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Original Article

Challenging the concept that late recurrence and death from tumor are common after fractionated radiotherapy for benign meningioma

Lillie O'steen, Robert J. Amdur *, Christopher G. Morris, William M. Mendenhall

University of Florida College of Medicine, Department of Radiation Oncology, Gainesville, FL, United States

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ABSTRACT

Background: There is debate about the curability of benign meningioma and the value of long-term follow-up. A major Scandinavian study reports a high recurrence rate after surgery alone, with the majority of recurrences presenting after 10 years and death from tumor in the majority of patients with recurrence. The purpose of our study is to report the rate and time-course of recurrence ≥10 years after fractionated radiotherapy for benign meningioma with visible tumor at the time of RT and to compare these results to surgery-alone series.

Methods: A single-institution study of all (149) adults treated with fractionated radiotherapy (50–52 Gy at 1.7–1.8 Gy in the vast majority) for visible intracranial benign meningioma between 1984 and 2006. The median follow-up in patients alive at last follow-up was 12.0 years.

Results: Seven (5%) of 149 patients developed recurrent meningioma with an actuarial recurrence rate of 3% at 10 years, 5% at 15 years, and 8% at 20 years. The majority (58%) of recurrences presented at least 10 years after radiotherapy. Only 4% of 149 patients died of recurrent meningioma but death was the result of recurrent meningioma in almost all (86%) patients with recurrence.

Conclusion: Our results contradict the conclusion based on patients treated with surgery-alone that recurrence of benign meningioma is common with long-term follow-up. After fractionated radiotherapy, the 20-year control rate is approximately 90%. Our results confirm that a substantial percentage of recurrences present >10 years after treatment. These findings have important implications for the choice of initial treatment and follow-up duration.

Based on national meeting presentations and prominent journal articles, there is major controversy about the curability of benign meningioma and the value of long-term follow-up [1,2]. The view that benign meningioma is a highly curable tumor stems from the many reports of high (~90%) control rates at 5 years after gross total resection or radiotherapy. The contradictory opinion derives from a small number of studies—mainly Scandinavian—that report high recurrence rates with very long-term follow-up. The highest profile study is from Pettersson-Segerlind and colleagues at the Karolinska Hospital (Stockholm, Sweden) with 25-year follow-up on a select group of patients treated with complete (75%) or near-complete resection of parasagittal benign meningioma [3]. Their major findings include an overall recurrence rate of 47%, a time course of recurrence wherein more than half of the recurrences developed >10 years after treatment, and that death from tumor occurred in most patients with a recurrence.

Accurate data on long-term outcomes of patients with benign meningioma are critical to determine the optimal initial treatment and follow-up intensity. Our department has the ability to evaluate long-term outcomes following fractionated radiotherapy for meningioma because we have maintained a clinical database since 1965 and have updated the outcomes of meningioma patients several times in the past 20 years [4]. The purpose of our study, which is the subject of this manuscript, was to report tumor outcomes in patients with ≥10-year follow-up with a specific focus on the endpoints of the time course of recurrence and cause of death in patients with recurrence.

Methods

The University of Florida Institutional Review Board approved this study as part of the RADTRAC protocol. Table 1 shows the characteristics of the study population. The main inclusion criteria were as follows: treatment of intracranial meningioma with fractionated radiotherapy in our department; benign (WHO grade 1) histology in cases with tissue diagnosis or treated as benign based on imaging characteristics when tissue diagnosis was considered

* Corresponding author at: Department of Radiation Oncology, University of Florida, 2000 SW Archer Rd., Gainesville, FL 32610, United States.
E-mail address: amdurr@shands.ufl.edu (R.J. Amdur).

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Table 1
Characteristics of the study population (149 patients).

