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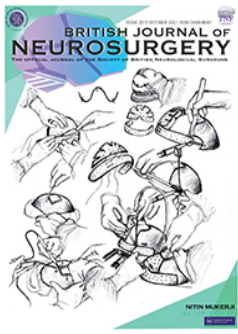
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ORIGINAL ARTICLE



Atypical meningioma: patterns of postradiotherapy recurrences

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ABSTRACT

Purpose: There is no consensus on a target definition and optimal dose in radiotherapy for atypical meningioma (AM). Insight into the postradiotherapy recurrence pattern is needed for optimal target definition and local control. The objective was to describe the patterns of recurrence after postoperative or salvage radiotherapy in patients with AM.

Materials and methods: A retrospective analysis was conducted of patients treated for intracranial AM with (fractionated) stereotactic radiotherapy (FSRT). The relationships between postradiotherapy recurrences, the dura and irradiated volume were established. Moreover, the dose prescriptions and fractionation schedules were converted to a reference to determine the relationship between dose and local control.

Results: The included patients received 57 (F)SRT treatments and 73 surgeries. Recurrent disease was found in 21 of 29 patients (72%) and after 39 of 57 (F)SRTs (68%). The median interval to first recurrence was 39.7 months. Of these recurrences, 25 were in-field, 11 were marginal, and 3 were out of field. In-field recurrence rates after biological equivalent doses < 60 Gy or ≥ 60 Gy were 50% and 21%. All recurrences were connected to the dura. Of the marginal recurrences, 64% were within 2 cm and 91% were within 3 cm of the volume receiving the prescribed dose.

Conclusions: AM frequently recurs after radiotherapy. All postradiotherapy recurrences were connected to the dura. Most marginal recurrences occurred within 3 cm of the irradiated abnormal dura. The lowest rate of in-field recurrences occurred after equivalent doses of least 60 Gy in 2 Gy fractions suggesting a dose–effect relationship.

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1. Introduction

Meningioma is one of the most common brain tumours in adults, with an incidence of 7.61 cases per 100 000 people in the United States.^{1,2} The 2016 World Health Organization (WHO) classification describes three histological grades: grade I (benign), grade II (atypical meningioma (AM), chordoid, and clear cell) and grade III (anaplastic or malignant).^{1,3} Gross total resection is considered the standard treatment for AM.⁴ There is no agreement on the role of postoperative radiotherapy after radical surgery.^{5–7} Retrospective series and one prospective phase II study reported more favourable local control rates with postoperative radiotherapy than without, suggesting a positive effect of adjuvant radiotherapy.^{8–11}

More agreement exists on the policy after incomplete surgery. Postoperative radiotherapy is generally advised due to the high local recurrence rates after irradiated surgical resection.⁴ Treatment of recurrent AM usually consists of surgery or radiotherapy alone or a combination of both modalities.¹² Recurrent disease is difficult to control, emphasizing the importance of aggressive initial treatment.¹³ Recurrences can occur at or near the original tumour site, but can also be found at distant intracranial locations.¹²

For radiotherapy of AM, the use of generous clinical target volumes (CTV), which include adjacent brain tissue, is

described.¹¹ As a consequence of these large radiation volumes, late brain toxicity may occur.^{9,11,14} To adequately treat microscopic residual or recurrent disease, without causing unnecessary toxicity, it is essential to determine the possible extension of residual disease. The most likely locations of residual disease can be deduced from the patterns of recurrence after radiotherapy. However, in our opinion, the recurrence patterns after radiotherapy of AM have not been sufficiently described.

A cohort of patients with AM, treated with stereotactic radiotherapy (SRT) for residual or recurrent disease, was examined. The patients were followed after SRT and the occurrence and timing of new recurrences were determined, as were their locations in relation to the treated volume. The purpose of this study is to describe the recurrence pattern in our patients with AM and, by using this information, to better define the CTV and optimal radiation dose.

