

Outcome of Atypical Meningioma

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Objective : Limited data are available concerning the outcome of the patients with atypical meningioma due to lack of the studies with large series. The authors review atypical meningioma retrospectively and analyzed various parameters concerning its outcome.

Methods : Of the 866 meningioma patients treated between 1990 and 2003, pathologically proven 54 atypical meningiomas were reviewed. Various factors of the patients were analyzed, and surgical specimens were re-examined blindly by neuropathologist without any patient information. Extent of surgical resection was determined according to Simpson's classification by reviewing the chart and postoperative scan if possible.

Results : Twenty-three (42.6%) had local recurrences during the follow-up, of which 13 (32.5%) of 40 complete excisions and 10 (71.4%) of 14 incomplete excisions. The median time to recurrence was 47 months, and the overall 3-, 5-, and 10-year local control rates were 62.4%, 41.5%, and 31.1%, respectively. Five (9.3%) died during follow-up period. The mean survival time was 123 months, and the overall 3-, 5-, and 10-year survival rates were 94.2%, 87.2%, and 78.5%, respectively. The extent of surgical excision was the most significant prognostic factor not for survival but for local control ($p=0.2179$ and 0.0005 , respectively). Extracranial metastasis was not seen in our cases.

Conclusion : Complete surgical excision is the most important factor in improving local control. Careful long-term follow-up is mandatory because atypical meningioma shows a broad range of aggressiveness and natural history.

KEY WORDS : Atypical meningioma · Excision · Radiotherapy · Local control · Survival.

Introduction

Meningioma is a relatively slow-growing benign lesion arising from the arachnoid cells that form the meninges. Overall, meningioma comprises 15% to 20% of intracranial neoplasms, with atypical meningioma (AM) representing 4~7% of all meningiomas^{3,5,7,8,10,13-15}. Because of the rarity and discordant pathologic criteria of AM, the literature on the natural history and treatment of AM is relatively scarce. Several studies mix the results of AM and malignant meningioma (MM)^{1,3,4,9,10,14,15,17,19,20,26}, making the data difficult to interpret, and likely decreasing the local control and overall survival rates reported for the AM group. Based on previous published series, the natural history of MM appears more aggressive than its atypical counterpart^{4,7,10,15,19,20}, suggesting that these two subtypes of meningioma justify separate analyses. Therefore, the authors reviewed our exper-

ience with 54 patients with AM to identify the biological behavior of AM including local control rates and survival rates.

Materials and Methods

Between 1990 and 2003, 54 patients with AM were treated at our institution. AM constituted 6.2% of all meningiomas during the same period (54 AMs: 866 all meningiomas). Data were collected from review of the clinical records and neuroradiological investigations. The extent of surgical resection was determined from the operative notes or postoperative scans when available, and assessed according to Simpson's classification, with Grade I being complete resection and Grade V simple decompression²⁴. For the purpose of this study, all pathologic specimens were re-examined by a single experienced neuropathologist without a previous knowledge of the patient's outcome. The diagnosis of AM was based

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on the 2000 World Health Organization(WHO) classification of tumors of the nervous system¹²⁾. The criteria used to diagnose AM were independent of meningioma subtypes. Tumor was classified as atypical if it had increased mitotic activity (≥ 4 mitosis per 10 high-power fields) or 3 or more of the following features : increased cellularity, small cells with a high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis. Informations on the postoperative courses were obtained from records of the outpatient clinic, phone contacts and questionnaire by mail. Patients were considered recurrent if there was pathological documentation of recurrence, radiological documentation of recurrence or progression, or specific exacerbation of presenting symptoms. The indicated time to survival and no evidence of disease or recurrence/progression were calculated from the day of surgery. The median followup period was 43months (range, 7~147months; mean, 49.2months).

