Review Article

The role of radiotherapy in the management of high-grade meningiomas

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Abstract: Meningiomas account for approximately one-third of primary central nervous system tumors with a subset that are aggressive and carry significant morbidity and mortality. Treatment of these high-grade meningiomas, classified by the World Health Organization as grade II (atypical) and grade III (anaplastic) meningiomas, typically includes the combination of surgery and radiotherapy. However, current data guiding the timing, dosage, and modality of radiation treatment (RT) has been limited to case series and retrospective studies. Nevertheless, most studies support that radiation therapy reduces recurrence risk and improves overall survival (OS) for patients with high-grade meningiomas. In this review, we examine the evidence for radiation therapy in the management of patients with atypical and anaplastic meningiomas and discuss current ongoing prospective trials that will further elucidate the optimal role of radiotherapy in the treatment of these aggressive tumors.

Keywords: Atypical meningioma; anaplastic meningioma; radiation; stereotactic radiosurgery (SRS); proton therapy

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Introduction

Meningiomas are the most common primary central nervous system tumors with approximately 25,000 new cases per year (1). While the majority of these tumors are indolent, there is an aggressive subset that exhibits higher recurrence rates with associated morbidity and mortality. As early as 1938, sub-types of meningiomas were identified by Dr. Harvey Cushing and Dr. Louise Eisenhardt based on a series of patients for which they examined the association between location and histology of tumors with recurrence and prognosis (2). Recognizing the need for standardized criteria, the World Health Organization (WHO) released pathological guidelines to help distinguish benign meningiomas from those with more aggressive clinical features beginning in the 1970s. These criteria have undergone a number of revisions with the most recent version published in 2016 (*Table 1*). Based on these guidelines, meningiomas can be divided into three groups: benign (WHO grade I), atypical (WHO grade II), and anaplastic/malignant (WHO grade III). Benign meningiomas, defined as those who do not meet the high-grade pathological criteria, constitute the vast majority of meningiomas. High-grade meningiomas, inclusive of both atypical meningiomas and anaplastic meningiomas, on the other hand, have increased in prevalence with changes in the WHO criteria and are now estimated to account for up to one-fifth to one-third of newly diagnosed meningiomas (6-8). Importantly, atypical and anaplastic meningiomas are more likely to display invasive behavior, locally recur following initial treatment, and have increased morbidity

Table 1 Summary of histopathological criteria of WHO classification of meningiomas from 1993–2016

WHO grade	Year			
	1993	2000	2007	2016
I (benign)	Without features of grade II/III	Without features of grade II/III	Without features of grade II/III	Without features of grade II/III
II (atypical)	Several of the following features: (I) frequent mitoses; (II) increased cellularity; (III) small cells with high n:c ratio and/or prominent nucleoli; (IV) uninterrupted patternless or sheet-like growth; (V) foci of spontaneous or geographic necrosis	4–19 mitoses per 10 hpf and/or 3 or more of the following: (I) increased cellularity; (II) high n:c ratio; (III) prominent nucleoli; (IV) uninterrupted patternless or sheet-like growth; (V) foci of spontaneous necrosis	4–19 mitoses per 10 hpf and/or 3 or more of the following: (I) increased cellularity; (II) small cells with high n:c ratio; (III) prominent nucleoli; (IV) uninterrupted patternless or sheet-like growth; (V) foci of spontaneous or geographic necrosis; (VI) brain invasion	4–19 mitoses per 10 hpf and/or brain invasion and/or 3 or more of the following: (I) increased cellularity; (II) small cells with high n:c ratio; (III) prominent nucleoli; (IV) uninterrupted patternless or sheet-like growth; (V) foci of spontaneous or geographic necrosis
III (anaplastic)	Features of frank malignancy far in excess of the abnormalities noted in atypical meningiomas	≥20 mitoses per 10 hpf and/or malignant characteristics resembling carcinoma, sarcoma or melanoma	≥20 mitoses per 10 hpf and/or malignant characteristics resembling carcinoma, sarcoma or melanoma	≥20 mitoses per 10 hpf and/or malignant characteristics resembling carcinoma, sarcoma or melanoma

hpf, high powered field; n:c, nuclear:cytoplasmic (3-5).

with decreased survival. With current treatment paradigms involving surgery and/or radiation treatment (RT), crude recurrence rates for atypical and anaplastic meningiomas are approximately 30–50% and 50–94%, respectively (6,9-13).

