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Atypical and Anaplastic Meningiomas – Does the New WHO-Classification of Brain Tumours Affect the Indication for Postoperative Irradiation?

W. Hoffmann[1], **H. Mühleisen**[2], **C. F. Hess**[1], **R. D. Kortmann**[1], **B. Schmidt**[3], **E. H. Grote**[4], and **M. Bamberg**[1]

[1] Department of Radiotherapy, [2] Institute of Neuropathology (Brain Research), [4] Department of Neurosurgery, University of Tübingen, and [3] Department of Radiotherapy, Katharinenhospital-Stuttgart, Federal Republic of Germany

Summary

We retrospectively analysed 13 patients (pts.) treated at the University of Tübingen from 1985 to 1993 to evaluate the results of radiation therapy (XRT) given as an adjuvant to totally or subtotally resected meningiomas. The overall survival was 38% at five years with a probability of relapse of 50% at this time. Reclassification of the tumours according to the new WHO-classification of brain tumours [14] revealed 10 grade-II-tumours (atypical meningioma) and 3 grade-III-tumours (anaplastic meningioma). Radiotherapy failed in all 3 pts. with macroscopically incomplete resection (Simpson's grade IV), who died with relapse between 4 and 51 months after radiotherapy. 5 out of 10 pts. with grade-II-tumours relapsed. All 3 pts. with grade-III-tumours died with relapse between 6 and 21 months after XRT. Morbidity was seen in 2 pts. after irradiation with 60 GY (ICRU dose specification).

Complete surgical exstirpation offers the best possibility of tumour control. Grade-III-tumours should be irradiated whatever the extent of the primary surgery was. Our results might indicate a possible indication for XRT in pts. with atypical grade-II-tumours especially when radical surgery must be in doubt. Prospective multicentre trials are warranted to prove the prognostic value of the new WHO-classification for atypical and anaplastic meningiomas and to define the ultimate role of radiotherapy in this setting.

Keywords: Atypical meningioma; anaplastic meningioma; postoperative radiotherapy.

Introduction

Meningiomas account for 15% to 20% of all primary intracranial neoplasms [3, 11, 20]. The majority of these meningiomas are benign, slow growing and well circumscribed tumours. By far less commonly and in about 8% of all meningiomas, malignant forms are described in which cure is often impossible and recurrence-free intervals are usually short [11].

In the past a two-tiered grading system for benign or malignant meningioma has been used [31] but the definitions of "malignancy" differed considerably between authors [11–13]. In order to define tumour grading, meningiomas of intermediate malignancy have been postulated [17, 27]. Thus a three-tiered grading system including "typical", "atypical", and "anaplastic" meningioma has been introduced in the recently published WHO-classification of brain tumours [14] (Table 1). As distinct criteria for tumour grading are now available the diagnosis of atypical or anaplastic meningioma is well defined. However,

Table 1. *WHO-Classification of Meningiomas*

1979 [29]	1993 [14]
Typical:	Typical:
meningotheliomatous	meningothelial
fibrous (fibroblastic)	fibrous (fibroblastic)
transitional (mixed)	transitional (mixed)
psammomatous	psammomatous
angiomatous	angiomatous
–	microcystic
–	secretory
–	clear cell
–	chordoid
–	lymphoplasmacyte-rich
–	metaplastic
haemangioblastic	–[a]
haemangiopericytic	–[b]
	Atypical
papillary	papillary
Anaplastic	Anaplastic
malignant	malignant

[a] Haemangioblastoma: "tumour of uncertain histogenesis".
[b] Haemangiopericytoma: "mesenchymal, non-meningothelial tumour".

guidelines for the clinical management of patients suffering from "typical", "atypical" or "anaplastic" meningioma are not yet established.

In our retrospective analysis we reviewed the histology, management and clinical outcome of 13 cases with meningiomas treated by postoperative irradiation between 1985 and 1993 for residual progressive tumour, "malignant meningioma" at primary histology, or recurrent tumour growth. We used the classification published by the World Health Organization (WHO) [14, 15] in 1993 to separate retrospectively "atypical" meningiomas from the group of "anaplastic" or "typical" meningiomas as defined at the time of primary histology. In addition we assessed microscopic brain invasion in order to evaluate the eventual role of this distinct feature on tumour recurrence.