2. Materials and methods

2.1. Study design

This is a single-centre retrospective review of patients with AM treated with fractionated stereotactic radiotherapy [(F)SRT]. We included all consecutive AM patients treated in our department between 2003 and 2018. Approval of the IRB was obtained;

patient consent was not necessary for this retrospective chart review. Pathological diagnoses were made using the classification system that was current in the year of diagnosis. An experienced neuropathologist reviewed all histological slides of patients diagnosed with AM from 2003 on. We included only those patients in this study who, throughout the course of their disease, were diagnosed at least once with AM using the 2016 WHO classification.³

Clinical variables, treatment data and follow-up information were extracted from medical records.

2.2. Treatment

Treatment decisions were discussed in the multidisciplinary neuro-oncology tumour board. Surgery was the preferred treatment for a macroscopic tumour at presentation and in cases of recurrence. Radiotherapy was added after first surgery in cases of macroscopic or suspected microscopic residual disease and after repeat surgery if deemed indicated by the multidisciplinary team. Moreover, radiotherapy for macroscopic recurrent disease was performed if patients were unfit for surgery or if the recurrence was considered irresectable.

Radiotherapy treatment planning was based on a computed tomography scan (CT-scan) that used (at most) 2 mm slice thickness, while immobilized using a non-invasive stereotactic head frame (Brainlab AG, Munich, Germany or, from June 2016 onward, Qfix, Avondale, PA). In all patients, an MRI planning scan was executed (T1-weighted 3D MPRAGE after gadolinium administration; voxel size $1.1 \times 1.1 \times 1.3 \text{ mm}^3$). Co-registration of CT and MRI, contouring, and treatment planning were done on Brainscan 5.31 or iPlan 4.0 (Brainlab AG, Munich, Germany). The gross tumour volume (GTV) was defined as the contrast enhancing macroscopic tumour. The clinical target volume (CTV) included the GTV, without additional margin, and areas of suspected tumour extension in thickened meninges next to the macroscopic tumour. Meninges that had been adherent to the tumour preoperatively were also included in the CTV. The area of the brain that had been compressed by the tumour preoperatively was not included in the CTV unless microscopic residual disease was suspected based on information provided by the surgeon or pathologist. The planning target volume (PTV) was created by a 3D expansion of the CTV of 2 mm.

All patients received linac-based fractionated stereotactic radiotherapy on a Novalis 'classic' (Brainlab AG, Munich, Germany) or Versa HD (Elekta AB, Stockholm, Sweden).

The treatment techniques used included intensity modulated radiotherapy (IMRT) or dynamic conformal arcs and depended on the shape of the PTV. As a rule, the prescribed doses for first radiation treatments were 35 Gy in seven fractions, specified on the 80% isodose in smaller PTVs, 54 Gy in 30 fractions specified on the 80% isodose in larger PTVs, or 60 Gy in 30 fractions specified on the 100% isodose in larger PTVs that also included relevant volumes of brain tissue. In patients with low-volume recurrent disease after previous radiotherapy, hypofractionated or single fraction regimens were used (Table 2). The dates of all surgeries and the first dates of all radiation treatments were determined. Simpson grades were retrieved from the available surgery reports or the hospital records by a neurosurgeon (R. N.).

2.3. Follow-up

Patients were followed in the outpatient clinic of the radiation oncologist or the referring neurosurgeon at 3–6 months' intervals

as long as their condition allowed them to come. The follow-up visits were combined with MRI scans. Telephonic follow-up was done if the patients were not able to come. For this study, follow-up data were used until 31 December 2018.

The recurrence pattern was studied in collaboration with an experienced neuro-radiologist. The location of the progressive lesion was determined on the first MRI that showed growth of this lesion. This progressive lesion was related to the treated volume (TV), that is, the volume covered by the prescription isodose of the last radiation treatment. Recurrences after surgery were not characterized, though if the patient had received radiotherapy before the surgery, the recurrence was assumed to be related to the radiation treatment before the surgery. In-field recurrence was defined as a recurrence located at least partly within the TV. Marginal recurrence was defined as a recurrence outside, but bordering the TV. Out-of-field recurrence was defined as a recurrence completely outside and not touching the TV. Furthermore, we assessed whether the recurrence was connected to the meninges or not at all. If multiple recurrences were found on the same MRI, they were characterized separately.

