Review Article

Radiation therapy for WHO grade I meningioma

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Abstract: Maximal safe resection has long been the cornerstone of treatment for WHO grade I benign meningioma. However, as technology for both imaging and radiation delivery has advanced, radiation therapy has played an increasingly important role in the management of patients with WHO grade I meningioma. Radiation therapy, whether delivered as standard fractionated treatment over several weeks, stereotactic radiosurgery over 1 session, or multisession stereotactic radiation therapy, has been shown to provide excellent local control when used as an adjunct to surgery or as primary treatment. Here, we review the indications for radiation therapy for patients with WHO grade I meningioma, as well as the various techniques that have been developed. We also review the toxicities and late effects associated with treatment.

Keywords: Meningioma; radiation therapy; stereotactic radiosurgery

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Overview

Meningiomas are the most common type of extraaxial primary brain tumor, representing a third of all primary central nervous system (CNS) neoplasms (1). They were first described by Cushing as a group of tumors arising from the dural coverings of the CNS, and they can arise anywhere dura is found (2). The prevalence of pathologically-confirmed meningioma is estimated to be approximately 97.5/100,000 in the United States, with 170,000 currently diagnosed patients (3). Approximately 75–90% of these tumors are WHO Grade I lesions that typically progress slowly.

Observation reveals that growth rates and patterns may vary among patients, even when all are WHO grade I and benign (4). Disease progression or symptomatic presentation may ultimately necessitate intervention in many patients with WHO grade I meningioma. Significant morbidity may occur due to mass effect or infiltration of adjacent brain and cranial nerves. Though gross total surgical resection (GTR) has long been the primary treatment for meningioma, it is not always possible or may be associated with considerable morbidity. Thus, radiation therapy has long had a role as adjunct therapy after subtotal resection (STR) for recurrence. In addition, radiation therapy has a role in the primary treatment of image defined meningioma especially in surgically inaccessible areas or for candidates who are medically inoperable or do not wish to undergo surgery.

As we continue to accrue long-term follow up for patients treated with radiation in conjunction with, or as an alternative to surgery, it is apparent that radiation therapy represents a valuable tool in the treatment of the various presentations of WHO grade I meningioma. Multiple treatment techniques including stereotactic radiosurgery (SRS), fractionated external beam radiation therapy, and particle therapy using protons have been used successfully for the treatment of these tumors. The use of radiation for the treatment of WHO grade I meningiomas will be reviewed here.

Radiation therapy after STR

When possible, a gross total resection (GTR) remains the cornerstone of definitive management of WHO Grade

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Table 1 Recurrence rates after subtotal resection alone for benign meningiomas

Author/year	n	5 y	10 y	15 y
Mirimanoff *et al.*, 1985 (7)	80	37	55	91
Barbaro *et al.*, 1987 (12)	30	40	100	–
Miralbell *et al.*, 1992 (13)	79	40	52 (8 y)	–
Condra *et al.*, 1997 (14)	55	47	60	70
Stafford *et al.*, 1998 (15)	116	39	61	–
Soyuer *et al.*, 2004 (16)	32	62	82	87
Total	392	37–62	52–100	70–91

1 meningioma. Since the 1950's, the extent of resection of meningioma has commonly been described by the Simpson grading scale (5). Simpson grading depends on intraoperative observations and categorizes resection quality along a scale from 1–5. A Simpson 1 resection removes all tumor, associated dural attachments and involved bone, whereas a Simpson 5 resection is simple decompression only. In most studies, a Simpson grade 1–3 resection is considered a GTR (5,6). Successfully achieving GTR has been an important prognostic factor in patients with all grades of meningioma (6), with STR resulting in increased risk of recurrence (7,8). In approximately 30% of cases, GTR is impossible owing to tumor location or proximity to neurologic or vascular structures (7,9,10); this is especially true for meningiomas involving the sphenoid ridge, posterior fossa, parasellar region, and optic nerve sheath (10,11).

