ABSTRACT

Purpose: The object of this study was to analyze treatment outcomes and to identify the prognostic factors, with a focus on the role of adjuvant radiotherapy (ART), predicting disease progression in atypical meningiomas

Patients and Methods: From May 1997 and December 2011, 88 patients with meningioma were included in this study. All patients were histologically confirmed to have atypical meningioma and were treated with surgical resection with or without postoperative ART at our institution. Among them, 4 patients were diagnosed as benign meningioma (WHO grade I) initially, but the tumors recurred as atypical meningioma (WHO grade II). As primary therapy, 30 patients received surgical intervention followed by ART, and 58 patients received no adjuvant therapy. Of 88 evaluable patients, 56, 29, and 3 patients underwent complete resection, incomplete resection, and resection of unknown extent, respectively. The median ART dose was 61.2 Gy (range, 40-61.2 Gy). The median age at diagnosis was 51 years (range, 16-78 years), and the male to female ratio was 35:53.

Results: The 5- and 10-year actuarial overall survival (OS) rates were 88.7% and 59.5% and the 5- and 10-year progression-free survival (PFS) rates were both 46.2%, with a median follow-up of 42.8 months (range, 2.7–160.0 months). The median time to progression was 24.7 months (range, 0.8-157.2 months). Addition of ART (p = 0.011) and complete tumor resection (p = 0.001) were associated with superior PFS. Age at diagnosis was the only

prognostic factor affecting OS (p = 0.028) on multivariate analysis. When s tratified to 4 groups according to resection status and ART, the groups of patient with incomplete resection without ART showed significantly worse PFS compared to other 3 groups (p = 0.000). Of 40 patients with disease progression, 33 (82.5%) received salvage treatment. The majority of first salvage-therapy was radiosurgery using Gamma Knife irrespective of previous radiotherapy history.

Conclusions: Surgical resection followed by ART led to lower local tumor progression in patients with atypical meningioma defined by the updated 2000/2007 WHO classification. Our results may contribute to the notion in favor of the routine use of radiotherapy as an adjuvant treatment for such lesions, especially after incomplete resection, until the outcomes of ongoing prospective trials are available.

Key words: Meningioma, Atypical meningioma, Radiotherapy, Postoperative radiotherapy, Adjuvant radiotherapy

Student number: 2010-21799

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INTRODUCTION

Meningiomas account for approximately 34% of all primary intracranial tumors(1). The majority of these tumors are benign (World Health Organization (WHO) grade I, ~90%). However, atypical(WHO grade II) and malignant(WHO grade III) meningiomas constitute approximately 5–7% and 1–3% of meningiomas, respectively(2, 3). Because of their high recurrence rate and poor prognosis, a combined-modality treatment approach using surgical resection followed by postoperative adjuvant radiotherapy (ART) has been commonly employed despite inconsistent reports regarding the benefit of ART.

The completeness of resection is a well known prognosticator for local recurrence of high risk meningiomas. Many advocate adjuvant radiotherapy for the treatment of malignant meningiomas regardless of the extent of surgery because of the extremely high rate of local recurrence(4, 5). However, the optimal treatment for atypical meningiomas is still controversial. Atypical meningiomas are rare tumors and are often integrated with benign or malignant histology when analysis is performed. Few studies have reported the outcomes and prognostic factors for sole atypical meningiomas, but the results are inconsistent(6-9). Some studies favor early addition of ART even after gross total resection of tumors to achieve better local control(6, 7). On the other hand, others argue that the role of ART remains unclear(9, 10). Therefore, the existing data is insufficient to establish the indications for ART in patients with atypical meningioma.

In this study, we retrospectively analyzed the outcomes of atypical

meningiomas in a relatively large series (n=88) of patients after surgical resection with or without ART with a special focus on the benefit of ART at a single institution, and identified the prognostic factors predicting disease progression in these patients.

PATIENTS AND METHODS

After Institutional Review Board approval, our patient database was used to select patients referred between 1997 and 2011 who were pathologically diagnosed with atypical meningioma at Seoul National University Hospital, Korea. Histological slides were not centrally reviewed, but all pathologic reports were thoroughly examined to exclude patients who did not meet the definition of atypical meningioma (WHO grade II) according to the WHO 2000/2007 classification(11, 12). A previous benign histology was permitted, as long as the patient was not treated with radiotherapy at that time. Patients with multiple intracranial meningiomas were excluded due to the difficulty in evaluating treatment response. However, we included one patient who had one benign lesion in the right convexity and another discrete atypical lesion in the left. Cases of spinal cord meningioma were also excluded. Considering the aim of our study, patients with preoperative radiotherapy or postoperative adjuvant radiosurgery, which did not target the whole surgical bed, were not included. Patients without resection were also excluded. The remaining 88 patients were analyzed in the present study.