Surgical resection is typically the first-line treatment for high-grade meningiomas when the tumor is in an accessible location, and the extent of surgical resection is an important prognostic factor for progression-free and overall survival (OS), with gross tumor resection (GTR) defined as Simpson grade 1–3 and subtotal tumor resection (STR) classified as Simpson grade 4 and 5. However, rates of recurrence are high, especially with STR, and radiotherapy may significantly decrease this risk (14). For the purposes of this review, we will exclusively focus on the role of RT for high-grade meningiomas. A separate article in this issue describes the role of radiotherapy for benign meningiomas.

The available evidence on management of high-grade meningiomas is limited to case studies and retrospective series with a handful of prospective trials on the horizon. Further compounding the difficulty in analyzing outcomes has been the periodic WHO re-classification of atypical and anaplastic meningiomas over the past few decades, which renders cross-comparison between studies difficult. Nevertheless, prior studies have demonstrated an important role for radiation therapy in both the adjuvant and recurrent settings.

Radiation therapy for anaplastic/malignant meningiomas

Anaplastic meningiomas have extremely high rates of recurrence such that even with complete surgical resection, OS is poor. Reported rates of recurrence have been estimated to be between 50–94% and median survival is approximately 3–6 years (10-13,15,16). Small retrospective studies suggest an important role for adjuvant radiotherapy but no randomized trials have been conducted. Jääskeläinen and colleagues retrospectively analyzed 936 resected meningiomas from 1953 to 1980, of which 1% were anaplastic, and found in this subset a recurrence rate of 78% following complete surgical removal with only five patients receiving RT (cobalt-60, range, 50–64 Gy) (17). Median time to recurrence in these anaplastic patients was 3.5 years (0.5–5.8 years). Of the five patients receiving RT, four recurred within 1 to 4.5 years. In a cohort of 38 patients with anaplastic meningiomas treated between 1984 and 1992, a significantly higher rate of recurrence was found in those undergoing surgical resection alone compared

to those who received both surgery and fractionated radiotherapy with a median dose of 54 Gy (range, 30.6–63 Gy) (18). In this study, they demonstrated a 5-year progression free survival (PFS) of 15% in the surgery arm compared to 80% in the surgery plus adjuvant radiotherapy arm (P=0.002).

In a contemporary study at the Cleveland Clinic of 18 patients with anaplastic meningioma based on the 2007 WHO criteria, all were treated with primary surgery and 10 received adjuvant radiation (80% received intensity modulated radiation therapy, IMRT) to a median dose of 59.4 Gy (range, 50.4–60 Gy). They found that 72% of patients recurred with an estimated median PFS of 14.5 months (95% CI: 6.9–22.2) (19). The 2- and 3-year PFS rates were 27% and 20%, respectively, and the 3- and 5-year OS rates were 69% and 40%, respectively. In a larger and more homogeneous study, Sughrue and colleagues examined 63 patients with anaplastic meningiomas at UCSF that were all treated with primary surgical resection followed by adjuvant fractionated radiotherapy, and found the 2-, 5-, and 10-year PFS were 80%, 50%, and 40%, respectively, and the 2-, 5-, and 10-year OS were 82%, 61%, and 40%, respectively (20). Several treatment options for recurrent disease were employed, including repeat resection with or without brachytherapy, and stereotactic radiosurgery (SRS). The addition of focal radiotherapy using brachytherapy or SRS did not result in a significant survival advantage after recurrence. Surprisingly, the authors noted that patients treated with near-total resection (NTR) and RT compared with patients treated with GTR and RT experienced significantly longer OS (107 *vs.* 50 months, P=0.035). They defined NTR as removing >90% of the tumor with residual tumor confined to areas associated with high surgical morbidity. The performance status in patients with GTR decreased substantially following surgery compared to that in the NTR group, suggesting that this difference in survival might be attributed to increased neurological morbidity from GTR. However, most other studies have documented that complete resection improves patient outcomes (12,13,18). Even when GTR is achieved, though, rates of recurrence are unacceptably high and therefore adjuvant radiation therapy is generally considered standard practice barring contraindications.

Atypical meningioma

The role for adjuvant radiotherapy in atypical meningiomas is much more controversial compared to that for anaplastic meningiomas. The recurrence rate of atypical meningiomas is intermediate compared with that of benign and anaplastic meningiomas but has nevertheless been associated with significant morbidity and possibly increased mortality. The role of RT to reduce the risk of recurrence following surgery has been retrospectively investigated. However, it is important to note that retrospective studies have included many differing definitions of atypical meningiomas. Prior to the 2000 WHO criteria, grade II meningiomas were only estimated to be 5% of total meningioma cases. However, updates to the criteria have increased the percentage to approximately 20–35% of new cases and is likely to increase further given the inclusion of brain invasion as a defining feature in the latest 2016 WHO criteria (3,8). Further complicating this, many retrospective trials have provided conflicting evidence pertaining to the role of adjuvant radiation therapy. Given these limitations, current ongoing prospective trials are of particular interest.