Clinical Material and Methods

Patient Selection

Between 1985 and 1993 a total of 13 patients (6 male, 7 female) have been irradiated at our institutions for the diagnosis of meningioma. Age ranged from 40 to 72 years. Radiotherapy was indicated in 8 patients (pts.) with "malignant" meningiomas, in 2 pts. with benign histology but incomplete resection and progressive tumour growth, and in 3 pts. who suffered from symptomatic recurrences following macroscopic complete resection.

Relapse was defined when symptomatic and/or progressive tumour growth was evident. All of the 13 meningiomas were intracranially located. The site of location was the convexity (9 pts.) followed by the base of the skull (3 pts.) and the sphenoid ridge area (1 patient) (Table 2). The completeness of resection was macroscopically assessed according to Simpson's classification of the operative procedures for the removal of meningioma [4, 23]. According to the extent of resection, 7 cases had Simpson's grade I, 2 grade II, 1 grade III, and 3 cases with Simpson's grade IV resection (Table 3).

Table 2. *Distribution of Anatomical Tumour Site*

Site	Pts.
Convexity	9
Frontal	1
Frontotemporal	3
Parietal	2
Parieto-occipital	3
Sphenoid-ridge	1
Base of skull	3
Spinal	0
Extracranial	0
Total	13

Table 3. *Extent of Tumour Removal According to Simpson's Grading (23)*

Simpson's grade	n
Grade I Macroscopically complete resection of the tumour with excision of its dural and bony attachment	7
Grade II Macroscopically complete resection with endothermy coagulation of its dural attachment	2
Grade III Macroscopically complete resection without resection or coagulation of its extradural extensions	1
Grade IV Partial removal leaving intradural tumour in situ	3
Total	13

Pathology

After surgery the tumours were fixed in 4% formaldehyde. From as many specimens as possible representative samples were embedded in paraffin. For routine histology 1 to 3 µm sections were stained by haematoxylin-eosin, periodine and Schiff's reagent and Novottny's silver impregnation for reticulin fibers. Initially the tumours were classified and graded according to the 1979 WHO-classification of brain tumours [31]. For the use of our study, the meningiomas were reviewed and graded according to the 1993 WHO classification (Table 1) [15]. Thus a meningioma was graded "atypical" (WHO grade II) when it displayed a focal increase in cellularity, small foci of necrosis, areas with prominent nucleoli, or, most importantly, an increase in mitotic activity [17]. The diagnosis of "anaplastic meningioma" (WHO grade III) was restricted to tumours devoid of meningothelial differentiation (i.e., whorls or onion bulb formations, nuclear invaginations, psammomatous bodies) with general increase in cellularity, focal necrosis, and more than one mitotic figure in several high power fields (×400 magnification). In addition, a meningioma was graded "invasive" when brain invasion occurred either by finger-like projections or by clusters of meningioma cells deep within the brain parenchyma. Superficial brain adherence was not indicative of invasiveness unless a focal loss of connective tissue membranes to seperate meningothelial cells from brain tissue was observed.

Data Analysis

Tumour histology was re-classified using the criteria of the new WHO 93 classification of brain tumours after a review of all samples. Microscopic brain invasion had additionally been assessed in order to evaluate its eventual role on tumour recurrence. Histological grading, extent of primary surgery, brain invasion and start of radiotherapy after primary surgery were analysed with respect to recurrence.*Radiation Technique*

All pts. were irradiated with 4 to 25 MeV linear accelerator using 1.8 to 2.0 Gy fractions 5 times per week.

The pts. were treated with limited volume irradiation to restrict irradiation of normal brain tissue and to minimize undesirable side effects. The planning traget volume included the typical enhanced tumour as demonstrated on the pre-operative CT-examination plus a safety margin of 1 cm for benign and 2 cm for malignant meningioma. Total doses of 54 to 65 Gy were given within 5,5 to 7 weeks using daily fractions of 1.8 to 2.0 Gy 5 times a week [10].