Characteristic	Value
Visible tumor at the time of radiotherapy	149 (100%) pts
Age at radiotherapy	
Median age (range)	54 (21–85) yrs
Sex	
Female	124 (83%) pts
Male	25 (17%) pts
Race	
White	128 (86%) pts
Black	15 pts (10%)
Other	6 pts (4%)
Subsite	
Cavernous sinus	86 (58%) pts
Petro-clival	39 (26%) pts
Orbital fissure	14 pts (9%)
Tentorial	7 pts (5%)
Frontal	3 pts (2%)
De novo or recurrent	
De novo	97 (65%) pts
Recurrent	52 (35%) pts
Tumor size at time of radiotherapy	
Median (Range)	3.0 (1–9) cm
Tissue diagnosis	
Yes (All Benign)	94 (63%) pts
No (Imaging only)	55 (37%) pts
Postoperative radiotherapy after subtotal resection	
Yes	65 (44%) pts
No (Radiotherapy after biopsy only or imaging-only diagnosis)	84 (56%) pts
Total radiotherapy dose	
Median	52.7 Gy
Range	45–60 Gy
Radiotherapy fractionation	
Once-a-day	128 (86%)
Twice-a-day	21 (14%)
Radiotherapy dose/treatment	
Once-a-day	1.8 (Median), 1.7–1.9 (Range) Gy
Twice-a-day	All 1.2 Gy
Radiotherapy technique	
3-dimensional conformal	147 (99%) pts
Intensity-modulated radiation therapy	2 (1%) pts

Abbreviations: yrs, years; pts, patients.

unnecessary; visible meningioma at the time of radiotherapy (this study excludes patients with the Simpson grades 1–3 resection); adult age ($\geq$21 years) at the time of radiotherapy; start date of radiotherapy no earlier than January 1984 to coincide with the era when computed tomography (CT) or magnetic resonance (MR) imaging was routinely available to our department; and start date of radiotherapy no later than December 31, 2006, so that all patients in this study could have follow-up of $\geq$10 years (most recent date of last follow-up update was January 1, 2016).

The usual follow-up routine included clinical examination and imaging (CT in the early years and then MR) at least annually forever beginning at 3 years; some patients had imaging follow-up less frequently and some patients were eventually lost to follow-up. Our analyses are based only on known status at last follow-up.

We did not attempt to report treatment-related toxicity because we were not confident in our ability to accurately evaluate most of the toxicities that are relevant in this patient population in a retrospective study reaching so far back in time. We were confident that we could determine the frequency of second tumors near the radiotherapy target area; therefore, we recorded any second tumors (tumors other than recurrence of the treated meningioma) that developed after radiotherapy in the brain, skull base tissues, orbit, paranasal sinuses, nasal cavity, or nasopharynx. We did not record the incidence of primary skin cancer.

Statistical analysis

SAS and JMP software were utilized for statistical analyses (SAS Institute, Cary, NC). The Kaplan–Meier product limit method provided actuarial outcome estimates. For crude calculations (fractions and percentages), only patients with known status were included in the calculation denominator. For all actuarial calculations, patients without an event were censored at the date of last known status. Patients lost to follow-up with no evidence of recurrence at last follow-up were censored at the data when tumor status was last evaluated. In the actuarial calculations of freedom from recurrence, the only event was meningioma recurrence. In the actuarial calculation of relapse-free survival, an event included meningioma recurrence or death from any cause. In the overall survival analysis, the only event was death from any cause. Clinical follow-up was defined as the time between radiotherapy and the last evaluation of tumor status by a qualified physician based on symptoms, signs, and/or cranial imaging. Imaging follow-up was defined as the time between radiotherapy and the last head CT or MR scan. Clinical and imaging follow-up calculations excluded patients with meningioma recurrence.

Results

Table 2 shows follow-up and non-actuarial outcome results. To more accurately describe the quality of our data, we report follow-up durations for patients with no evidence of recurrence during the study period. Tables 3 and 4 show the details of the 7 patients with recurrence and the 3 patients with second tumors, respectively. Fig. 1 shows the actuarial plots.

To estimate the risk of recurrence if a patient survives 5, 10, or 15 years with no evidence of recurrence, we calculated the number of recurrences presenting >5, 10, or 15 years after RT divided by the number of patients alive without recurrence at each time point. For patients who survived 5 years without recurrence, the risk of future recurrence was 5/121 (4%). For patients who survived 10 years without recurrence, the risk of future recurrence was 3/88 (3%), and for patients who survived 15 years without recurrence, the risk of future recurrence was 1/37 (3%).