Complete excision (Simpson grade I or II) was possible in 40patients; remaining 14patients had incomplete excision (Simpson grade III, IV, or V). Eleven patients received postoperative adjuvant conventional external beam radiotherapy with a median dose of 5400cGy (range 3800 to 5940cGy), 5 after the first operation and 6 after at least one recurrence. Of these 11patients who received radiotherapy as an adjuvant therapy, 5 underwent complete excision and remaining 6 had incomplete excision. Among the 40patients who underwent complete excision at the first operation, only 2patients received radiotherapy. On the contrary, we performed radiotherapy for 3 residual tumors among 14patients who had incomplete excision at the first operation. Gamma knife radiosurgery(GKR) was applied to 8patients. Among these 8 patients, GKR was used for 1 small residual tumor instead of conventional external beam radiotherapy after the first operation. It was also used later for 2 small recurrent tumors those underwent complete excision at the first operation. We performed GKR for 3 small residual tumors instead of conventional external beam radiotherapy after the second operation (conventional radiotherapy was not done after the fist operation for these tumors). Additional GKR was also used for the remaining 2 small tumors those already had been treated with conventional external beam radiotherapy after at least one recurrence. None was treated with chemotherapy. Age, gender, location, extent of surgery for primary disease, irradiation status for primary disease, and excision/irradiation status for primary disease were analyzed to test their impact on local control and survival. Local control and survival rates were calculated using KaplanMeier method, and the probability of them in different groups was evaluated with log-rank test. The pvalue below 0.05 was considered

Table 1. Patient and tumor characteristics of 54 atypical meningiomas

Characteristics	No. of patients
Age (range: 21~77 years old, median: 52 years old)	
≤ 60	39
> 60	15
Gender	
Male	19
Female	35
Karnofsky Performance Score	
≥ 80	45
< 80	9
Location	
Convexity	14
Parasagittal/Falx	18
Others	22
Histologic dedifferentiation	
Benign to atypical	2
Atypical to malignant	5
Benign to atypical to malignant	0
Extent of surgery for primary tumor	
Complete excision	40
Incomplete excision	14
Conventional radiotherapy	
For primary tumor	5
For recurrent tumor	6
Excision/conventional radiotherapy status for primary tumor	
Complete excision	38
Complete excision + conventional radiotherapy	2
Incomplete excision	11
Incomplete excision + conventional radiotherapy	3

* complete excision : Simpson grade 1~2, incomplete excision : Simpson grade 3+

significant. Patient and tumor characteristics of 54 AM are summarized in Table 1.

Results

Between 1990 and 2003, 866 meningiomas were operated on at our institute : of these, 792 (91.5%) were benign, 54 (6.2%) atypical, and 20 (2.3%) malignant. Ages at the first operation of AM ranged from 21 to 77years, with a median age of 52years. There was a female predominance in AM, and the male : female ratio was 1 : 1.84. The mean duration of preoperative symptoms and signs was 9months. No difference was noted between atypical and other meningiomas regarding their presenting symptoms and signs, with the most common complaints of headache and limb weakness. The most common location was the parasagittal/ falx area (18cases, 33.3%), followed by the cerebral convexity (14 cases, 25.9%). Among the remaining 22cases, 3 (5.6%) were located in the infratentorial area, another 2 (3.7%) in the ventricle, and the other 2 (3.7%) in multiple sites.

Twenty-three of the 54patients (42.6%) had local recur-

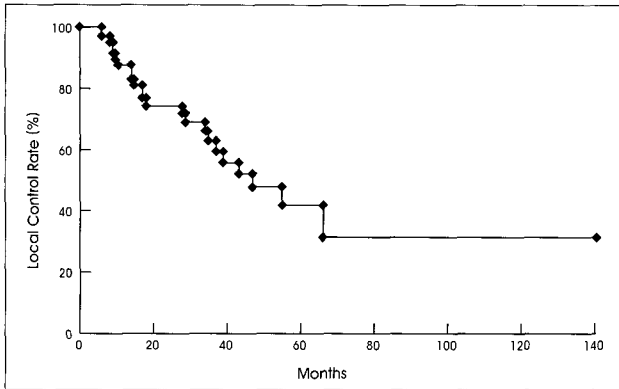


Fig. 1. Kaplan-Meier plot : overall local control rates in 54 atypical meningioma patients.