In a single-institution retrospective analysis by Aghi and colleagues of 108 patients with atypical meningiomas, defined by the WHO 2000 and 2007 criteria, all of whom had GTR, the actuarial recurrence rates were 7%, 41%, and 48% at 1, 5, and 10 years, respectively (21). Only eight of these patients received adjuvant fractionated stereotactic radiotherapy with a mean dose of 60.2 Gy (range, 59.4–61.2 Gy) and none suffered tumor recurrence, though this did not receive significance on univariate (P=0.1) and multivariate (P=0.1) analysis because of the small numbers. The authors noted that there were no apparent differences in the irradiated and non-irradiated patients in terms of baseline parameters such as tumor location, age, and duration of follow-up. Review of their clinical records did not suggest specific concerns for elevated recurrence risk in the irradiated cohort and therefore the differences in management likely reflected the heterogeneity of clinical practice for atypical meningiomas, even within individual institutions. Despite these limitations, the findings in this study are consistent with benefit from the use of adjuvant radiation therapy in even completely resected atypical meningiomas. Another small series by Komotar and colleagues included 45 patients with atypical meningiomas and also showed a benefit of adjuvant radiation therapy on the risk of recurrence (22). Of these patients, 32 underwent GTR alone while 13 patients had GTR with adjuvant radiation therapy to a median dose of 59.4 Gy. They showed overall actuarial recurrence rates of 7.9%, 35.5%, and 55.3% at 1, 5, and 10 years, respectively, and the median time to recurrence was 24 months. In the group

that recurred, 92.9% had not received adjuvant radiation therapy and only one of the 13 patients who had received adjuvant radiation therapy recurred at 52.5 months. Univariate analyses revealed an association between use of adjuvant radiation therapy and lower recurrence rate that trended towards significance (HR 5.05, 95% CI 0.65-39.15 without postoperative RT; P=0.12); multivariate analysis revealed a similar trend (HR 4.97; 95% CI: 0.55–44.68 without postoperative RT; P=0.15). Moreover, Aizer and colleagues investigated 91 patients with atypical meningiomas treated between 1997 and 2011, of whom 34 received RT (33 received adjuvant fractionated radiotherapy to a median dose of 60 Gy (IQR, 55.8–64 Gy), while one patient was treated with SRS at a dose of 16 Gy (23). Significantly more patients in the radiation arm had STR (35% *vs.* 9%, P=0.004). Using propensity-score matching to account for factors that may contribute to treatment allocation, they found that adjuvant radiation was associated with a significantly lower risk of recurrence in patients who had GTR (HR 0.25; 95% CI: 0.07–0.96; P=0.04). Notably, the 5-year freedom from local recurrence rate of those treated with GTR and adjuvant radiation therapy was 82.6% (95% CI: 55.2–94.1%) compared to 67.8% (95% CI: 50.3–80.2%) in those with GTR alone. After a median follow up of 4.9 years, there was no difference in OS with adjuvant radiation therapy. In a large study of 228 patients with atypical meningiomas that were graded based on the 2007 WHO criteria, the overall recurrence rate was 22% during a 52-month follow-up period with a median time to recurrence of 20.2 months (24). In this study, 31% were treated with adjuvant radiation therapy: 32 patients received stereotactic radiation to a dose of 14–16 Gy in 1 fraction or 21–27 Gy in 3–5 fractions while 39 patients received IMRT to a dose of 54–59 Gy. While adjuvant radiation therapy was not associated with statistically significant improvement of PFS, the number of patients undergoing adjuvant radiation therapy was small. Furthermore, it is important to note that of those who had GTR, 23 were treated with adjuvant radiation therapy and none recurred. In patients with STR, there was a trend toward increased PFS in those treated with adjuvant radiation (RR =0.567; P=0.16). In another study of 114 patients with atypical meningiomas classified by the 2000 WHO criteria, 30 patients received postoperative radiation therapy with a mean dose of 51.8 Gy (25). They found on multivariate Cox regression analysis that only the extent of tumor resection significantly impacted tumor recurrence (HR 2.522; P=0.018) whereas addition of postoperative radiotherapy was only borderline significant (HR 2.179; P=0.086).