Table 2
Patient follow-up and non-actuarial results.

Characteristic	Value
Clinical follow-up	
Patients without recurrence	142 pts
Median time (range)	11.2 (0.6–25.4) yrs
Last clinical follow-up	
Patients alive at last follow-up without recurrence	97 pts
Median time (range)	12.0 (0.9 to 25.4) yrs
Imaging follow-up	
Patients without recurrence	142 pts
Median time (range)	5.9 (0.5–25) yrs
Meningioma recurrence	7 (5%) pts
Histology of meningioma recurrence	
Benign	2 pts
Atypical	3 pts
Imaging-only	2 pts
Second tumor	
Percent of all patients	2% (3/149 pts)
Percent of patients without meningioma recurrence	2% (3/142 pts)
Died from sinonasal undifferentiated carcinoma	3 pts
Status at last follow-up	
Alive without recurrent meningioma	97 pts
Alive with recurrent meningioma	1 pts
Dead without recurrent meningioma	42 pts
Dead from recurrent meningioma	6 pts
Dead from second tumor	2 pts

Abbreviations: yrs, years; pts, patients.

Table 3
Patients with meningioma recurrence (7 patients).

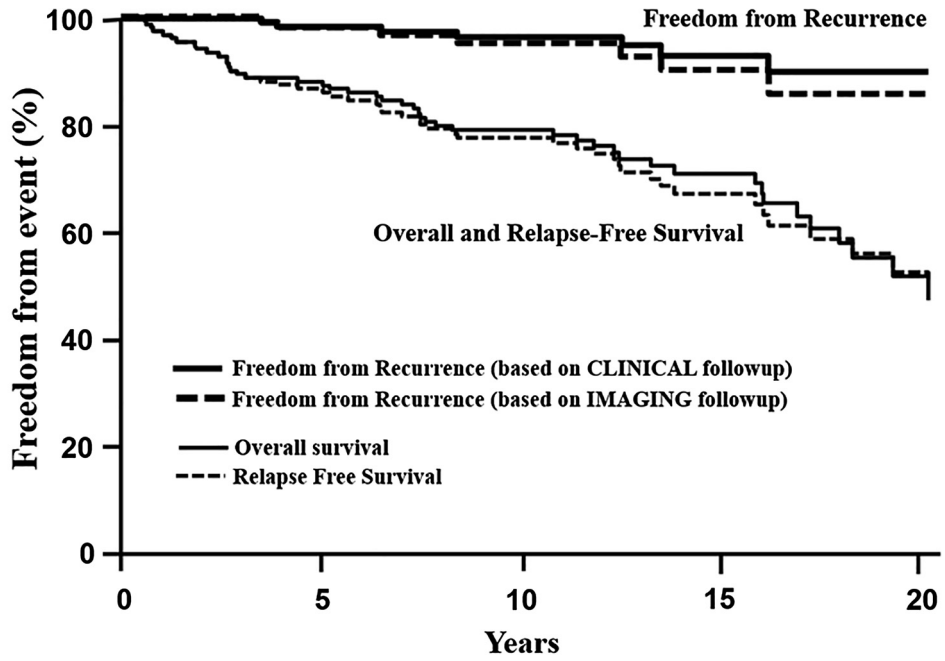
Age, race, gender, and date of RT	Location and size	Prior surgery	RT	Time to recurrence (recurrence histology)	Status last follow-up
Age 31 yrs, WM 1990	Cavernous sinus 3.0 cm	RT for recurrence soon after 2nd STR	55 at 1.7 Gy	7.2 yrs (Benign)	Dead from tumor 10 yrs after initial recurrence
Age 68 yrs, WF 1991	Sub frontal 4.5 cm	RT for recurrence 2 yrs after STR	45 at 1.8 Gy	4.3 yrs (Atypical)	Dead from tumor 4 yrs after initial recurrence
Age 51 yrs, WF 1999	Cavernous sinus 3.0 cm	STR immediately prior to RT	52.7 at 1.2 Gy BID	15.9 yrs (Imaging-only)	Dead from tumor 2 yrs after recurrence
Age 74 yrs, BF 2004	Greater sphenoid wing 2.2 cm	RT for recurrence 2 yrs after GTR	50.4 at 1.8 Gy	5.2 yrs (Imaging-only)	Dead from tumor 3 yrs after recurrence
Age 57 yrs, WF 1998	Cavernous sinus 5.0 cm	No prior surgery; Imaging-only diagnosis	54 at 1.8 Gy	3.9 yrs (Imaging-only)	Dead from tumor 2.5 yrs after recurrence
Age 37, AF 2001	Cavernous sinus 2.7 cm	RT for recurrence 7 yrs after STR	50.4 at 1.8 Gy	13.5 yrs (Atypical)	Dead from tumor 3.5 yrs after initial recurrence
Age 40 yrs, WF 2001	Cavernous sinus 1.3 cm	Biopsy only	50.4 at 1.2 Gy BID	14.1 yrs (Atypical)	Alive with tumor 3 yrs after recurrence