The relationship between dose and in-field recurrence rate was studied separately. As the prescribed target dose and fractionation have been very diverse, it was necessary to convert these different dose prescriptions and fractionation schedules to a reference.

Dose has been prescribed to the PTV. This was done using a prescription either to the 80% isodose, with the 100% dose being specified in the isocentre and at least 98% of the PTV receiving the prescribed dose, or to the 100% dose, being the median dose to the PTV, with the constraint that at least 98% of the PTV should receive 95% of the prescribed dose.

To be able to compare these two prescriptions, we chose to calculate the generalized equivalent uniform dose (gEUD) for each clinical target volume (CTV) from the dose volume histogram (DVH) of that treatment plan (Niemierko A. *Reporting and analyzing dose distributions: a concept of equivalent uniform dose*. Med Phys. 1997 Jan;24(1):103-10.):

$$gEUD = \left(\sum_i v_i D_i^a \right)^{1/a}$$

With D_i being the dose of the i th bin; v_i being the volume receiving this dose; a being the tissue-specific parameter.

For each CTV, a gEUD for that plan was computed. For α/β , we have assumed a value of 10 Gy, as atypical meningioma are fast-growing tumours. However, in view of the lack of data concerning the α/β of AM, we also fitted the data with α/β 's of 7 Gy and 14 Gy.

To correct for the differences in fractionation, we applied the EQD2 method to the calculated gEUD values to calculate an equivalent dose in 2 Gy fractions (Joiner M, Kogel vd A. *Basic clinical radiobiology*. London: Hodder Arnold; 2009.). This yields an gEUD2 value for each CTV:

$$gEUD2 = n \times d[(1 + d/(a/b))/(1 + 2/(a/b))]$$

with n being the number of fractions; d being the fraction dose.

2.4. Statistics

Descriptive statistics were used to describe the patients and treatments. Overall survival and local recurrence were evaluated at the patient level. Survival was calculated from the first day of the first radiotherapy treatment. Patients were censored at date of death or date of last visit to the hospital until 31 December 2018.

The local progression-free interval was determined after every first (F)SRT treatment and was defined as the time interval between the first day of the first (F)SRT treatment and the day the first progression was established via MRI. The patients without recurrences were censored at date of death or date of last visit to the hospital until 31 December 2018. Overall survival and local tumour control were estimated using the Kaplan–Meier method. Analyses were performed using the IBM SPSS statistics version 26 software package (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

3. Results

3.1. Patients and treatments

Between August 2003 and November 2018, 31 patients were treated in the department of radiotherapy with a diagnosis of atypical meningioma (AM). Pathological diagnoses were made using the classification system that was current in the year of diagnosis AM. After histopathology revision using the WHO 2016 classification, 29 patients remained with a definitive diagnosis of AM. In this cohort no patients had a chordoid or clear cell meningioma. The median follow-up of these 29 patients was 11.3 years [IQR 6.0–12.5]. Patients characteristics are shown in Table 1 and treatment characteristics in Table 2. AM patients ($N=29$) underwent 73 resections and 57 irradiations. The majority of radiation treatments (47/57; 82.5%) were for macroscopic residual or recurrent disease. Seven treatments were for microscopic residual disease. Four patients received postoperative radiotherapy for initially diagnosed grossly resected AM. For three treatments, this information was unknown. Four patients had low-dose treatments (5×5 Gy or 28×1.8 Gy), as they were diagnosed with a benign meningioma. However, at a later stage, there appeared to be a recurrence with a histologically proven AM.

3.2. Survival and local control

The median survival of the patients was 8.7 years [IQR 4.6–12.8], while the 2- and 5-year survival rates were 90% and 71%, respectively (Figure 1).