Given the limitations of retrospective studies, the results of two multi-institutional prospective trials examining the role of radiation therapy in meningiomas, RTOG 0539 and EORTC 22042, are highly anticipated. RTOG 0539 recently reported preliminary results at the 2015 American Society for Radiation Oncology Meeting. Fifty two patients with intermediate-risk meningiomas, defined as completely resected WHO grade II tumors or recurrent WHO grade I tumors, were treated with adjuvant radiation therapy (IMRT or 3DCRT, 54 Gy in 30 fractions following GTR and 60 Gy in 30 fractions after STR) (26). They showed an excellent early 3-year PFS of 96% and local recurrence rate of 2%; however, longer-term follow up is necessary to address whether this level of local control is maintained. The only grade ≥3 adverse events were two patients with subjective hearing loss. Similarly, EORTC 22042 is an ongoing phase II study evaluating the outcomes of atypical or anaplastic meningiomas treated with adjuvant radiation therapy following GTR or STR and has completed accrual with 78 patients enrolled. The radiation dose following GTR will be 60 Gy and that following STR will be 60 Gy plus a 10 Gy boost. The main study will only include completely resected grade II meningiomas with a primary endpoint of 3-year PFS. Secondary outcomes include adverse events, mini-mental status exam performance, and OS. Incompletely resected grade II meningiomas and all grade III meningiomas will be described in a separate observational cohort. When mature, these studies should provide key data on the role of adjuvant RT in atypical and anaplastic meningiomas, and if the results are promising compared to historical controls, will likely motivate randomized studies.

Radiation techniques

Dose-escalated external beam radiotherapy and treatment planning using cross-sectional imaging (CT or MRI) are associated with improved clinical outcomes in the treatment of high-grade meningiomas (*Figures 1*,*2*). Goldsmith and colleagues demonstrated that for 23 incompletely-resected malignant meningiomas treated between 1967 and 1990 at UCSF, a total dose of greater than 53 Gy was associated with a 5-year PFS of 63% compared to 17% for lower doses (P=0.01) (14). Milosevic and colleagues studied 59 patients with high-grade meningiomas treated with surgery and radiation between 1966 and 1990 at Princess Margaret Hospital and found on multivariate analysis that