Abbreviations: yrs, years; W, white; B, black; A, Asian; F, female; M, male; GTR, gross total resection; STR, subtotal resection; BID, twice-a-day fractionation; RT, radiation therapy.

Table 4
Patients with second tumor possibly caused by radiotherapy (3 patients).

Age, race, gender and date of RT	Location of meningioma	RT dose	Second tumor histology and location	Time between RT and second tumor	Status last follow-up
Age 50 yrs, WM 1992	Cavernous Sinus	50.4 at 1.8 Gy	SNUC of the superior ethmoid sinus in 90–100% isodose area	23.2 yrs	Dead from SNUC 0.7 yrs later without salvage treatment
Age 42, WF 1998	Cavernous Sinus	52.7 at 1.7 Gy	SNUC of the superior ethmoid sinus in 90–100% isodose area	17.1 yrs	Dead from SNUC 0.9 yrs later following salvage attempt with chemotherapy
Age 21 yrs, WF 2002	Optic Nerve Sheath	50.4 at 1.8 Gy	SNUC of the superior ethmoid sinus in 50–90% isodose area	12.2 yrs	Dead from SNUC 1.5 yrs later following salvage attempts with surgery and chemotherapy

Abbreviations: yrs, years; W, white; F, female; M, male; SNUC, sinonasal undifferentiated carcinoma.



# at risk at	0 years	5 years	10 years	15 years	20 years
Freedom from Recurrence (based on CLINICAL FU date)	149	122	89	38	11
Freedom from Recurrence (based on IMAGING FU date)	149	88	54	24	7
Overall survival (event only death) based on CLINICAL FU date	149	124	90	41	11
Relapse Free Survival (event is either recurrence OR death) based on CLINICAL FU date	149	122	89	38	11

Fig. 1. Actuarial plots of freedom from recurrence, overall survival, and relapse-free survival. The rate of meningioma recurrence based on clinical follow-up was 2% at 5 years, 3% at 10 years, 5% at 15 years, and 8% at 20 years.

Table 5
Major series with ≥10-year results after treatment of benign meningioma.