In the 29 patients, 57 (F)SRT treatments were performed. Recurrent disease was found in 21 of 29 patients (72%) and after 39 of 57 (F)SRT treatments (68%). Recurrence occurred after five of all seven treatments for microscopic residual disease and after two of four postoperative treatments for initially diagnosed grossly resected AM. The median interval to first recurrence was 39.7 months. Two- and five-year rates of freedom from first recurrence were 76% and 26% (Figure 2). Radiotherapy resulted in one recurrence in 10 patients, in two recurrences in 10 patients, and in nine recurrences in one patient.

Table 1. Patients characteristics.

Patients	N	%	Median (range)
Age			56 (26–81)
Gender			
Male	14	48	
Female	15	52	
KPS at first (F)SRT			
70–80	21	72	
90–100	8	28	

3.3. Location of recurrences

After the 57 (F)SRT treatments, 39 recurrences were found. Out of these 39 recurrences, 25 were classified as in-field, 11 as marginal recurrence, and three as out-of-field recurrence. All recurrences were connected to the dura. No recurrence was found in the brain unattached to the dura.

In 91% of the 11 marginal recurrences, the maximum distance between the recurrence and the treated volume was up to 3 cm. In 64% of these cases, the distance was up to 2 cm.

In two patients, an out-of-field recurrence was their first recurrence and in one patient the out-of-field recurrence was the second recurrence.

Eight patients had no recurrence (8/29). Fifty per cent of the patients had a microscopic residual tumour before (F)SRT.

In nine patients, repeat irradiation was given on an infield recurrence. This resulted again in infield recurrence in seven of these nine patients.

3.4. In-field recurrence rate versus dose

In this retrospective cohort, we could retrieve the treatment planning data of 51 (F)SRT treatments. Figure 3 shows the relationship between the calculated gEUD2 and the in-field recurrence rate. It appeared that in-field recurrences occurred more often if the corrected dose (gEUD2) was 60 Gy or less compared to higher doses (50% versus 21%).

Table 2. Treatment characteristics.

Treatments	N (treatments)
Surgeries : total	73
First surgeries	29
Simpson grade	
I	8
II	12
III	3
IV	0
Unknown	6
Repeat surgeries	44
Simpson grade	
I	19
II	8
III	3
IV	3
Unknown	11
(F)SRT treatments: total	57
for microscopic disease	7
After surgery for initially diagnosed AM	4
After surgery for recurrent AM	3
For macroscopic disease	47
For disease with unknown size	3
(F)SRT dose	
Atypical meningioma at first (F)SRT	25
30×1.8 Gy (80%)	9
30×2 Gy (100%)	8
28×1.8 Gy (80%)	1
7×5 Gy (80%)	7
Grade I meningioma at first (F)SRT	4
28×1.8 Gy (80%)	1
5×5 Gy (80%)	3
Atypical meningioma at repeat (F)SRT	27
30×1.8 Gy (80%)	1
28×1.8 Gy (80%)	1
10×3 Gy (80%)	1
7×5 Gy (80%)	13
3×8 Gy/ 3×9 Gy (80–100%)	2
1×21 Gy/ 1×18 Gy (80%)	9
Grade I meningioma at second (F)SRT	1
5×5 Gy (80%)	1

