrocytomas and oligodendrogliomas). Historically, treatment decisions have been based on glioma grading (grade 2 vs anaplastic, grade 3). The clinical trials that inform management of anaplastic gliomas did not incorporate molecular findings, although post hoc analyses of these trials have demonstrated the importance of molecular changes for prognosis and response to therapies. The NOA-04 trial, evaluating chemotherapy versus RT alone upfront, did not find a survival advantage to chemotherapy alone,[41] and standard treatment paradigms generally include both RT and chemotherapy. Interim results from the ongoing CODEL trial have reinforced this notion in *IDH*-mutant, 1p/19q-codeleted tumors as temozolomide alone was inferior to regimens incorporating RT.[42]

Standard treatment paradigm

For patients with *IDH* wild-type glioma, patients with molecular features of GBM are felt to have a similar natural history as grade IV GBM and can be treated with standard GBM therapy with RT and concurrent and adjuvant temozolomide (discussed previously).

For patients with *IDH*-mutant, 1p/19q non-codeleted tumors, generally adjuvant chemoradiation is recommended regardless of extent of resection. RT with chemotherapy (temozolomide or procarbazine, lomustine, vincristine [PCV]) is recommended. Support for chemoradiation comes from the CATNON trial, which randomized patients with newly diagnosed 1p/19q non-codeleted tumors to RT alone, RT with concurrent TMZ, and RT with concurrent and adjuvant TMZ. Early results show that adjuvant temozolomide is associated with a survival benefit (5-year-survival 56% vs

Table 1
Randomized trials evaluating adjuvant therapy in elderly glioblastoma patients

Trial	National Clinical Trial 00482677	National Clinical Trial 1450449	International Standard Randomised Controlled Trial Number 81470623	National Clinical Trial 01502241[a]	National Clinical Trial 00430911	Roa and Colleagues,[36] 2004
Randomization	RT_{3wk} + TMZ vs RT_{3wk}	RT_{1wk} vs RT_{3wk}	RT_{6wk} vs RT_{2wk} vs TMZ	RT_{6wk} vs TMZ	$RT_{5.5wk}$ vs supportive care (SC)	$RT_{6\ wk}$ vs RT_{3wk}
Patients (n)	562	98	291	373	81	95
Age, minimum	65	50^{+}	60	65	70	60
MGMT status						
MGMT methylated	47% (165/354)	N/A	45% (91/203)	35% (73/209)	N/A	N/A
MGMT unmethylated	53% (189/354)	N/A	55% (112/203)	65% (136/209)	N/A	N/A
Unknown	208 (37%)		88 (30%)	164 (44%)	81 (100%)	
Extent of resection						
Biopsy	32%	18%	26%	39%	52%	39%
Partial or complete resection	68%	82%	74%	61%	48%	61%
Median overall survival estimates	RT_{3wk} + TMZ: 9.3 mo RT_{3wk}: 7.6 mo		RT_{6wk}: 6.0 mo RT_{2wk}: 7.5 mo TMZ: 8.3 mo	RT_{6wk}: 9.6 mo TMZ: 8.6 mo	$RT_{5.5wk}$: 6.7 mo SC: 3.9 mo	RT_{6wk}: 5.1 mo RT_{3wk}: 5.6 mo

Abbreviations: N/A, not applicable; TMZ, temozolomide.
[a] Included GBM and anaplastic astrocytoma.

44%, respectively),[43] whereas a subsequent analysis did not show a significant benefit with concurrent TMZ in the overall population but a trend toward benefit in *IDH*-mutant anaplastic astrocytomas.[44]

For patients with *IDH*-mutant, 1p/19q codeleted tumors, grade 3 oligodendroglioma treatments generally are treated with radiation and chemotherapy, supported by favorable outcomes in RTOG 9402[13] and EORTC 26951.[45] In these trials, survival was increased significantly with the addition of PCV chemotherapy to upfront RT with median survival of 14.7 years in the former.[13]

Radiation dose

IDH wild-type; *IDH*-mutant, 1p/19q non-codeleted anaplastic astrocytomas; and *IDH*-mutant, 1p/19q co-deleted anaplastic oligodendrogliomas generally are treated to 59.4 Gy to 60 Gy, per prior and ongoing trials.[13,41,43] Some ongoing trials incorporating molecular features allow for lower doses to anaplastic gliomas based on molecular findings (eg, NRG BN-005 is designed for *IDH*-mutant patients with an RT dose of 54 Gy, regardless of grade).