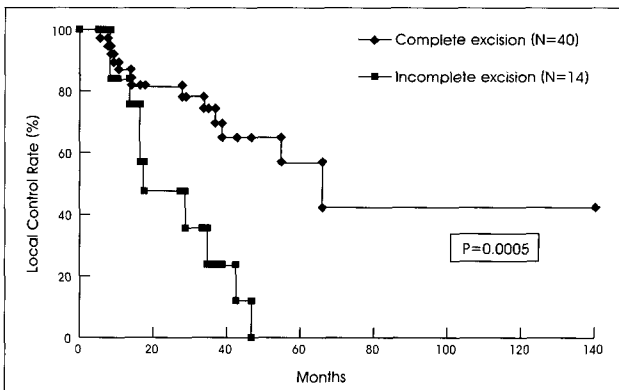


Fig. 2. Kaplan-Meier plot : local control rates according to surgical resection grade.

rences during the follow-up, including 13 (32.5%) of 40 complete excisions and 10 (71.4%) of 14 incomplete excisions. The median time to recurrence was 47 months (range, 6~66 months), and the overall 3-, 5-, and 10-year local control rates for the entire group were 62.4%, 41.5%, and 31.1%, respectively (Fig. 1). When local control data were analyzed by the extent of surgical resection, there was a significant statistical difference between complete and incomplete excisions ($p=0.0005$) (Fig. 2). Patients with complete excision had 3-, 5-, and 10-year local control rates of 74.2%, 56.8%, and 42.6%, respectively, while patients with incomplete excision had 3- and 5-year local control rates of 23.4% and 0%, respectively. The median time to recurrence was 66 months for completely excised tumor and 18 months for incompletely excised tumor. Serial imaging studies were reviewed to determine the sites of the first local failures. It appeared that in the majority of patients (in 22/23 patients (95.7%) with AM) the first failure originated within the primary tumor sites. In only 1 patient, the failure occurred outside the margin of the treatment field. The number of recurrences per patient varied from 1 to 7, with a mean of 3.

Five (9.3%) died during the follow-up period. Two (5%) of the 40 patients who had complete excision died of disease

Table 2. Statistical analysis of prognostic factors affecting local control and survival rates in 54 atypical meningiomas

Factor	Variable	Local control rate	Survival rate
		p-value	p-value
Age	≤60	0.1102	0.2318
	>60		
Gender	Male	0.8591	0.1947
	Female		
Location	Convexity	0.0503	0.4878
	Others		
Extent of surgery for primary tumor	Complete excision	0.0005	0.2179
	Incomplete excision		
Irradiation for primary tumor	Yes	0.0571	0.7893
	No		

* irradiation : conventional radiotherapy + Gamma knife radiosurgery

progression. Three (21.4%) of the 14 patients who underwent incomplete excision died, 2 of disease progression and 1 of unknown cause. The mean survival time was 123 months, and the overall 3-, 5-, and 10-year survival rates for the entire group were 94.2%, 87.2%, and 78.5%, respectively (Fig. 3). When survival data were analyzed by the extent of surgical resection, there was no statistical significance between complete and incomplete excisions ($p=0.2179$) (Fig. 4). The 3-, 5-, and 10-year survival rates for the patients who underwent complete excision were 97.5%, 88.2%, and 88.2%, respectively, whereas the 3- and 5-year survival rates for patients who underwent incomplete excision were 83.9% and 67.1%, respectively. The mean survival time was 131 months for completely excised tumor and 81 months for incompletely excised tumor.

Table 2 demonstrates statistical analysis of prognostic factors affecting local control and survival rates in 54 patients. As we described above, extent of surgical resection for primary disease was the only independent prognostic factor for local control ($p=0.0005$). Irradiation for primary disease and location of the tumors seemed to influence local control, but there were no statistical significances ($p=0.0571$ and 0.0503 , respectively). Age and gender also had no statistically significant impact on either local control or overall survival.