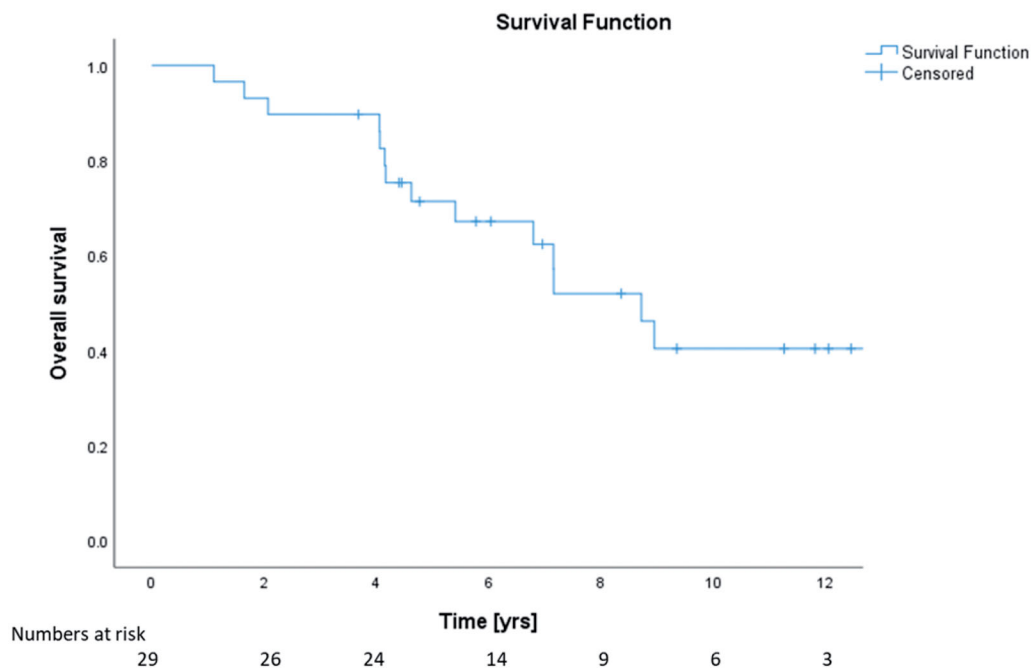


Figure 1. Overall survival of all 29 patients.

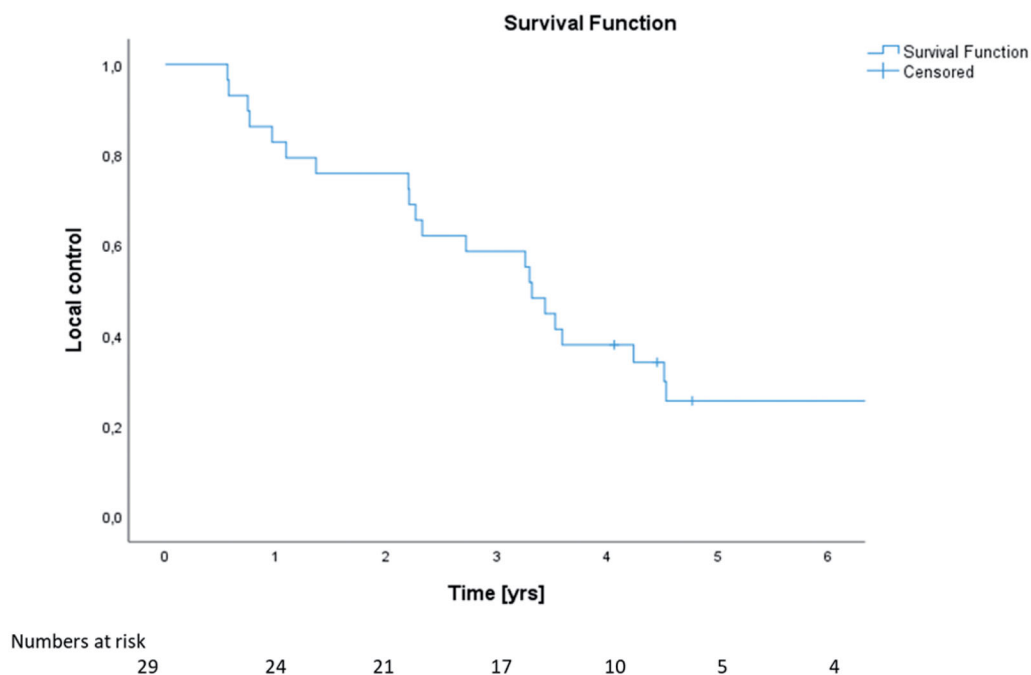


Figure 2. Rate of freedom of first recurrence in all 29 patients.

4. Discussion

This study examined the patterns of recurrence after surgical resection and radiotherapy for AM. In this unfavourable subset of patients, the majority of whom underwent multiple surgeries and radiation treatments, recurrent tumour after radiotherapy was found in 72% of patients and after 70% of radiation treatments. The majority (64%) of recurrences were found to be in-field. A dose-effect relationship was suggested, as the lowest rate (20%) of in-field recurrences occurred after equivalent doses (gEUD2) of least of 60 Gy. All recurrences had a connection with the dura. In 91% of cases, marginal recurrences were found in normal-appearing dura within 3 cm of the radiation fields.