Patient and tumor characteristics

Our study included 53 female and 35 male patients. The median age at diagnosis of atypical meningioma was 51 years (range, 16-78 years). There were 4 patients who had benign meningioma initially and then were diagnosed as having atypical histology at the time of recurrence. Tumor locations were divided into the following 5 categories: 1) convexity (n=46), 2)

parasagittal/falx (n =20), 3) skull base/sphenoid ridge (n=10), 4) sella/parasella (n=7), 5), and other (n=5). Of the 88 patients, 81 (92%) had clinical symptoms before diagnosis. Frequent symptoms at presentation were headache, visual deficits, gait disturbance, aphasia/dysphasia, seizures, and dizziness. One patient had neurofibromatosis type 2, and 2 patients had a history of leukemia. The median mitosis number per 10 high power fields was 5. The proliferation index Ki-67 was available in 71 patients. The details of the characteristics are summarized in Table 1 and Table 2.

Treatment characteristics

All 88 patients had surgical resection of the tumor with radical aim. Completeness of resection was evaluated based on surgical records. Gross total resection or Simpson Grade I-II was regarded as complete resection, which was achieved in 56 patients (63.6%). Information regarding resection status was unavailable in 3 patients. Thirty out of 88 (34.1%) patients received ART following surgical intervention, and 58 (65.9%) were observed without adjuvant treatment. Seventeen patients were treated with ART even after complete resection, and 19 patients were not treated despite incomplete resection (Table 2). The median ART dose was 61.2 Gy (range, 40-61.2 Gy). Clinical target volume (CTV) encompassed residual enhancing lesions, if existed, and the entire resection cavity with a 1.5cm margin for the large field and with a 0.5cm margin for the cone-down field adhering to the anatomical borders. To account for setup inaccuracy, a 0.3cm margin was added to CTV for planning target volume. Twelve(13.6%) patients underwent conventional radiotherapy and 76(86.4%) underwent 3D-conformal radiotherapy,

Table 1. Patient and treatment characteristics

Characteristics	Number of Patients		
	Total (%)	ART(+) group	ART(-) group
Age			
≤60	65 (73.9%)	18	47
>60	23 (26.1%)	12	11
Gender			
Male	35 (39.8%)	14	21
Female	53 (60.2%)	16	37
Location			
Convexity	46 (52.3%)	14	32
Parasagittal/Falx	20 (22.7%)	10	10
Skull base/Sphenoid ridge	10 (11.4%)	2	8
Sella/Parasella	7 (8.0%)	2	5
Other	5 (5.7%)	2	3
First presented histology			
Benign	4 (4.5%)	3	1
Atypical	84 (95.5%)	27	57
Mitosis/10 high-power fields			
≤5	54 (61.4%)	23	31
>5	33 (37.5%)	7	26
Unknown	1 (1.1%)	0	1
Ki-67			

≤10%	63 (71.6%)	18	45
>10%	8 (9.1%)	2	6
Unknown	17 (19.3%)	10	7
Resection status			
Complete	56 (63.6%)		
Subtotal	29 (33.0%)		
Unknown	3 (3.4%)		
Adjuvant radiotherapy			
Yes	30 (34.1%)		
No	58 (65.9%)		

Table 2. 4 groups according to resection status and adjuvant radiotherapy

	ART (+) (n = 30)	ART (-) (n = 58)
Complete resection (n = 56)	17	39
Imcomplete resection (n = 32)	13	19

Abbreviations: ART = adjuvant radiotherapy

respectively.

Statistical analysis

Survival was calculated from the date of surgical resection. Statistical analysis was done using SPSS software (release version18; SPSS Inc. Chicago, IL). Actuarial overall survival (OS) and progression-free survival (PFS) rates were calculated according to the Kaplan-Meier method, and comparisons between groups were performed using log-rank tests. A p-value smaller than 0.05 was regarded statistically significant(13). For multivariate analysis, potentially confounding variables with a p-value smaller than 0.1 on univariate analysis were incorporated into the Cox proportional hazard model, using the backward stepwise method.