Numerous single institution studies with extended follow-up of benign meningiomas suggest that the 5-year local progression rate after STR alone may range from 37–62%, and 10-year local progression may be as high as 52–100% (*Table 1*) (7,12-17). There remains controversy regarding whether patients with meningioma after STR should undergo active surveillance or radiation therapy. Some studies have suggested that small amounts of residual tumor can be observed with high PFS rates. For example, a 2010 analysis by Sughrue *et al.* found a 81% 5 y PFS rate after Simpson 4 resection (18). Thus, patients with advanced age or multiple comorbidities and small residual tumor may not recur, or perhaps more importantly, may not grow enough to cause symptoms.

However, others argue that especially in young patients with tumor locations that are likely to become symptomatic, adjuvant radiation therapy is indicated. Multiple observational studies have demonstrated the benefit of fractionated EBRT in the adjuvant setting following STR of benign meningioma. Across these series, 74–96% of patients remained progression-free on long-term follow-up (generally 10 years) after GTR alone. After STR without adjuvant treatment, PFS ranges dropped to 18–52%. Adjuvant radiation prevented local control failures after STR with results ranging from 68–100% of patients free from progression at extended follow-up (*Table 2*).

Furthermore, certain series suggest that there may be a survival benefit to adjuvant radiation therapy after STR. Condra and colleagues noted that STR significantly affected cause specific survival (CSS) in patients with benign meningioma. They reported that the 15-year CSS dropped from 88% to 51% when comparing GTR to STR in patients with resected grade 1 lesions. They noted that the addition of radiation therapy after STR reversed this drop in survival, with a return to a 15 y CSS of 86% in patients treated with EBRT following STR (14). Of note, this work likely included patients that would now be categorized as WHO grade II, thus potentially overestimating the true benefit of radiation in the lowest risk patients. However, in a modern single-pathologist analysis of 236 grade 1 lesions that utilized WHO 2007 classifications, STR was found to be a significant factor in reduced PFS (HR 4.18, P=0.007), and overall survival (OS) (HR 2.69, P=0.009). The median age in this series was 56 years and median follow up was 75 months (24). Of note, this study defined GTR as Simpson 1 or 2 resections, and considered Simpson 3 resections as STR.

Though most of the early series utilized standard external beam radiation therapy with margins added, more recent series have used improved imaging and targeting capabilities with stereotactic localization to successfully treat skull base tumors with higher precision. These studies show excellent local control rates with the use of fractionated stereotactic radiotherapy (FSRT) or SRS after STR (*Table 3*). Although longer-term follow up will be required given the risk of late recurrences, the initial results in over 1,100 patients across multiple reports with 3, 5 and 10 years follow up show LC rates in excess of 92–100% at five years, and 88–95% at ten years. Patients in these studies were generally treated using fractions of 1.8–2 Gy to a total dose of 50.4–54 Gy for FSRT and to 13–16 Gy in a single fraction for SRS. There is accruing long-term evidence that EBRT, FSRT and SRS are attractive tools for management of patients after STR or with surgically difficult presentations.

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Table 2 PFS following GTR, STR alone, or STR plus EBRT for patients with benign meningioma

Author/year	n	Technique	GTR	STR	STR + RT	Timepoint (y)	Dose
Adegbite *et al.*,1983 (19)	114	EBRT	74	34	82	10	Undefined
Barbaro *et al.*, 1987 (12)	135	EBRT	96	40	68	–	Mean: 52 Gy
Taylor *et al.*, 1988 (20)	132	EBRT	77	18	82	10	50–63 Gy
Glaholm *et al.*, 1990 (21)	117	EBRT	96	43	77	10	50–55 Gy
Miralbell *et al.*, 1992 (13)	115	EBRT	–	48	88	8	54–64 Gy
Peele *et al.*, 1996 (22)	86	EBRT	–	52	100	4	45 Gy
Condra *et al.*, 1997 (14)	246	EBRT	80	40	87	10	50–70 Gy
Soyuer *et al.*, 2004 (16)	92	EBRT	77	38	91	10	54 Gy
Ohba *et al.*, 2011* (23)	281	FSRT/ SRS	88	64	92	5	Mixed

*, patients treated with a variety of techniques, GKRS, 13 Gy to the 50% isodose line, or SRT 35 Gy in 10 fractions. GTR, gross total resection; STR, subtotal resection; EBRT, external beam radiation therapy; FSRT, fractionated stereotactic radiation therapy; SRS, stereotactic radiosurgery.