Radiation volumes

The CATNON study recommended treatment of T2 abnormality, enhancement, and cavity with a 1.5-cm to 2-cm expansion for CTV and additional 0.5-cm to 0.7-cm expansion for planning target volume (PTV). The CODEL study used a 1-cm expansion for CTV1 (50.4 Gy) and enhancement and cavity representing CTV2 (9-Gy boost) with a 5-mm PTV.

Future directions

The ongoing CODEL and CATNON trials have released interim analyses, and they will continue to help inform the management of anaplastic gliomas in the era of molecular characterization. The CODEL trial now is redesigned to specifically compare RT with PCV (per RTOG 9402) with RT with temozolomide to evaluate this important question in *IDH*-mutant, 1p/19q codeleted tumors.[42]

Low-grade Gliomas

Historical perspective

As with anaplastic glioma trials, historical low-grade glioma (LGG), generally grade 2 astrocytomas or oligodendrogliomas, clinical trials were completed prior to understanding of molecular changes. The Non-Believers Trial (EORTC 22845) evaluated the timing of radiation, randomizing patients with LGG to receive postoperative RT versus observation. Although RT provided a progression-free survival (PFS) at 5 years (55% vs 35%, respectively) and reduced prevalence of seizures, there was no significant difference in overall survival.[46] For dose, there were 2 large prospective trials by the EORTC and an Intergroup trial (North Central Cancer Treatment Group/RTOG/ECOG, Believers' Trial) that demonstrated no difference in outcomes between lower dose (45–50.4 Gy) and higher dose (59.4–64.8 Gy) approaches.[47,48]

Standard treatment paradigm

A framework to approaching the management of LGGs has come from RTOG 9802, which stratified patients with LGG as high risk (>40 years or <40 years with subtotal resection) or low risk (<40 years old and with gross total resection). High-risk patients were randomized to RT or RT + PCV chemotherapy, and patients receiving chemotherapy had a significant survival benefit (median survival 13.3 years vs 7.8 years, respectively). Subsequent genomic analysis has shown a benefit to the addition of chemotherapy to RT for *IDH*-mutant non-codeleted and codeleted LGG, but there

was no benefit for IDH wild-type LGG.[49] For low-risk patients, in particular patients with gross total or near-total resection without neurologic symptoms, observation can be considered as delaying RT postpones toxicities of therapy. In the low-risk RTOG 9802 cohort who underwent observation, approximately half of the patients did not have progression at 5 years.[50]

Radiation dose

The most common doses employed for LGG are 45Gy to 54 Gy.

Radiation volumes

GTV generally includes surgical cavity and T2/FLAIR abnormality, and a 1-cm expansion can be used to make CTV. Older trials treated 2 cm to block edge that would approximate a similar treatment volume.

Future directions

Given that LGGs can have better outcomes and long-term survivorship (in particular, patients with favorable molecular features), NRG BN-005 is a phase II trial randomizing IDH-mutant gliomas to proton RT or IMRT to evaluate the possible benefit of proton therapy in lower integral dose with respect to long-term neurocognitive outcomes. Along with the use of protons, there is exploration of delaying treatment because recent trials incorporating chemotherapy and radiation have not evaluated the question of timing. The EORTC IWOT trial is a phase 3 study for *IDH*-mutant 1p/19q non-codeleted patients that evaluates upfront treatment versus active surveillance for patients with a primary outcome of next intervention-free survival.