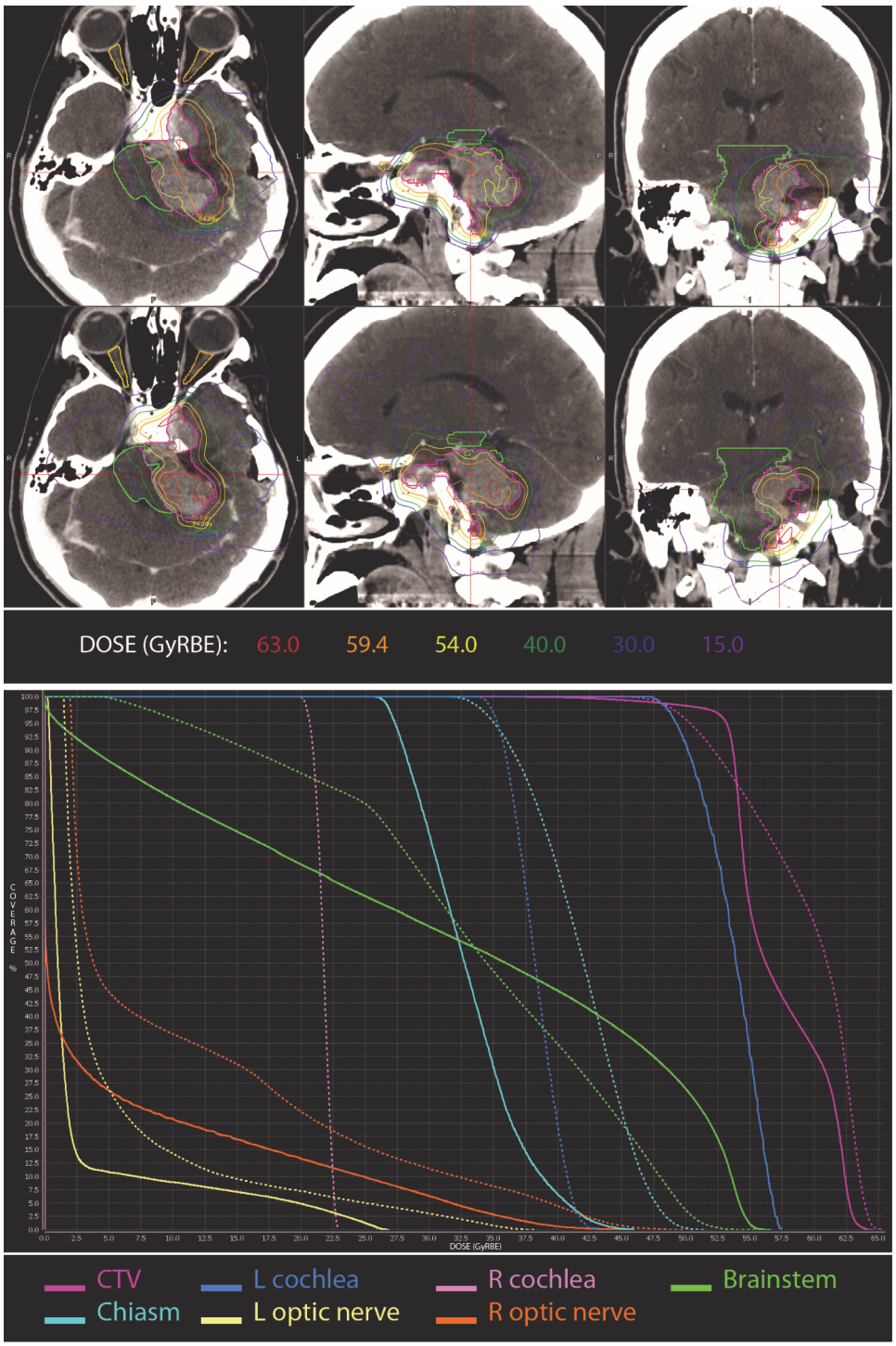

Figure 1 Radiation plans for left base of skull atypical meningioma receiving 59.4 Gy (RBE) in 33 fractions comparing proton stereotactic radiotherapy (upper) and photon volumetric-modulated arc therapy, VMAT (middle). The proton plan uses six passively scattered non-coplanar fields while the VMAT plan uses four non-coplanar arcs. Dose-volume histogram (lower) comparing CTV and OARs for the two plans. Solid lines represent the proton plan, dotted lines represent the photon plan. The passively scattered proton plan spares the optic chiasm and nerves more effectively whereas the photon plan spares the ipsilateral cochlea and brainstem (at doses above 34 Gy) more. VMAT, volumetric-modulated arc therapy; CTV, clinical target volume; OARs, organs at risk.