Extracranial or distant metastases were not seen in our cases. Transformation from previous BM to AM was noted in 2 (0.25%) of 792 BM patients : these 2 patients recurred with atypical histology 36 months and 86 months after the previous resection for BM. In 5 (9.26%) of the 54 AM cases, there was a worsening of the histological features from atypical to malignant when it was recurred : this was observed 4 months to 38 months after the first operation of AM.

Discussion

Of all the meningioma subtypes, AM represents 4 to 7%^{3,5,7,8,10,13-15}. This varying incidence partly points

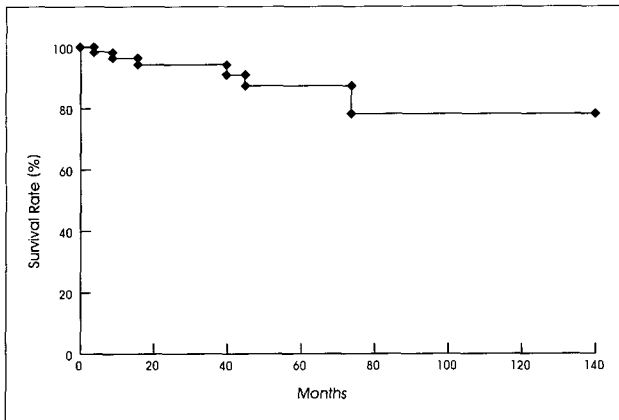


Fig. 3. Kaplan–Meier plot : overall survival rates in 54 atypical meningioma patients.

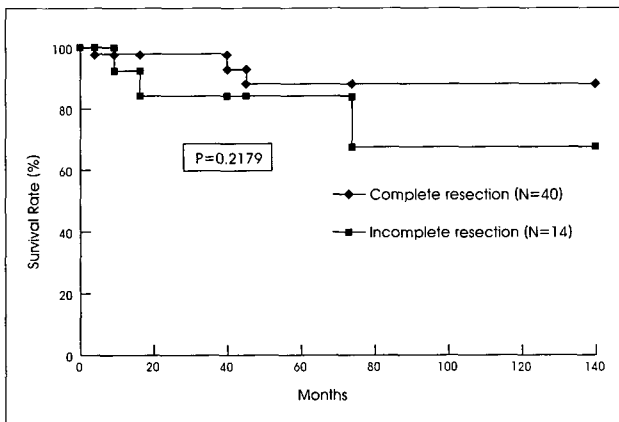


Fig. 4. Kaplan Meier plot : survival rates according to surgical resection grade.

out the lack of uniform agreement on histological criteria for malignancy. For example, one prominent classification system of meningioma is the graded scoring system of Jaaskelainen¹⁰. This system grades a meningioma by scoring for the following features : hypercellularity, loss of architecture, nuclear pleomorphism, brain invasion, mitotic figures, and necrosis. Using this score, tumors are classified as benign, atypical, malignant, or sarcomatous. The 2000 WHO classification of the tumors of the nervous system¹² lists meningiomas under the heading of tumors of meninges and the subheading tumors of meningotheelial cells. As outlined in the Materials and Methods section, the criteria used to diagnose AM in the 2000 WHO classification is independent of meningioma subtypes. Tumor is classified as atypical if it has increased mitotic activity (≥ 4 mitosis per 10 high-power fields) or 3 or more of the following features : increased cellularity, small cells with a high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis. Tumor is classified as malignant if it exhibits histologic features of frank malignancy far in excess of the abnormalities

present in AM. Such features include obvious malignant cytology (e.g. having an appearance similar to sarcoma, carcinoma, or melanoma) or a high mitotic index (≥ 20 mitosis per 10 high-power fields). Brain invasion has typically been thought to be a malignant characteristic of any tumor, and previous classification systems used it as criteria for malignancy. But, brain invasion was found in tumor with a wide variety of clinical courses, and brain invasion is no longer required to qualify as AM or MM. Also, there are the other classification systems for division of meningioma that provide meaningful prognostic information^{16,21,22}. Previous studies of the response of meningioma to various treatment modalities have used these different WHO classification¹², Jaaskelainen's¹⁰ scoring system as well as other variants^{16,21,22}. So, this discrepancy of classification in the literatures makes direct comparisons between the treatment results of AM in different series difficult, and limited long-term follow-up data are only available for patients with AM.