BRAIN METASTASES

Historical Perspective

BMs are the most common intracranial tumor and occur in up to 40% of patients with certain cancer diagnoses.[51,52] The most frequent primary locations are cancers originating from the lung, breast, skin, kidney and gastrointestinal tract.[53–55] Treatment of BMs includes surgery, WBRT, stereotactic radiation (SRS/SRT), and systemic therapy.[56–58] Standard treatment of BMs includes surgery and SRS/SRT, which offer the best outcomes,[59,60] whereas the WBRT still is an important treatment option for patients with multiple BMs or patients who cannot tolerate surgery and SRS/SRT.[61]

Standard Treatment Paradigm

WBRT has long been the standard of care for the management of patients with BMs. Toxicities associated with WBRT have led to greater selectivity for its use. Multiple randomized trials have shown WBRT is an effective treatment of controlling intracranial metastases and reducing risk of new distant BMs.[62–65] Studies also have reported that WBRT is associated with both stabilized or improvements in neurologic signs and symptoms. Despite the benefits of tumor control and neurologic improvements, routine use of WBRT for all patients still is controversial. The QUARTZ trial examined patients with non–small cell lung cancer (NSCLC) patients with BM.[66] More than 500 patients were evaluated comparing patients receiving WBRT to best supportive care. The trial reported no difference in survival, quality-adjusted life years, or steroid use. This study concludes that WBRT provided little to no benefit for NSCLC patients unsuitable for surgical resection or SRS.

Novel WBRT techniques have been developed to preserve neurocognitive and quality of life by using hippocampal avoidance (HA)-WBRT treatment (**Fig. 1**). RTOG 0933 explored the use of HA-WBRT to minimize risk of neurocognitive decline with WBRT. In this single-arm phase II trial, there was a 7% decline in Hopkins verbal learning test

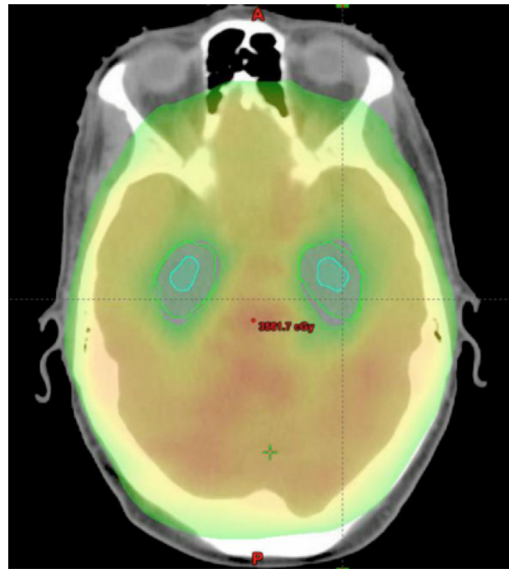

Fig. 1. HA-WBRT. Representative RT isodose plan for HA-WBRT. IMRT is utilized to cover the brain while reducing dose to the bilateral hippocampus. This approach has demonstrated a reduction in risk of cognitive function failure in a randomized phase III trial.[69]

(HVLT)-delayed recall from baseline at 4 months, significantly less in comparison with a historical control comparison.[67] A subsequent phase III trial,[68] NRG CC-001, evaluated the use of HA in WBRT for patients being treated with memantine. With median 7.9 months' follow-up, NRG CC-001 demonstrate that HA reduces risk of cognitive function failure (hazard ratio 0.74; 95% CI, 0.58–0.95; $P = .02$), including HVLT-R total recall, delayed recall, and recognition.[69] There was less deterioration of executive function at 4 months and executive function at 6 months without a significant difference in overall survival, intracranial progression, or toxicity. With these findings, HA-WBRT should gain acceptance as the standard-of-care approach to patients requiring WBRT with good performance status and without metastases in the peri-hippocampal region.[70]

Pharmacologic therapy has provided another method for providing neuroprotection after WBRT. Memantine and donepezil have been evaluated in their role to possibly reduce the rate of cognitive decline and memory loss in patients. In RTOG 0614, a randomized placebo-controlled trial of 554 patients, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speech.[71] The study did not meet its primary endpoint for reduction in the decline in delayed recall at 24 weeks, but the study lacked statistical power due to patient death from progressive disease, resulting in a small number of patients analyzable at that time point.[71] Since this trial, many consider memantine as a standard-of-care addition for patients receiving WBRT. Donepezil is another agent used in Alzheimer disease and vascular dementia, among other indications, that has been tested in patients receiving cranial RT for brain tumors. In a phase III randomized placebo-controlled trial of 198 patients who had received partial or WBRT over 6 months prior, donepezil did not significantly improve the overall composite score encompassing memory, attention, language, visuomotor, verbal fluency, and executive functions at 12 weeks and 24 weeks but did result in modest improvements in several cognitive functions among patients with greater pretreatment impairments.[72]