Table 3 Local control rates after STR followed by FSRT at the skull base

Author/year	n	LC %	Timepoint (y)	Modality	Dose
Jalali *et al.*, 2002 (25)	41	100	3	FSRT	50–55 Gy: 30–33 fx
Selch *et al.*, 2004 (26)	45	97	3	FSRT	50.4 Gy: 28 fx
Henzel *et al.*, 2006 (27)	224	97	3	FSRT	56 Gy: 28 fx
Metellus *et al.*, 2010 (28)	53	94	10	FSRT	50.4–54 Gy: 28–30 fx
Tanzler *et al.*, 2011 (29)	57	96/93	5/ 0	FSRT	50.4–54 Gy: 28–30 fx
Fokas *et al.*, 2014 (30)	318	93/88	5/10	FSRT	56 Gy in 28 fx
Davidson *et al.* 2007 (31)	36	100/95	5/ 0	GKRS	16 Gy: 50% IDL
Ohba *et al.*, 2011 (23)	30	92	5	GKRS (27/30)	13 Gy: 50% IDL
Kondziolka *et al.*, 2008 (32)	384	91	10	GKRS	14 Gy: 50% IDL

LC, local control; GKRS, Gamma Knife radiosurgery; FSRT, fractionated stereotactic radiation therapy; IDL, isodose line.

Radiation therapy as primary treatment

Radiation therapy has emerged as a viable alternative when the patient has a surgically inaccessible tumor, is medically inoperable, or prefers radiation therapy over surgical intervention. Initially, radiation therapy was used in tumors that were not surgically accessible. For instance, though initially surgical resection was pursued for optic nerve sheath meningiomas, high rates of blindness were associated with optic nerve infarction during surgery (33,34). Thus, standard fractionated external beam radiation therapy to 50–54 Gy was utilized. Published data suggests that treated tumors regress or remain stable in greater than 90% of cases after primary radiotherapy alone (34-37), and that vision can be maintained after irradiation.

Similarly, surgical resection of cavernous sinus meningioma was often associated with cranial neuropathies and thus multiple series outline good outcomes after radiation therapy alone, either standard fractionated external beam radiation therapy or stereotactic radiosurgery (28,38-43). These experiences led to the successful treatment of meningioma with radiation therapy in other locations and for patients who were medically inoperable or preferred radiation therapy over surgical resection.

The increase in use of SRS has also been influenced

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Table 4 Local control rates after radiotherapy alone, largely for WHO Grade I or presumed grade I meningiomas

Author/year	n	LC % at 5 y	LC % at 10 y	Modality	Mean/Median dose
Stafford *et al.*, 2001 (45)	190	93	–	GKRS	16 Gy
Flickinger *et al.*, 2003 (46)	219	93	–	GKRS	14 Gy
Kreil *et al.*, 2005 (47)	200	99	97	GKRS	12 Gy
Henzel *et al.*, 2006 (27)	224	97	–	FSRT	–
Kollova *et al.*, 2007 (48)	331	98	–	GKRS	12.5 Gy
Hamm *et al.*, 2008 (49)	183	93	–	FSRT	55.8 Gy
Kondziolka *et al.*, 2008 (32)	972	97	87	GKRS	14 Gy
Santacroce *et al.*, 2012 (50)	4565	95	89	GKRS	14 Gy
Pollock *et al.*, 2012 (51)	251	99	99	GKRS	15.8 Gy
Starke *et al.*, 2012 (52)	255	96	79	GKRS	14 Gy
Unger *et al.*, 2012 (53)	173	89	–	LINAC SRS	15 Gy
Soldà *et al.*, 2013 (54)	222	93	84	FSRT	50–54 Gy
Sheehan *et al.*, 2014 (55)	763	95 (5 y PFS)	82 (10 y PFS)	GKRS	16 Gy
Jang *et al.*, 2015 (56)	628	95	–	GKRS	13.9 Gy
Sheehan *et al.*, 2015 (57)	675	92	81	GKRS	13.6 Gy
Cohen-Inbar *et al.*, 2017 (58)	189	95 (6 y PFS)	85 (10 y PFS)	GKRS	14 Gy