Follow-up Examination

Follow up examinations were performed 6 weeks after the end of radiotherapy and every 3 months afterwards in the first two years, then every 6 months. Additional examinations were made in cases where detoriation of neurological function or of clinical performance status had occurred. They included detailed clinical examinations and CT scanning before and after intravenous injection of contrast media. Recurrence was diagnosed if progressive and/or symptomatic tumour growth was evident with increase in contrast enhancing tumour volume as compared with the first post-treatment CT examination.

Results

Median observation time was 24 months (range 4 to 69 months) and median relapse free survival was 15 months (range 0 to 69 months). In our analysis the overall survival was 38% at five years with a 50% probability of relapse at this time (Fig. 1 a, b).

Histopathological re-classification of all 13 meningiomas according to the recently published WHO-classification [13, 14] revealed 7 meningotheliomatous, 5 transitional and 1 fibrous meningioma. These include 10 atypical meningiomas (grade II WHO 93) and 3 anaplastic meningiomas (grade III WHO 93).

From 8 tumours where the initial diagnosis has been "malignant meningioma" only 3 were re-classified as "anaplastic" (grade III WHO 93). The remaining 5 tumours, however, were classified as "atypical" (grade II WHO 93). 5 cases with the previous diagnosis of "benign" meningioma were upgraded according to the new classification to grade II tumours.

In 3 out of the 6 tumours without microscopic brain invasion, resection was macroscopically incomplete (Simpson's grade IV). In 4 out of 7 pts. with microscopic brain invasion resection of the tumour including excision of its dural and bony attachment was complete (Simpson's grade I).

Radiotherapy failed in all 3 pts. with macroscopically incomplete resection (Simpson's grade IV) who died between 4 and 51 months after radiotherapy. In two pts. the base of the skull was the unfavourable primary location compromising the probability of radical surgery.

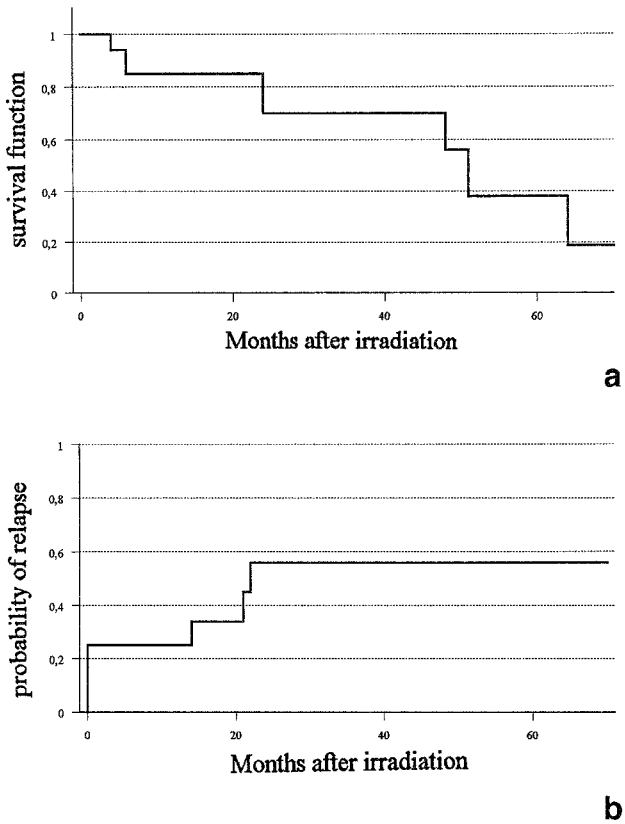

Fig. 1. (a) Overall survival of all 13 patients (Kaplan-Mayer method). (b) Probability of relapse

6 pts. showed no macroscopic brain invasion of whom 4 relapsed. In 3 out of these pts. tumour resection was macroscopically incomplete (Simpson's grade IV). 4 out of 7 pts. with proven macroscopical brain invasion had undergone macroscopically complete resection of the tumour including excision of its bony and dural attachment (Simpson's grade I).