Many trials have demonstrated the value of stereotactic radiation (SRS/SRT) in the management of BMs.[73–76] In many cases, SRS/SRT can be performed as a direct alternative to surgical resection, and SRS/SRT often is preferred over surgical resection for tumors located within or near eloquent brain structures, including areas that may be challenging to access, such as the brainstem, thalamus, and basal ganglia. In addition, SRS/SRT may be used as an adjuvant therapy following resection.[63,77] Because survival outcomes are similar for surgical resection and SRS/SRT, many institutions perform resection in cases of unclear histology or significant mass effect or in patients with neurologic deficits. Radiosurgery may be the primary option for tumors smaller than 3 cm in diameter. Overall, SRS/SRT provides high local tumor control rates, low toxicity, and reduced risk of hemorrhage, infection, and tumor seeding.

Radiation Dose

A typical WBRT fractionation schedule consisted of 20 Gy in 5 fractions, 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions. For SRS, the typical single-fraction doses are 20 Gy to 24 Gy for tumors less than 2 cm and 18 Gy to 20 Gy for tumors 2 cm to 3 cm in size, and 15 Gy for 3 cm to 4 cm is common.[78] Multifraction courses of SRT (ie, hypofractionated SRS) are utilized with typical doses of 24 Gy to 30 Gy in 3 fractions and 25 Gy to 30 Gy in 5 fractions.[8]

Radiation Volumes

For WBRT, typical volumes include coverage of all brain tissues with confirmation of adequate coverage of intracranial contents, including temporal fossa and cribriform plate. Intact BMs treated with stereotactic radiation include the GTV defined on thin-slice T1 postcontrast magnetic resonance imaging (MRI) with a typical planning volume expansion of 0 mm to 1 mm. When treating postoperative cases, there can be inclusion of the surgical cavity plus any residual tumor at a minimum. In some cases, more generous volumes at postoperative dural areas may be appropriate to lower risk of dural/leptomeningeal recurrence.[79–81] Typical planning expansions of 1 mm to 2 mm is utilized around the resection cavity.

Future Directions

Intracranial response to systemic treatment is being evaluated by numerous clinical trials assessing systemic therapy alone or in conjunction with RT. A combination of targeted radiation with targeted systemic agents or immunotherapy offers an attractive strategy, with the potential to reduce CNS recurrence, therefore, the need for salvage RT. There are numerous clinical trials on ClinicalTrails.gov Web site exploring this approach. Ongoing clinical trials include randomized trials evaluating the use of stereotactic radiation versus HA WBRT (National Clinical Trial [NCT] 03075072) and the use of single-fraction SRS compared with fractionated radiosurgery (NCT04114981).

MENINGIOMA

Historical Perspective

Meningiomas are the second most common primary brain tumors, with approximately 30,000 cases seen per year in the United States.[82] A majority of meningiomas are low grade (85%), with an increased incidence for women relative to men (2–3:1) and an increasing incidence in the sixth to seventh decades of life.[83] The leading acquired risk factor for the development of meningioma is exposure to ionizing radiation.[84] The median recurrence-free survival is 12.5 years for grade I meningiomas, for grade II less than 7 years, and for grade III less than 2.5 years.[85]

Standard Treatment Paradigm

Surgery represents the primary modality in management of meningioma.[86] Extent of resection and grade of tumor then dictate adjuvant radiation volumes and dose. Gross total resection often is performed on meningioma along convexities, anterior parasagittal/sagittal sinus area, olfactory groove, and some tentorial and posterior fossa lesions. Subtotal resection may be feasible only in less accessible tumors, including the skull base, clivus, and posterior parasagittal/sagittal sinus area. The risks and benefits of partial resection need to be weighed on an individual basis. Biopsy alone or empiric RT without biopsy may be appropriate for high-risk areas, such as the cavernous sinus, skull base, and optic nerve sheath.