We studied the relation between dose and in-field recurrence rate and found fewer in-field recurrences with higher corrected radiation doses (gEUD2). Other authors have reported a relationship between dose and local control as well, but definitive conclusions have not been possible because the series are small due to the infrequent occurrence of AM. In a series of 19 patients treated with postoperative combined photon and proton therapy, survival – but not local control – was reported to be significantly better with total dose >60 Gy.¹⁵ In another series of 15 AM patients treated with photons or with a combination of photons and protons, a significantly improved local control is reported with doses of 60 Gy or more.¹⁴ These data seem to confirm that,

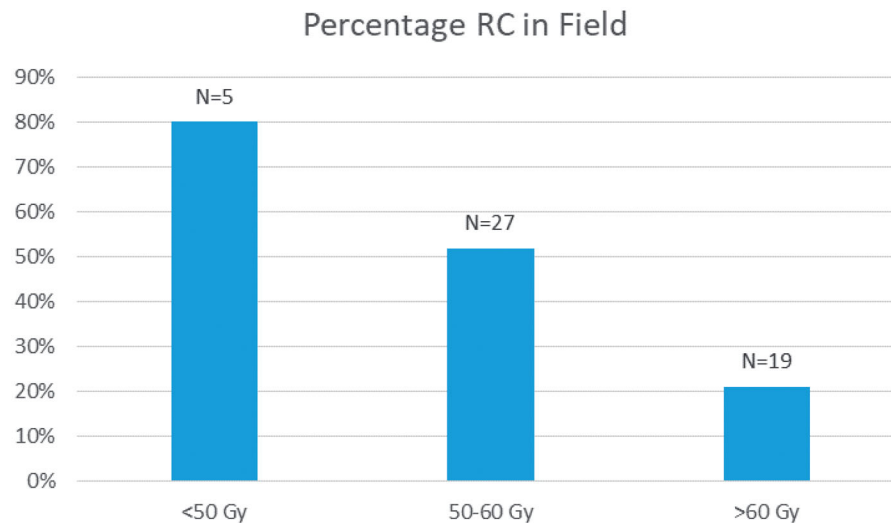


Figure 3. In-field recurrence rates versus equivalent dose in 2 Gy fraction (gEUD2) treatment groups receiving < 50 Gy ($n = 5$); 50–60 Gy ($n = 27$); > 60 Gy ($n = 19$).

for AM, at least 60 Gy, but possibly higher doses are needed to control macroscopic disease. Because normal brain tissue is always adjacent to the target, one could argue that (in these cases) it would potentially be safer to use protons instead of photons to deliver doses over 60 Gy.

Another important finding is that all recurrences were connected to, and, therefore, probably originating from, the dura. Moreover, in our cohort, 28% of all recurrences were classified as marginal. The extension of most marginal recurrences was within 3 cm of the prescription isodose volume. This indicates that in these cases, the normal classified dura, that is dura beyond the dural tail, probably did contain tumour cells. In benign meningiomas, the dural tail contains tumour cells in the majority of cases, though normal-appearing dura may contain tumour cells as well.¹⁶ In another study, a rim of seemingly normal dura was biopsied in eight GI and three GII meningioma patients. In one of eight GI and all three GII cases, tumour cells were found in these biopsies.¹⁷ The authors of this study recommend, if feasible, the removal of the dural tail and a rim of 1-cm normal-appearing dura, especially in AM. Some authors suggest that this rim of normal dura mater should be 2–4 cm.^{18,19} This finding, i.e. that normal-appearing dura near the dural tail frequently contains tumour cells, may explain the relatively frequent occurrence of marginal recurrences in our study. Based on our results and published data, we believe there is evidence to include the following structures in the CTV of patients with recurrent AM or after macroscopically incomplete resection: the dura previously connected to the tumour, the dural tail, and, if feasible, 2–3 cm of normal-appearing dura. None of the recurrences in our series seemed to originate from brain tissue and, therefore, in contrast to the study protocol of NRG Oncology/RTOG 0539, we see no reason for including the entire surgical cavity or brain tissue in the CTV, at least in AM patients without brain invasion.²⁰ As most of our patients (seven of nine) who received repeat irradiation of an infield recurrence experienced another infield recurrence, we believe that in this situation the target volume should only consist of the recurrent gross tumour. Here, the risk of toxicity of re-irradiated normal tissue probably outweighs the risk of a marginal recurrence. To our opinion, relatively large volumes can be treated safely with fractionated stereotactic radiotherapy up to 60 Gy, as in most cases, brain tissue does not have to be included in the CTV.