Following the actual WHO-classification 5 out of 10 pts. with atypical grade-II-tumours recurred. In 2 out of 3 cases in whom radiotherapy was given immediately after primary surgery, local tumour control could be achieved. All 3 pts. with grade-III-tumours relapsed and died between 6 and 21 months after XRT (Tables 4 and 5).

Of the 13 pts. irradiated only 2 showed neurological impairment which might be attributed to irradiation. Both pts. suffered from weakness, forgetfulness and lack of initiative, 50 and 22 months after irradiation, respectively. Relapse was excluded by CT and MRI in these cases. Both pts. received a dose of 60 GY according to ICRU dose specification [10]. Other and severe complications such as blindness or cerebral necrosis have not been observed so far.

Table 4. *Clinical Summary and Results of Treatment in 13 pts. with Irradiated Meningiomas*

Case no., sex, age (at primary) diagnosis)	Location	Simpson's grading at prim. OP	micr. invasion	Grading at prim. OP		XRT after prim. OP	XRT for recurrent disease (GY)	Recurrence free interval after XRT in months	Status at last follow up/ (months after XRT)
				WHO 79	WHO 93				
1, ♀, 61	sphenoid ridge	I	yes	III	II	yes	no (60)	50	ALNED (50)
2, ♂, 40	parietal	I	yes	III	III	no	after 1st RL (65)	14	DwD (48)
3, ♂, 52	parieto-oc.	I	yes	III	II	no	after 1st RL (60)	22	DwD (24)
4, ♀, 56	parieto-oc.	I	no	III	II	yes	no (60)	22	ALNED (22)
5, ♂, 53	base of skull	III	yes	III	II	no	after ist RL (60)	15	ALNED (15)
6, ♂, 52	frontal	I	yes	I	II	no	after 1st RL (54)	22	ALNED (22)
7, ♀, 60	fronto-temp.	IV	no	I	II	no	after 3rd RL (60)	0	DwD (4)
8, ♂, 72	fronto-temp.	I	no	I	II	no	after 2nd RL (60)	69	ALNED (69)
9, ♀, 66	parietal	II	yes	III	II	no	after 3rd RL (65)	n.a.	DwD (64)
10, ♀, 51	base of skull	IV	no	I	II	no	after 1st RL (60)	0	DwD (6)
11, ♂, 50	occipital	I	no	III	III	yes	no (55)	6	DwD (6)
12, ♀, 45	base of skull	IV	no	III	III	no	after 1st RL (55)	21	DwD (51)
13, ♀, 67	fronto-temp.	II	yes	I	II	no	after 3rd RL (55)	0	LwD (15)

ALNED alive no evidence of disease, *RL* relapse, *n.a.* not assessable, *LwD* living with disease, *DwD* dead with disease.

WHO-Grading: *I* benign, *II* semi-benign, *III* semi-malignant.

Table 5

A Simpson's Grading	Recurrence/n	C Microscopic brain invasion	Recurrence/n
I	3/7	present	4/7
II	2/2		
III	0/1	not present	4/6
IV	3/3		
Total	8/13	Total	8/13

B Grading	WHO 79 Recurrence/n	WHO 93 Recurrence/n	D XRT after primary OP	Recurrence/n
I	3/5	0/0	yes	1/3
II	0/0	5/10		
III	5/8	3/3	no	7/10
Total	8/13	8/13	Total	8/13

Recurrence with respect to *A* extent of surgery (Simpson's grade), *B* pathological grading, *C* microscopic brain invasion, and *D* onset of radiotherapy.

Discussion

A. Pathology

The highly variable histology of meningiomas as well as the dependence of recurrence rates on the completeness of surgical resection have put morphological criteria for malignancy under discussion for a long time [4, 13, 14, 26, 27]. In the previous WHO-classification the entity of malignant anaplastic meningioma has already been described [31]. In the meanwhile there was increasing evidence for the presence of a meningioma type with intermediate biological behaviour which is now included in the recently published WHO-classification as the atypical meningioma [14, 15].