In the postoperative management of meningiomas, typically a risk-stratified approach is implemented based on pathologic grade and extent of resection. Based on RTOG 0539, low-risk tumors are classified as pathologically grade I with gross total or subtotal resection. Low-risk meningiomas typically do not receive adjuvant radiation. Intermediate-risk meningiomas are recurrent grade I tumors or any grade II after gross total resection and were treated adjuvantly to 54 Gy. Higher-risk tumors are subtotally resected or recurrent grade II tumors as well as all grade III meningioma and were treated to a maximal dose of 60 Gy.

Interim analysis for patients treated on RTOG 0539 showed low-risk patients that were observed had a 3-year PFS of 92%. Intermediate-risk patients treated to 54 Gy had a 3-year PFS of 94%, significantly higher than historical control rates.[87] High-risk patients treated to 60 Gy had a 3-year PFS of 59%.[88] Although practice patterns favor observation for grade I meningioma in noneloquent locations and immediate adjuvant treatment to 60 Gy for grade III meningiomas, the role of adjuvant radiation for grade II meningiomas remains variable and controversial.

Treatment with SRS also a is viable option for low-grade meningiomas with sufficient distance from critical structures, such as the optic apparatus. SRS increasingly is used for treating skull-based meningiomas not amenable to surgical resection.[89,90] Doses for single fractions can range from 12 Gy to 16 Gy and provide greater than 90% actuarial local tumor control at 5 years and 10 years for benign meningiomas of appropriate size. SRS also may be indicated for recurrent meningiomas that previously have received fractionated RT as a salvage option that limits surrounding radiation dose and improves PFS.[91]

Radiation Dose

The dose of radiation used in meningioma is contingent on grade of tumor. For grade 1 meningioma, conventional radiation dose typically is 45 Gy to 55 Gy. When SRS is employed, the dose typically is 12 Gy to 16 Gy. For grade 2 meningioma, typically conventionally fractionated radiation is utilized, with a dose range of 54 Gy to 60 Gy. Stereotactic radiation may be considered in select cases. In grade 3 meningioma, adjuvant radiation is administered to a dose of 59.4 Gy to 60 Gy, with some consideration of higher doses, particularly for gross residual disease.

Radiation Volumes

In conventionally fractionated radiation, the GTV typically is defined on T1 postcontrast MRI. The surgical cavity typically cavity included in adjuvant RT cases. A CTV is created by using a 3-mm to 5-mm expansion on GTV for grade I to grade II meningiomas. CTVs can be shaved off anatomic barriers of spread and can be minimized at brain parenchymal interface in the absence of pathologic brain invasion. Brain parenchyma should be included in the setting of brain invasion. In the setting of suspected

or confirmed bone involvement, CTVs should not be shaved off bone. CTV expansions for grade III meningiomas may be 0.5 cm to 2 cm, depending on institutional practice and generally include brain parenchyma The RTOG 0539 used generous expansions (1 cm for intermediate risk and 1–2 cm for high risk); however, due to the predominately in-field pattern of failure and low rates of marginal failures, the follow-up NRG BN003 (grade II meningiomas status post GTR) uses smaller margins with 5-mm CTV expansions, which can be reduced to 3-mm around critical structures. A PTV is created typically by utilizing a 2-mm to 5-mm expansion on CTV based on institution-specific technical and image-guided RT standards.

For cases treated with SRS, a GTV is generated by defining a gross tumor on T1 postcontrast MRI. CTV/PTV expansions are dependent on institutional practice but often no expansion or 1 mm to 2 mm is used.

Future Directions

Two ongoing radiation studies in meningioma will define standard of care. The ongoing NRG BN003 (NCT03180268) and Radiation versus Observation Following Surgical Resection of Atypical Meningioma/EORTC 1308[92] seek to evaluate the use of adjuvant radiation in grade II meningioma post-GTR. Both randomize patients to adjuvant RT (59.4 or 60 Gy) versus close observation and likely will define standard management for these subgroups.

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