Series	Treatment	Tissue diagnosis	Clinical and imaging follow-up[1]	Recurrence rate and timing	Death from tumor
University of Florida O'Steen, Present Series (149 patients)	Fractionated RT for visible tumor following: SG 4–5: 28% Recurrent: 35% Imaging-only: 37%	63% Benign 37% Imaging-only	Median values: Clinical, all patients: 11.2 yrs Clinical, survivors: 12.0 yrs Imaging: 5.9 yrs	Actuarial results: At 10 yrs: 3% At 15 yrs: 5% At 20 yrs: 8% % of recurrences presenting after5 yrs: 43% (3/7 pts)10 yrs: 43% (3/7 pts)15 yrs: 14% (1/7 pts)	4% overall (6/149)86% (6/7) in patients with recurrence
Massachusetts General Hospital Sanford, 2017 [2] (44 patients)	Fractionated RT for visible tumor following: STR: 52% Recurrence: 48%	100% Benign	Median values: Clinical, all patients: 17.1 yrs Clinical, survivors: 14.8 yrs	At 10 yrs: 2% At 15 yrs: 10% % of recurrences presenting after 5 yrs: not stated10 yrs: 80% (4/5 pts)	Not reported
Consortium of 15 European Institutions Santacroce, 2012 [7] (3768 patients)	Gamma Knife Radiosurgery for visible tumor following: SG 4–5: 44% Imaging only: 56%	44% Benign 56% Imaging-only	Median values: Clinical: 5.1 yrs Imaging: 5.3 yrs	At 10 yrs: 11% At 15 yrs: ∼30% % of recurrences presenting after 5 yrs: ∼40% 10 yrs: ∼20%	Not reported
U. Amsterdam Alkemade, 2012 [6] (205 Patients)	Surgery alone: 86% Fractionated RT: 14%	100% Benign	Clinical Median: 11.5 yrs	At 10 yrs: 26% At 15 yrs: 32% % of recurrences presenting after 5 yrs: not stated After 10 yrs: ∼25%	Not stated
U. Heidelberg Combs, 2013 [8] (472 Benign Patients)	Fractionated RT: 100%	50% Benign 50% Imaging-only	Clinical Median: 8.9 yrs	At 10 yrs: 91% At 15 yrs: Not stated % of recurrences presenting after 5 yrs: not stated	Not stated
MD Anderson Cancer Center Soyuer, 2004 [6] (92 patients)	GTR only: 52% STR only: 35% STR + RT: 13%	100% Benign	Clinical Median: 7.7 yrs Other values not reported	At 10 years: 51% overall GTR alone: 49% STR alone: 63% STR + RT: 10% % of recurrences presenting after: 5 yrs: ∼50% 10 yrs: no data	Not reported
Karolinska Hospital Pettersson, 2011 [3] (51 patients)	Surgery only (no RT) Most had GTR: 75% SG 1–3 25% SG 4	90% Benign 10% Atypical	Clinical: 25 yrs in surviving patients. Other values not reported	At 25 yrs: 47% with SG 1–4 39% with SG 1–3 69% with SG 4 % of recurrences presenting after 5 yrs: 61% 10 yrs: 35%	29% overall (15/51)48% (15/31) in patients with recurrence
Helsinki University Jaaskelainen, 1986 [5] (657 patients)	Surgery only (no RT) All had GTR with SG 1–3	100% Benign	Clinical: 10 yrs in 41% 20 yrs in 11% Other values not reported	At 20 yrs: 19% overall 1 risk factor: 15–24% 2 risk factors: 34–56% % of recurrences presenting after: 5 yrs: ∼80% 10 yrs: ∼50%	Not reported

Abbreviations: RT, radiotherapy in multiple treatments; SRS, radiosurgery with a single treatment; GTR, gross total resection; STR, subtotal resection; SG, Simpson grade of resection, yrs: years.
[1] Clinical follow-up includes symptoms, physical examination, and imaging studies. Imaging follow-up requires a computed tomography or magnetic resonance scan.

Discussion

Many series report high 5-year control rates (≥90%) for benign meningioma treated with gross-total resection, fractionated radiotherapy, or single-fraction radiosurgery. The Karolinska series challenged the concept that benign meningioma is a highly curable tumor because tumor recurrence, and death from tumor, was common with long-term follow-up raised the question if tumor recurrence is common with long-term follow-up [3]. Specifically, the 2011 Karolinska series reported a recurrence rate of 39% at 25 years in a select group of 51 patients following potentially curative resections [3]. A major point in this analysis was that most recurrences (61%) presented >5 years after treatment. The importance of this "late recurrence" observation was magnified by the

finding that meningioma recurrence was fatal in almost half of the patients with a tumor recurrence (48%). Given the discouraging results in this surgery-only report, the purpose of our study was to determine if the same findings were seen following fractionated radiotherapy. Table 5 summarizes major publications with results from a substantial number of patients with at least 10 years of follow-up. The contribution of our series is that it is the largest series with more than 10 years of follow-up in patients treated with fractionated radiotherapy for visible meningioma at the time of radiotherapy.