In our series the re-classification of histology according to the new classification scheme led to a high proportion of grade-II-tumours, mainly by upgrading from tumours formerly described as grade I. In addition, a number of previously "malignant" meningiomas were now included in the group of atypical meningiomas. The impact of the re-diagnosed and adjusted grading on the clinical behaviour is still unclear, but it has been stressed that recurrence rates of atypical meningiomas are probably intermediate between those of classic and anaplastic type [17, 28]. The present study further supports this view, as all of the previously graded "benign" but unexpectedly recurring meningiomas show the histological criteria of atypical meningiomas. At present this also makes therapeutic considerations for meningioma patients difficult, as previous clinical trials used the old, two-tiered classification scheme. Our data indicate that these studies cannot easily be adapted to the new three-tiered classification scheme.

B. Surgery

In terms of recurrence the completeness of initial surgery turned out to be the most important prognostic factor in our analysis. Irrespect of histopathological grading in all our pts. where surgical resection was macroscopically incomplete (Simpson's grade IV), recurrent tumour growth was noted within 4 to 13 months. Also in the literature there is wide agreement that the most important prognostic factor for the patient is the extent of removal of the tumour [1, 7, 10, 11, 16–18, 23]. Our histopathological findings of focal brain invasion by some meningiomas was not associated with a higher risk for recurrences as compared with meningiomas that did not show invasive growth (Table 5).

C. Radiotherapy

The controversy about the value of postoperative irradiation in all types of meningiomas is till ongoing. Because of their tendency ro relapse after incomplete resection or in the case of disadvantageous histology, the question comes up whether radiation therapy can improve the outcome of pts. [3, 6, 25]. For benign meningiomas there have been encouraging reports on the beneficial effects of postoperative radiotherapy. The discussion regarding irradiation concludes that radiotherapy can help to prolong survival in pts. with incomplete tumour resection or with inoperable and progressive tumour growth [3, 6, 7, 12, 16, 18, 19, 24, 25, 30]. Furthermore, it is today accepted that neurological improvement may occur in a significant proportion of pts. [6–8, 19]. Due to their rarity comparable data on malignant meningiomas are difficult to assess and all reports in the literature about the clinical course of malignant meningiomas mention only very few pts. Unlike benign meningiomas which are estimated to recur in 7% at 5 years and 32% at 15 years [5, 7, 11, 13] the recurrence rate was found to be 35% in atypical meningiomas in smaller series and 72% in anaplastic meningiomas after 5 years [8, 9,

17]. For "malignant" meningiomas it has been reported that the mean survival in 6 pts., treated with surgery alone, was 7.2 months but it was 3.1 years in 12 pts. treated with both surgery and immediate postoperative irradiation [11].

We observed a five year survival rate of 38% in a group of pts. in whom re-classification of the primary histology according to the 1993 WHO classification revealed grade-III and grade-II-tumours only. Interestingly, there is a risk for late recurrences since the survival curve has not reached a plateau after 5 years. In all pts. who finally died progressive tumour relapse was present.

In the 3 pts. with anaplastic tumours (grade III) the disease free survival time ranged from 6 to 21 months. The pts. died 6, 48, and 51 months after XRT. So far there are no reports on the eventual benefit of postoperative radiotherapy in the "new" group of pts. with atypical grade-II-tumours. The 5 pts. in our study with grade-II-tumours are in complete remission and free of disease for a minimum of 15 months and a maximum of 69 months following surgery and XRT.

In our analysis we observed a relapse in all pts. with grade-III-tumours and in 50% of the pts. with grade-II meningiomas. As there is a lack of comparable data so far these results are difficult to interpret but they might indicate a poor prognosis for anaplastic tumours in the new classification scheme while atypical meningiomas can be controlled despite their tendency to relapse by XRT following surgery.

It is still an open question whether to irradiate meningioma-pts. following the primary operation, or only when signs of disease progression and relapse appear [10]. Some authors have found, irrespective of histological grade, that there is no difference with either option. Others have found that initial postoperative radiation is the treatment of choice, as a recurrence might not respond to radiotherapy then and together with repeated surgery, the rate of side effects to irradiation increases adversely influencing outcome [11, 24, 25, 29]. From our own experience we support the former point of view because 2 of our 3 pts. who underwent radiation therapy immediately after operation remained relapse-free over the observation time of 22 and 50 months, respectively. It is not clear, however, whether in pts. with complete resection of grade-II-tumours but reduced performance status or advanced age should be given radiotherapy only in the event of a relapse.