In our cohort, the 2- and 5-year rates of freedom from first recurrence were 76% and 26%, respectively, with a median interval to first recurrence of 39.7 months. This means that patients should be followed for at least five years to detect the majority of recurrences. In a recently published paper with results from the EORTC study 22042-26042, a 3-year progression-free survival of 88.7% is reported after macroscopically radical surgery and post-operative radiotherapy.¹¹ This suggests a favourable prognosis after macroscopically radical surgery followed by radiotherapy. However, the patient cohort from our study is much less favourable, as most patients in our study received (F)SRT for macroscopic residual or recurrent disease and, therefore, are high risk patients as defined in NRG Oncology/RTOG study 0539.²⁰ In these patients, multiple recurrences were encountered, for which repeat (F)SRTs and surgeries had to be given. These recurrences could be found in the dura either close to or at a distance from the irradiated areas. This is a reflection of the natural course of AM, probably because large areas of seemingly normal dura may contain tumour cells. It is difficult to compare our results with the literature data, as not many series have been published with AM patients treated with modern fractionated photon radiotherapy after incomplete surgery. Recently, the results of NRG Oncology/RTOG 0539 were published. This study describes the results of IMRT in 57 patients with high-risk meningioma. After a median follow-up period of 4.0 years, a 3-year local control rate was reported of 68.9%, which is comparable to our results.²⁰ A study by Chen et al.¹² describes the outcomes of multiple modalities of salvage therapy for AM.¹² The authors report a disease-free interval after a first salvage treatment of 2.9 years, which is comparable to the median time to first recurrence of 39.7 months that we report. In a retrospective multicentre study, results are reported in 119 patients with G II–GIII meningiomas, 71% of whom had undergone macroscopic radical surgery. Five-year disease-free survival after fractionated radiotherapy (40–66 Gy) was 62% for G2 tumours.²¹ Two older papers report 5-year progression free rates of 34–48%.^{22,23} Some series have been published with results of radiosurgery of residual and recurrent AM with varying prescribed doses and follow-up lengths. Reported tumour control rates varied (widely) between 16% and 83%.^{24–31} Based on these data, we conclude our recurrence rates are similar to those reported in the literature and are a reflection of the behaviour of recurring AM. Strong points of this study are the length and completeness of the follow-up.

Limitations are the well-known shortcomings of its retrospective nature. Another weakness is the limited sample size, which is due to the relatively infrequent occurrence of AM. For the calculation of the gEUD2, we needed to assume an α/β of 10 for AM, in the absence of literature data. However, when we fitted the data with α/β 's of 7 Gy and 14 Gy, the results remained unchanged. Numbers were too small to note a distinction in recurrence patterns after first versus second or later radiation treatment or in AM patients with versus without a history of grade I histology.

5. Conclusion

AM frequently recurs after radiotherapy. Post-radiotherapy intracranial recurrences are most often local, not seldom marginal or distant, but always have a connection with the dura. In-field recurrences occur less often after corrected doses > 60 Gy. Marginal recurrences mostly occur within 3 cm of the irradiated abnormal dura. A dose-effect relation was suggested to be the lowest rate (21%) of in-field recurrences that occurred after equivalent doses of at least 60 Gy in 2 Gy fractions.

Disclosure statement

The authors report no conflict of interest.

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