LC, local control; GKRS, Gamma Knife radiosurgery; LINAC, linear accelerator radiosurgery; FSRT, fractionated stereotactic radiation therapy; PFS, progression-free survival.

by the increase in the number of radiographically detected, clinically occult lesions being discovered in the era of widespread medical imaging (5,44). Many of these asymptomatic lesions are small enough for active surveillance or treatment with SRS. Statistically, most of these incidental lesions are be WHO grade I meningiomas, and success in treating imaging-defined meningioma suggests that radiotherapy may be effective in a majority of cases. Given the slow growth of these tumors and the possibility of late recurrence, longer term follow-up is warranted, but the evidence supporting the use of primary radiotherapy in imaging defined meningioma is accumulating. A number of series reporting patients treated with FSRT alone or GKRS alone show similarly excellent LC rates, ranging from 89–99% at 5 years and 79–97% at 10 years (*Table 4*). One of the largest studies published is a retrospective analysis of more than 4,500 patients with a median follow-up of 63 months. It included approximately 3000 imaging-defined meningiomas treated with radiosurgery alone and tumor control, defined as a reduction in volume or stable size, was 92.5% (50).

Stereotactic radiosurgery versus fractionated external beam radiation therapy

Though initial experience with radiation therapy included standard external beam radiation therapy, in an effort to minimize toxicity including long-term effects clinicians began using more precisely targeted approaches. This was facilitated by advances in imaging including the more prevalent use of magnetic resonance imaging (MRI) and in stereotactic delivery including cobalt-60 machines, linear accelerators, robotic linear accelerators, and proton therapy. Throughout the 1990s, reports on standard external beam radiation therapy for meningioma were published. However, by the 2000s, most reports were on FSRT and SRS.

Typically SRS is reserved for tumors that are less than 3 cm in diameter or about 10 cm^3 in volume. Multiple studies have suggested that efficacy is based on tumor size. For instance, DiBiase and colleagues reported a 5-year disease free survival of 91.9% for patients with meningiomas less than 10 cm^3 as opposed to 68% for larger tumors (59). In addition, toxicity is quite dependent on size. Pollack

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and colleagues reported on a 22-year experience with SRS for presumed meningioma, with complication rates of 4.8% for patients whose tumors were less than 3.2 cm^3 and 22.6% for patients whose tumors were greater than 9.6 cm^3 (51). These complications included cranial nerve deficits, headaches, hemiparesis, new/worsened seizure, cyst formation and stroke.

For larger tumors or those that are close to dose limiting normal structures such as the optic nerves and chiasm, fractionated radiation therapy has been most used. However, there are increasing reports of multisession stereotactic radiation therapy utilizing many of the same platforms used for SRS (53,60-63). These studies demonstrate comparable local control compared to single fraction treatment and its proponents argue that side effects may be fewer.

For instance, Unger and colleagues reported on 173 patients with meningiomas where 56% underwent single fraction radiosurgery with Gamma Knife and the remainder received multisession radiation therapy over generally 2 to 5 fractions with CyberKnife. The median dose for SRS was 15 Gy and the usual regimen was 25 Gy in 5 fractions for multisession stereotactic radiation therapy. Two-year actuarial risk of symptomatic edema was 3.2% for multisession stereotactic radiation therapy, and 12.5 % for SRS. Tumor size greater than 4.9 cm^3 was also a significant predictor of symptomatic edema (53). However, recently Conti and colleagues have published on 229 patients treated with single or multisession radiosurgery with Cyberknife and found that tumor volume, tight brain/tumor interface, non-basal tumor location and atypical histology were associated with post-treatment edema. The treatment modality (single versus multisession) was not significantly associated with post-treatment edema (61).