So far it is not known what radiation doses are necessary exactly to control grade-II- or grade-III-tumours. For the treatment of malignant meningiomas in general doses between 50 and 65 GY are reported in the literature [2, 5, 6, 8, 12, 18, 19, 24, 25, 29]. We administered doses between 54 and 65 GY in our pts. [10].

The pts. who received doses above 60 GY in our analysis did not show a better outcome and today we recommend 60 GY (ICRU reference point) both for grade-II- and for grade-III-tumours. It should be evaluated in further studies, however, whether similar to the situation in low and high grade astrocytomas lower doses (e.g. 54 GY) are also effective for local control in gradeII-tumours.

The rate of severe neurological complications following radiotherapy for meningiomas is reported in larger series to be 3,6% [8]. The actual rate of complications attributable to radiotherapy, however, is difficult to assess. The symptoms of side effects may be imitated by the disease and also vice versa. In our study we observed neurological impairment in 2 pts. who are free of disease after radiation with 60 GY (ICRU reference point) but both suffer intellectual deficiences.

Histopathological postmortem examinations have not been performed in our analysis and so the real rate of radiation damage to healthy brain tissue remains unclear. But although the delivery of radiotherapy to the CNS in doses between 55 and 60 GY is never totally without the potential risk of side effects, such a risk is small and offset by the danger of tumour relapse.

Conclusions

1. Complete surgical exstirpation offers the highest probability of tumour control in all types of meningiomas.

2. The feature of microscopic brain invasion has not been found to predict recurrence in our analysis.

3. Anaplastic grade III-tumours of the new WHO 93 classification should be irradiated, whatever the extent of primary surgery was, immediately following operation. We recommend a total dose of 60 GY (ICRU).

4. For the new category of grade II-tumours the indication for radiotherapy cannot yet be defined. Our results, however, indicate a possible beneficial effect of radiotherapy especially when radical surgery could not be achieved. In such cases we advise XRT with 60

GY (ICRU) immediately after primary surgery in pts. with good performance status and under the age of 70 yrs. In elderly pts. or in pts. with poor condition a "wait and see" strategy might be justifiable.

5. Larger prospective multicentre trials using the new WHO-classification of 1993 are warranted to evaluate the role of radiotherapy in the treatment of meningiomas. As therapeutic considerations based on studies using the old WHO-classification of 1979 cannot easily be extrapolated to the new three-tiered grading system for meningiomas we would ask the following questions of future investigations:

a) Does the histopathological classification of meningiomas in grade-II- and grade-II-tumours really reflect the biological behaviour of the individual tumour type?

b) Is it possible to identify other predictive parameters such as proliferation index, nuclear size or allelic loss of chromosome 22 [21, 22] for relapse in grade-II- or grade-III-tumours other than the extent of surgical removal?

c) Are radiation doses of 60 GY (ICRU) necessary in both categories of tumours (grade III and II) or are lower doses (e.g., 54 GY/ICRU) equally effective at least for local tumour control in grade-II-tumours?

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Correspondence: W. Hoffmann, M.D., Department of Radiotherapy, University of Tübingen, Hoppe-Seyler-Str. 3, D-72076 Tübingen, Federal Republic of Germany.

Editorial Comments

This is obviously the first analysis of grade II and grade III meningiomas according to the new WHO-classification of CNS tumours (1993). The publication offers more questions than answers on the prognostic value of the new classification and on the value of postoperative radiotherapy.

The series is small and conclusions are therefore impossible. The statement that complete surgical removal offers the highest probability of tumour control has been known for nearly half a century (since Simpson's publication) and the assertion that grade III meningiomas should be irradiated is questionable.

The value of postoperative RXT in grade III meningiomas is not known as all the patients died (max. within 21 months).

The results mentioned in this paper seem to indicate that RXT could be beneficial for grade II meningiomas; nevertheless 2 patients showed neurological impairment attributed to irradiation.

The value of this well written paper consists in indicating the framework for a large prospective multicentre trial and we hope the authors will achieve their task.

K. A. J. and *L. C.*