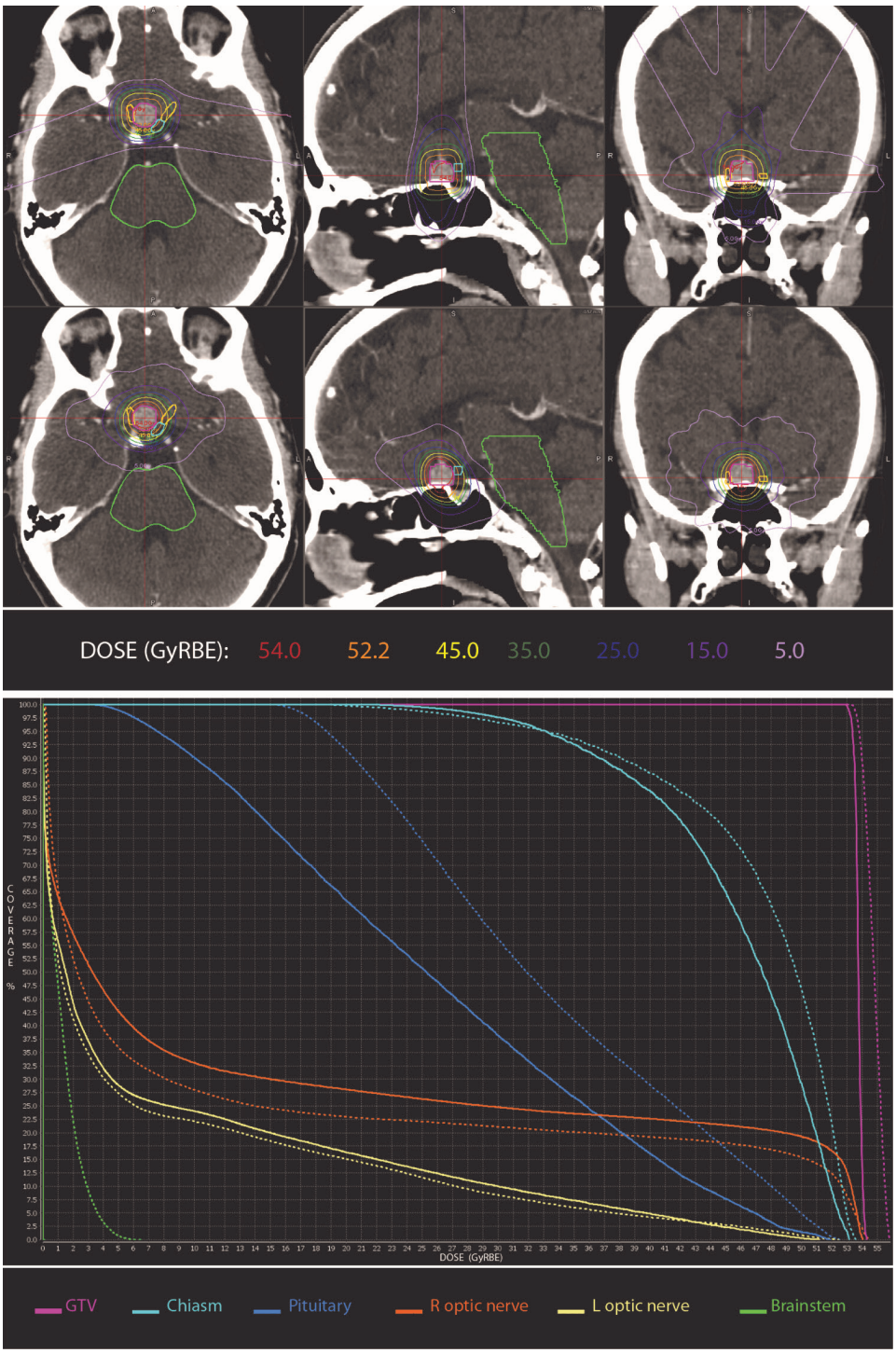

Figure 2 Radiation plans for right anterior base of skull atypical meningioma receiving 52.2 Gy (RBE) in 31 fractions normalized to 96% comparing proton stereotactic radiotherapy (upper) and photon stereotactic static arc radiotherapy using conical cones (middle). The proton plan uses five passively scattered non-coplanar fields while the photon cone plan uses four non-coplanar arcs spanning 570° using three different cone diameters (18, 22, 24 mm). Dose-volume histogram (lower) comparing GTV and OARs for the two plans. Solid lines represent the proton plan, dotted lines represent the photon plan. The proton plan spares the optic chiasm, pituitary, and brainstem more effectively whereas the photon plan spares the optic nerves more. GTV, gross tumor volume; OARs, organs at risk.

age less than 58, treatment after 1975, and a radiation dose of at least 50 Gy were independently associated with better disease-specific survival (27). A meta-analysis of 14 studies from 1994 to 2011 investigating the role of adjuvant radiotherapy for high-grade meningiomas with median follow-up of 28–64 months showed that doses below 50 Gy were associated with significantly inferior 5-year PFS (28). Other studies suggest that even higher radiation doses, greater than 60 Gy (RBE), using combined proton and photon irradiation further improve local control and possibly survival compared to lower doses and photon irradiation alone (29-31). For example, Hug and colleagues investigated the outcomes of 15 patients with malignant meningiomas treated with either photons alone or combined protons and photons to doses ranging from 40 to 72 Gy (RBE) (30). Notably, 5 year PFS was 90% with doses >60 Gy (RBE) compared to 0% with lower doses. In another study of 24 high-grade meningiomas treated with combined protons and photons, the 5 year cause-specific survival was 80% with doses greater than 60 Gy (RBE) compared to 24% with lower doses (31).

There are several alternative forms of radiotherapy that can be deployed for the treatment of high-grade meningiomas in certain situations. SRS has become a convenient and effective option for meningiomas that are less than 10 cc in volume with a maximum diameter less than 3–4 cm and a sufficient distance from critical structures to permit appropriate dose falloff. Stafford and colleagues reported on 22 patients with atypical or malignant meningiomas treated with SRS to a median margin dose of 16 Gy, which yielded a 5-year local control rate of 68% and 0%, and 5-year cause-specific survival of 76% and 0%, respectively (32). In another series of 12 recurrent high-grade meningiomas treated with SRS, Kano and colleagues demonstrated a higher 5-year PFS of 63% with at least 20 Gy marginal dose compared to 29% with lower doses (33). While local control within the treated volume has been acceptable with single-fraction SRS, marginal failures are problematic and associated with lower conformality indices (i.e., greater conformality) (34). The optimal definition of treatment volume is not well-studied. In benign meningiomas treated with SRS, inclusion of the dural tail in the treatment volume was associated with a higher 5 year DFS (96% *vs.* 78%, P=0.038) (35) but this has not been systematically studied in high-grade meningiomas. Recently, there has been increased interest in hypofractionated stereotactic radiotherapy (five fractions or less) for meningiomas too large for single-fraction SRS. The results have been promising for benign meningiomas but it is unknown how this will translate to high-grade meningiomas (36-38). Interstitial brachytherapy can be an effective adjunct to surgical resection and external beam radiotherapy, especially for aggressive, recurrent, and/or large meningiomas, but is associated with high complication rates (39,40). In one series of 21 patients with recurrent atypical and malignant meningiomas treated with brachytherapy at the time of surgery, there was a 27% rate of wound breakdown requiring surgical intervention and a 27% rate of radiation necrosis, half of whom required additional surgery (40).