Clinical features are not helpful in differentiating BM from AM and MM because there are no differences between BM and non-benign meningioma regarding their presenting symptoms and signs. AM and MM present at an earlier age than BM. Mahmood et al¹⁴ reported that the peak incidence for BM was in the ninth decade (range, 11~84year), whereas for AM and MM, the peak incidence occurred in the seventh decade (range, 29~81year) and sixth decade (range, 30~60year), respectively. In our series, age at the first diagnosis of AM ranged from 21 to 77years, with a median age of 52years. This difference in age distribution may be because AM and MM grow more rapidly and become symptomatic at an earlier age. It is also generally believed that in children, MM represents a higher percentage of all meningiomas. Regarding gender distribution, the female predominance seen in BM is not found in its non-benign counterpart that shows the increased proportion of male^{5,9,14}. Hug et al⁹ reported that the male to female ratio was 1:1.5 for AM and 1:1.1 for MM. Mahmood et al¹⁴ also noted that the male to female ratio was 1:2.3 for BM, 1:1 for AM, and 1:0.67 for MM, respectively. The absence of female predominance in AM and MM suggests that endocrinological influences apparently important in the genesis of BM are not active in non-benign ones. However, there was a female predominance (the male to female ratio was 1:1.84) in our AM series as before.

Comparable to benign histology, there have been few reports of non-benign tumor situated either infratentorially or intraventricularly^{9,14,23,25}. Hug et al⁹ found that the majority of AMs occurred in the cerebral convexity. Only one tumor was located within the ventricles and there were two tentorial meningiomas with supra- and infratentorial extensions.

In our 54 AM series, 3 (5.6%) were located in infratentorial area, and 2 (3.7%) in ventricle. CT or MRI is not completely reliable in differentiating benign from non-benign meningioma. Marked peritumoral edema, heterogenous contrast enhancement, minimal or no calcification, indistinct or irregular margins, and mushroom-like projections from the main tumor mass are CT or MRI signs suggestive of non-benign behavior, but the aggressive potential of meningioma cannot be predicted by CT or MRI alone^{14,23,25}. Extracranial metastases have been referred to as the strongest evidence for malignancy in meningioma, and some authors found metastases in 11~43% in the cases of MM^{6,22}. However, it is very difficult to find metastatic spread of AM in the literatures. Similarly, there were no extracranial or distant metastatic lesions in our series of 54 AMs.

AM remains a controversial topic because of the lack of universally accepted criteria for grading histological malignancy. The overlap of pathological features between AM and MM in the reported literatures and few large series of AM make the data difficult to interpret^{3,10,14,15,19,26}. The natural history of AM is usually known to appear less aggressive than its malignant counterpart. Many authors^{4,7,10,15,19} noted that AM showed better outcomes in terms of survival, recurrence-free survival, and median time to recurrence than MM. Coke et al⁴ found that the 5- and 10-year survival rates for AM were 87% and 58%; for MM the 5- and 10-year survival rates were 60% and 60%, respectively. Palma et al¹⁹ reported the 5-year survival rate for AM was 95%, while it was 64% for MM; the median time to recurrence was 5 years for AM and 2 years for MM. In the series from Goyal et al⁷, the 5- and 10-year survival rates for AM were 91% and 76%, respectively, and the entire group had a 10-year local control of 55%. In the Jaaskelainen et al series¹⁰, the authors found the 5-year recurrence rate for AM of 38% and the recurrence rate of 78% for MM after complete surgical removal. Maier et al¹⁵ reported that the recurrence rate for AM and MM was found to be 34.6% and 72.6%, respectively, and the authors concluded that AM, as defined in their study, did in fact have an intermediate prognosis with respect to benign and malignant tumor. However, some authors¹⁴ failed to differentiate atypical from malignant form in considering the problem of the influence of malignant histological features on meningioma survival and recurrence.