As we continue to accrue follow up and data on the long-term efficacy of multisession radiosurgery, clinicians continue to use techniques for more precise delivery of standard fractionated radiation therapy (25-30). This includes utilization of stereotactic frames and/or masks, skull based fiducials for localization and more recently, onboard imaging with CT scans.

Particle therapy in the form of proton therapy has also been reported for the treatment of patients with benign meningioma. The unique property of the Bragg peak that prevents exit dose reduces the integral radiation dose to the normal brain, temporal lobes, hippocampi, cochleae, brainstem, and pituitary. Because of this dose reduction, protons are predicted to lower the risk of neurocognitive decline and excess risk of second tumors (1.3 *vs.* 2.8 per 10,000 patients per year; P<0.002) (64). Based on several proton therapy series of incompletely resected or recurrent benign meningioma, the five- or ten-year LC is 88–100% with acceptable toxicity (37,65-67).

Late effects

As illustrated above, the large majority of patients with benign meningioma will achieve long-term tumor control. Thus, the toxicity and late effects associated with treatment are important to consider. Many have questioned whether radiation causes benign meningiomas to transform to a higher grade. However, malignant transformation has not been definitively linked to radiation therapy. It is difficult to determine the rate of malignant transformation with and without radiation therapy since for a subgroup of recurrent or progressive meningiomas, the natural history is to transform to a higher grade (68,69) Regardless, transformation after treatment for benign meningioma is relatively rare. Pollock and colleagues found that 2.2% of patients with meningioma with at least 5 years imaging follow up (median follow up 9.2 years) had transformation to a higher grade after radiosurgery (70).

Aside from malignant transformation, radiation therapy is also associated with secondary tumors. Estimates vary, however perhaps best illustrated by long-term follow up of patients treated with external beam radiation therapy for pituitary adenomas. Minniti and colleagues reported on 426 patients with pituitary adenoma treated with surgery and external beam radiation therapy with 5,749 person years. They found a risk of second brain tumor at 20 years of 2.4%. Of the 11 second tumors, 5 were meningiomas (71). Breen and colleagues reported on 120 patients with median follow up of 9 years, and found 2.7% developed radiation-induced neoplasms at 10 and 30 years (72). This rate is likely to be lower with modern techniques with smaller radiation fields and/or with radiosurgery. Pollock and colleagues recently reviewed 1,837 patients with 11,264 patient-years of follow-up after SRS for benign tumors and found that the 15-year risk of developing a radiation-induced tumor was 0.0% (95% confidence interval 0.0–2.8%) (70). There have been very few reported cases of radiation-induced tumor after SRS.

In addition, patients receiving radiation therapy to the brain are at risk for other late effects including neurocognitive decline and hypopituitarism. The impact of radiation therapy on long term neurocognitive function is not well described for patients with meningioma. It has been shown that neurocognitive function in patients with

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benign or low-grade tumors is related radiation dose to the bilateral hippocampi (73). In addition, other areas of the brain are also likely to be involved with neurocognition. The risk of hypopituitarism is likewise related to the dose received (74). Thus, continued efforts to minimize radiation dose and extent to normal brain and pituitary are likely to improve the risk of late effects but not completely eliminate them. Ongoing trials such as the ROAM/EORTC-1308 trial for radiation versus observation following surgical resection of atypical meningioma may help to characterize the neurocognitive outcomes for our meningioma patients in the future (75).

Conclusions

Overall, radiation therapy for benign meningioma is associated with excellent local control rates with minimal toxicity. Late effects of radiation therapy appear rare but possible, and further study of their true prevalence would be helpful to determining the risks and benefits of treatment. Future advances will concentrate on advanced imaging and molecular testing of pathology that can help to further differentiate the risk of recurrence. This information could help us determine not only which patients could be observed, but also which patients may need a higher dose or extent of radiation therapy.

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Footnote

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