In patients with imaging-defined meningiomas who are not surgical candidates, a histologic diagnosis is often not available. In one series of 41 patients with meningiomas diagnosed by imaging alone who were treated at Emory with definitive radiation between 1985 and 2003 using various techniques, the 8-year actuarial local control rate was 94%, which is comparable to modern surgical series (41). While empiric radiotherapy for unresected meningiomas should certainly not be viewed as standard of care in most situations, it is an important option with at least several years of durable control for patients who have contraindications to surgery.

Conclusions and future directions

As we look towards the future of meningioma treatment, the ability to predict which patients are most likely to recur following resection will enable allocation of adjuvant treatments to those most likely to benefit and avoid overtreatment. Beyond histopathologic grade, there is significant interest in identifying other high-risk features to optimize clinical management. For example, a retrospective study found brain invasion and/or bone involvement and a high Ki-67 index, which marks proliferation, to be highly associated with progression and/or recurrence after primary treatment of high-grade meningiomas (42). Furthermore, low apparent diffusion coefficient on diffusion-weighted MRIs and less extensive resection have also been identified as predictors for increased risk of progression and/or recurrence (43). Importantly, patients with these high-risk features benefited significantly from adjuvant radiotherapy.

Cytogenetic and genetic alterations may also have predictive value for tumor recurrence following resection. Aizer and colleagues correlated copy number aberrations (CNAs) to histologic grade (44). They found that the total number of CNAs increased on average with higher

histologic grade. Interestingly, atypical meningiomas showed the greatest heterogeneity in CNAs, which is consistent with the broad range of clinical outcomes in this intermediate-risk group. The authors further investigated whether a cytogenetic abnormality score (CAS) derived from the number of CNAs could predict recurrence following GTR. Intriguingly, in a cohort of 32 patients with atypical meningiomas that were treated with GTR but no radiation, CAS was strongly associated with recurrence in a continuous fashion. The hazard ratio per unit increase was 1.52 (95% CI: 1.08–2.14, P=0.02). Further studies on how adjuvant radiation may modulate the recurrence rates of patients with high CAS are warranted. Screening studies searching for potentially exploitable alterations in the genetics and cellular biology of meningiomas have only scratched the surface of these complex tumors. Moreover, translation of laboratory findings into patient-specific treatments is largely unexplored. For example, the most established genetic alteration found in meningiomas is loss of the *neurofibromatosis 2 (NF2)* gene, a regulator of the Hippo signaling pathway, which has been shown to be associated with cancer. With loss of *NF2* expression, there is an accumulation of the downstream transcriptional co-activator YAP in the nucleus (45). Decreased *NF2* expression has been seen across meningioma subtypes and has been observed in 70% of anaplastic, 60% of atypical, and 50% of benign meningiomas with concurrent loss of DAL-1, another tumor suppressor (46,47). While studies examining whether YAP mediates radiation response have not been conducted on meningiomas, other tumor types such as head and neck squamous cell carcinoma and medulloblastoma have suggested that YAP overexpression predicts poor response to radiation therapy (48,49). To determine if YAP could be a therapeutic molecular target in *NF2*-mutant meningiomas, investigators used siRNA to decrease YAP expression in *NF2*-mutant meningioma cell lines and showed that suppression of YAP indeed resulted in decreased cell proliferation and migration (50). Molecular targeting of YAP to decrease its expression in combination with RT may improve outcomes in these potentially radioresistant meningioma subtypes.