There is a broad agreement in the literature that extent of surgical resection is a significant independent predictor for survival and local control^{5,7,9,10,15,19,26}. In the series from Goyal et al⁷, 8 of the 22 patients had local recurrence, including 2/15 with gross total resection (GTR), 3/4 with subtotal resection (STR), and all 3 patients who underwent resection of unknown extent. At 10 years, patients with GTR had a

higher local control rate than those who had either a STR or a resection of unknown extent (87% vs. 17%; $p=0.02$). Patients who had GTR had 5- and 10-year overall survival of 87% and 87%, respectively. Patients with STR or resection of unknown extent had 5- and 10-year overall survival rates of 100% and 75%, respectively. They noted that the extent of surgical resection plays an important role in predicting the risk of recurrence, and possibly defines the need for adjuvant therapy. The favorable prognostic influence of radical surgery is further emphasized by the low recurrence rate observed in convexity AM treated in this way. The recurrences in parasagittal and basal tumors even after Simpson Grade I resection seem contradictory but can be explained by the fact that true Simpson Grade I resection can only be accomplished for tumors located in the cerebral convexity. In other locations, some neoplastic cells promoting tumor re-growth are always left behind because of the unfavorable surgical conditions intrinsic to the site. Although extent of surgical resection for primary disease was the significant prognostic factor not for survival but for local control in our series, authors also agree that radical surgery has a positive influence on survival as well as local control of AM.

Adjuvant radiotherapy after surgical resection of AM continues to be controversial. Many advocate adjuvant radiotherapy for MM regardless of extent of surgical resection because of the extremely high rate of local recurrence. Because of the rarity of AM and differences in the way it is classified, the literatures on the role of radiation in treating AM are difficult to interpret. In the majority of published literatures, they do not use radiotherapy for completely excised AM because of the complications of radiotherapy and because there is no proven benefit of radiotherapy for such cases in their experience^{2,10,17}. There appears to be general support for radiotherapy following incomplete resection for AM, noting that incomplete resection without postoperative radiotherapy in AM is associated with higher local failure rate, with a trend toward lower overall survival^{7,14,17}. However, some authors^{9,10} did not recommend radiotherapy for AM without regard to the extent of surgical resection because the majority of patients with AM would ultimately experience local recurrence despite a course of conventional radiation treatment. Although no conclusions regarding therapeutic benefits for AM can be drawn because of the small number of patients receiving radiotherapy, we consider that radiation for AM following incomplete excision should be considered. But, we need to wait for results from larger series before drawing any significant conclusions on the role of postoperative radiotherapy in treating completely excised AM. Furthermore, further details with regard to radiation treatment dose or analysis of radiation versus local control/

survival must be provided. The nature of recurrence and spread of meningioma along the dura directly call into question the rationale of focal treatments such as radiosurgery as it is often difficult to accurately target the extension of the tumor, however, a few published studies have defined the role of radiosurgery for AM^{4,8,11,18}. Eight patients received GKR for the treatment of the residual or recurrent AM in our series. Although our data need further confirmation with large numbers and long-term follow-up period that radiosurgery is an effective treatment for AM, both as an adjunctive to subtotal resection and as a primary treatment for selected patients, we consider that radiosurgery seems to be an attractive option to treat AM, especially in patients who have already undergone radiotherapy. The efficacy of radiosurgery relative to other therapies for AM as well as the value of radiosurgery as a boost to radiotherapy will require further evaluation.

Conclusion

Based on our study, AM shows a broad range of aggressiveness and natural history. Even after failure, long-term survival is possible for patients with AM treated with appropriate therapy. We recommend treating AM with complete excision. Complete excision is associated with better local control than is incomplete excision. Although the role of radiotherapy in the management of AM remains unclear and requires further investigation before definitive recommendations are made, adjuvant radiotherapy for AM following incomplete excision can be considered to reduce the risk of recurrence and improve the survival. We experienced a fewer cases of AM treated with GKR, but alternative strategy such as GKR may be of value for the treatment of incompletely excised AM and recurrences of smaller size (volume), even in previously irradiated fields or after multiple resection. A multi-center, prospective trial with uniformity of the patient population will be needed to settle the limitation of the current studies.

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