RESULTS

Survival outcomes after primary treatment

The median follow-up time from the date of surgical intervention of atypical meningiomas was 42.8 months (range, 2.70–160.0 months). At the time of survival analysis, 13 patients (14.8%) died and 9 of them had progressed disease. The actuarial 5-year and 10-year OS were 88.7% and 59.5%, respectively. At last follow-up, 40 patients (45.5%) presented with local disease progression, and all of them had occurred within 5 years. The median time to progression was 24.7 months (range, 0.8-157.2 months).The actuarial 5-year and 10-year PFS were both 46.2%. Two patients showed distant metastasis accompanied by local disease progression. One patient had local disease progression and distant metastases to the lung, liver, and bone, concurrently. The other patient had lung metastases 2 years after local disease progression.

Prognostic factors affecting survivals

PFS was significantly higher in patients undergoing ART after surgical resection than those not undergoing ART (54.8% vs. 43.5% at 5 years, p = 0.032) (Fig. 1). Resection status had a significant impact on PFS (58.6% in complete resection vs. 27.9% in others at 5 years, p = 0.007) (Fig. 2). Female patients showed marginally lower PFS (p = 0.063). A high Ki-67 proliferation index with a cutoff value of 10% was also marginally correlated with lower PFS (p = 0.054), but it was excluded from multivariate analysis due to missing data. Other variables including age at diagnosis, mitotic count, and

Figure 1. Progression-free survival rate according to adjuvant radiotherapy

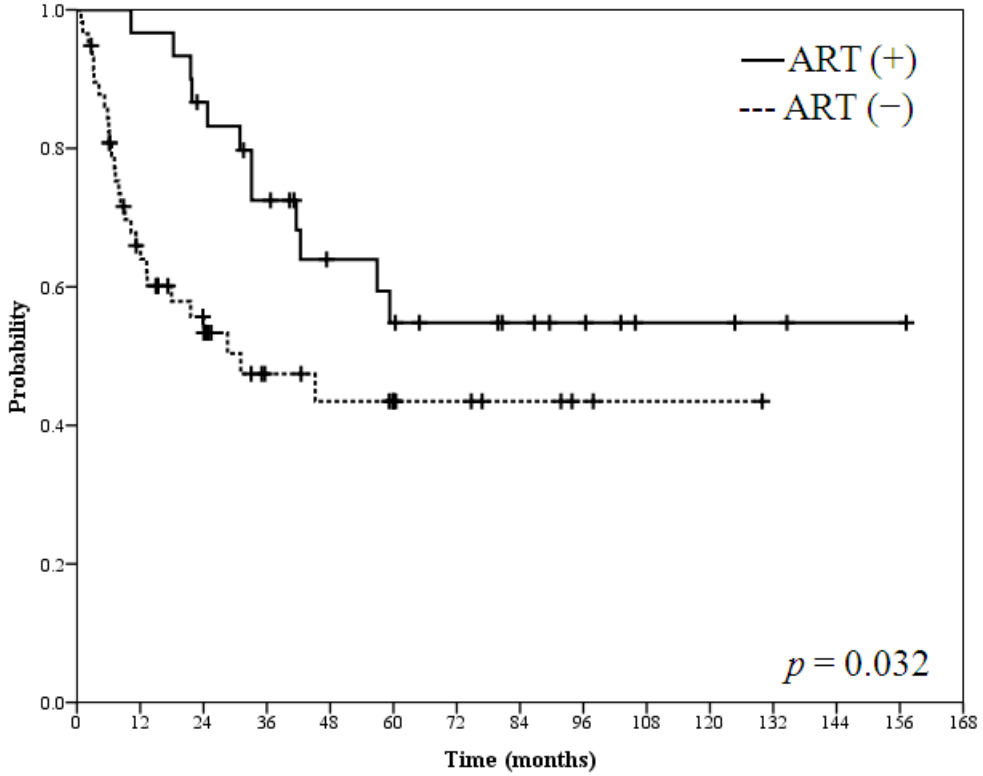
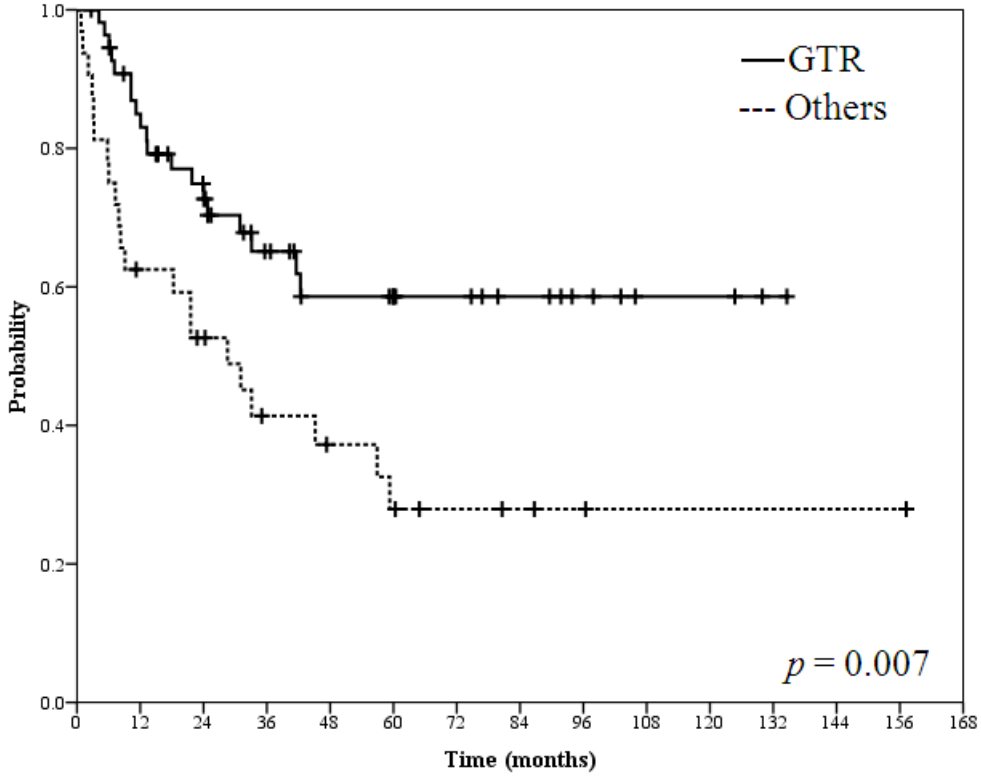