Recurrence rate

The studies by Jaaskelainen and Pettersson have longer follow-up than most other studies, but their major difference is that the primary treatment was surgery alone (without radiotherapy) [3,5]. The study by Alkemade and colleagues from Amsterdam is primarily a surgery-alone study because only 14% of patients received radiotherapy [6].

The overall recurrence rates in these surgery-alone studies are higher than in the studies in which treatment involved radiotherapy. More specifically, the recurrence rate following potentially curative resection (the Simpson grade 1–3) was 20% in the Jaaskelainen study, 39% in the Pettersson study, and 32% in the Alkemade study. These results are at least double the recurrence rate following fractionated radiotherapy: 8% at 20 years in our study, 10% at 15 years in the small series from the Massachusetts General Hospital (Boston, MA) [2], 10% at 10 years in a small group of patients treated with subtotal resection and fractionated radiotherapy at MD Anderson Cancer Center (Houston, TX) [7], and 9% at 10 years in the large series from the University of Heidelberg [8].

The Santacroce radiosurgery study is unique in that the data come from a consortium database comprised of 15 European institutions [9]. Although follow-up in this study is the shortest among the studies, the investigators report recurrence rates of 11% at 10 years and approximately 30% at 15 years. These results are better than those from the Scandinavian surgery-alone studies, but not as good as the results with fractionated RT.

Time to recurrence

Every study with long-term follow-up reports a substantial percentage of "late recurrences" after potentially curative treatment for benign meningioma, meaning that at least 50% of the recurrences do not present until 5 or more years after treatment. Our data and that from the prospective series from the Massachusetts General Hospital solidify this concept for patients treated with fractionated radiotherapy because more than half of the recurrences did not present for at least 10 years after treatment.

Death from recurrence

The studies that report the frequency of death from recurrent meningioma confirm the finding of the Pettersson study that recurrence is usually fatal, even when additional surgery confirms benign histology of the recurrence.

Complications

Many of the papers in Table 5 report a range of complications that could be related to treatment. As explained above, we are skeptical about the accuracy of toxicity reports from studies that were not designed to report long-term toxicity and especially in those from multi-institutional databases that were designed to track general survival endpoints. We are concerned about our finding of 3 patients with high-grade tumors that were likely caused by radiotherapy. Adding these events to the cases of recurrent meningioma does not change the finding that an unfavorable outcome was uncommon (about 10%) in the overall study population. But, since all second tumors presented more than 10 years after treatment, it strengthens the conclusion that very late tumor-related events occur in this patient population.

Conclusions

Our data contradict the concept suggested by several large Scandinavian studies that the rate of tumor recurrence is high with >-10-year follow-up after treatment for benign meningioma. There are many limitations to comparing data from the available publications, but the small number of studies with long-term follow-up suggests that the recurrence rate is lower in patients treated with fractionated radiotherapy than with the favorable Simpson grade resections. In view of this observation, radiotherapy is our preferred primary treatment when curative resection is likely to cause substantial morbidity. Data comparing the relative efficacy of fractionated versus single-fraction (radiosurgery) radiotherapy are so scarce that discussing this issue is beyond the scope of this paper. Also, it is important to note that histologic grade is a powerful prognostic factor such that our results apply only to benign (Grade 1) tumors [10].

Our data confirm other series that observed that the majority of recurrences of benign meningioma do not present until at least 5, or even 10, years after primary treatment. This finding means that series with less than 10-year follow-up likely overestimate treatment efficacy, especially in patients treated with surgery alone.

The need for regular follow-up for decades after treatment for benign meningioma remains controversial. The observation of late recurrences (and second tumors) argues for long-term follow-up; however, with a 20-year recurrence rate of only 8% in our series and a very low salvage rate, earlier detection of recurrence is unlikely to improve overall outcome to a meaningful degree. Recognizing these limitations, our practice is to follow patients (preferably with MR imaging) for the remainder of their lives annually for the first 5 years and then every 2 years thereafter.

Conflicts of interest

None.

Funding

None.

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