Further improvements in RT are being developed to maximize efficacy while decreasing toxicity. One such area of investigation is the use of carbon ion RT in meningiomas. Carbon ion RT offers the advantages of particle beams with respect to allowing a highly localized deposition of energy in the tumor while minimizing damage to surrounding tissues due to the Bragg peak phenomenon, similar to proton RT. However, it offers the additional advantage of a higher relative biological effectiveness and may have theoretical biological advantages, such as reduced cell cycle-dependent radiosensitivity and increased efficacy for cancer stem-like cells (51-53). In a small phase I/II trial of ten patients with mostly high-grade meningiomas, all patients had resection of the meningioma and then were treated with a combination of photon RT (median dose 50.4 Gy) followed by a carbon ion boost [median dose 18 Gy (RBE)] (54). Eight of the patients in the study had primary disease whereas two patients had recurrent disease. Median follow-up was 77 months. In patients treated for primary disease, the actuarial local control was 86% and 72%, and OS was 75% and 63% at 5 and 7 years, respectively. There were no severe acute or long-term treatment-related adverse effects observed. A follow-up analysis compared volumetric response of intracranial meningiomas after photon, proton, and mixed photon/carbon ion boost RT (55). In this study, 39 patients were treated with conformal photon RT to a median dose of 56 Gy, 27 patients received proton therapy to a median dose of 56 Gy (RBE), and 11 patients received photon RT and carbon ion boost to a total dose of 68 Gy (RBE). In all groups, there was significant tumor volume shrinkage, as measured by MRI, at 1- and 2-year follow up, with no significant differences among groups. Based on these results, a phase II trial (MARCIE Trial, ClinicalTrials.gov NCT01166321) evaluating 3-year progression-free survival in patients with incompletely resected atypical meningiomas treated with carbon ion boost and photon radiotherapy has been initiated (56).

Currently, a number of prospective trials aim to further evaluate the role of radiation therapy in the treatment of anaplastic and atypical meningiomas. An observational study based at University Hospital, Montpellier will study the impact of postoperative radiotherapy for WHO grade II/III meningiomas on OS, tumor growth, and quality of life (ClinicalTrials.gov NCT02973256). To address the use of proton therapy in meningiomas, a feasibility/Phase II study of proton radiation for WHO grade I–III meningiomas and hemangiopericytomas at the University of Pennsylvania (ClinicalTrials.gov NCT01117844) is currently accruing patients. If more than 10% of patients cannot be treated due to dosimetric constraints or if the patient cannot complete treatment within seven days of the estimated date of treatment, then the study will be deemed infeasible. Secondary objectives includes acute adverse effects; quality of life outcomes; late complications; dose distribution comparisons with corresponding photon

plans; and 1-year local control, progression-free and OS. Another combined phase I/II trial at Massachusetts General Hospital and MD Anderson Cancer Center (ClinicalTrials.gov NCT02693990) is currently enrolling 60 patients to prospectively determine whether dose escalation with proton therapy improves local control and reduces toxicities for atypical meningiomas with STR and anaplastic meningiomas with any extent of resection. The primary outcome is dose-limiting toxicity using NCI CTC 4.0. Secondary outcomes include 5-year progression/recurrence-free survival, 2-year OS, and calculations of linear energy transfer using computer simulations based on the treatment plans. The German Cancer Consortium is also studying whether proton dose escalation in patients with atypical or anaplastic meningiomas impacts 5-year progression-free survival (ClinicalTrials.gov NCT02978677) but this study is not yet open. Collectively, these studies will provide critical information regarding the utility of radiation therapy for patients with atypical and anaplastic meningiomas.

In conclusion, the morbidity and mortality associated with high-grade meningiomas motivates the need for improved therapeutic paradigms to manage this disease. Surgical resection is the preferred initial treatment whenever possible. There are numerous adjuvant radiotherapy options that have differing applications, benefits, and associated complications including fractionated external beam radiotherapy (photons or particle therapy), SRS, hypofractionated stereotactic radiotherapy, and interstitial brachytherapy. Moreover, definitive radiation can be considered in patients with contraindications to surgery.

Despite the dearth of prospective data, numerous retrospective series have shown a local control and likely survival benefit associated with adjuvant radiotherapy for WHO grade III meningiomas regardless of resection extent, and WHO grade II meningiomas that are incompletely resected. The jury is still out with regard to whether adjuvant radiation should be employed when GTR is achieved for WHO grade II meningiomas. The results of RTOG 0539, EORTC 22042, and other ongoing trials will be critical in addressing this issue but prospective randomized trials will ultimately be necessary to definitively answer this question. Furthermore, improving our ability to identify which patients within each of the heterogeneous histologic grades are most likely to benefit from adjuvant treatment will be critical to maximize efficacy, allocation of resources, and avoidance of unnecessary treatment-related toxicity.

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Footnote

Conflicts of Interest: HA Shih: writer, *UpToDate*; senior editor, *International Journal of Radiation Oncology, Biology, Physics*. The other authors have no conflicts of interest to declare.

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