Figure 2. Progression-free survival rate according to resection status of tumors



benign histology at first meningioma presentation did not have any influence on PFS. On multivariate analysis, addition of ART (p = 0.011) and complete tumor resection (p = 0.001) were associated with superior PFS, whereas gender was not (p = 0.080) (Table 3).

OS was significantly inferior in patients over 60 years of age (92.1% vs. 78.9% at 5 years, p = 0.002). Atypical histology as recurrent disease also predicted poor OS (90.0% vs. 66.7% at 5 years, p = 0.015). Interestingly, surgical resection without postoperative ART showed better OS (p = 0.045). On multivariate analysis, age at diagnosis was the only prognostic factor affecting OS (p = 0.028) (Fig. 3), whereas ART or benign meningioma at initail presentation were not (p = 0.366 and p = 0.098, respectively) (Table 3).

When stratified to 4 groups according to resection status and ART (Table 2), the group which did not receive ART despite incomplete resection showed far worse PFS compared to the other 3 groups (Fig. 4) (p = 0.000). Addition of ART after gross total resection did not increase PFS (p = 0.858). On the other hand, it was beneficial to the patients whose tumors were not successfully removed (p = 0.000).

Salvage treatments after disease progression

Of 40 patients with disease progression, 33 (82.5%) received at least one course of salvage therapy. Treatment of choice as the first-salvage treatment at our institution was radiosurgery using Gamma Knife (GKS) irrespective of previous radiotherapy history, which constituted 69.7% (23 out of 33 treatments) of first-salvage therapy. Twenty-eight out of 58 (48.3%) in the resection only group and 12 out of 30 (40.0%) in the ART addition group

Table 3. Prognostic factors for progression-free survival and overall survival

	PFS		OS	
	univariate	multivariate	univariate	multivariate
Age (≤60 vs. >60)	0.412		0.002	0.028
Gender	0.063	0.080	0.487	
ART	0.032	0.011	0.045	0.366
Completion of resection	0.007	0.001	0.736	
High mitotic rate (≤5 vs. >5,/10HPF)	0.315		0.449	
Benign histology at first presentation	0.273		0.015	0.098
Ki-67* (≤10% vs. >10%)	0.054		0.849	

*72 patients' data available for anaylsis

Abbreviations: PFS = progression-free survival; OS = overall survival; ART = adjuvant radiotherapy; HPF = high-power fields

Figure 3. Overall survival rate according to age at diagnosis

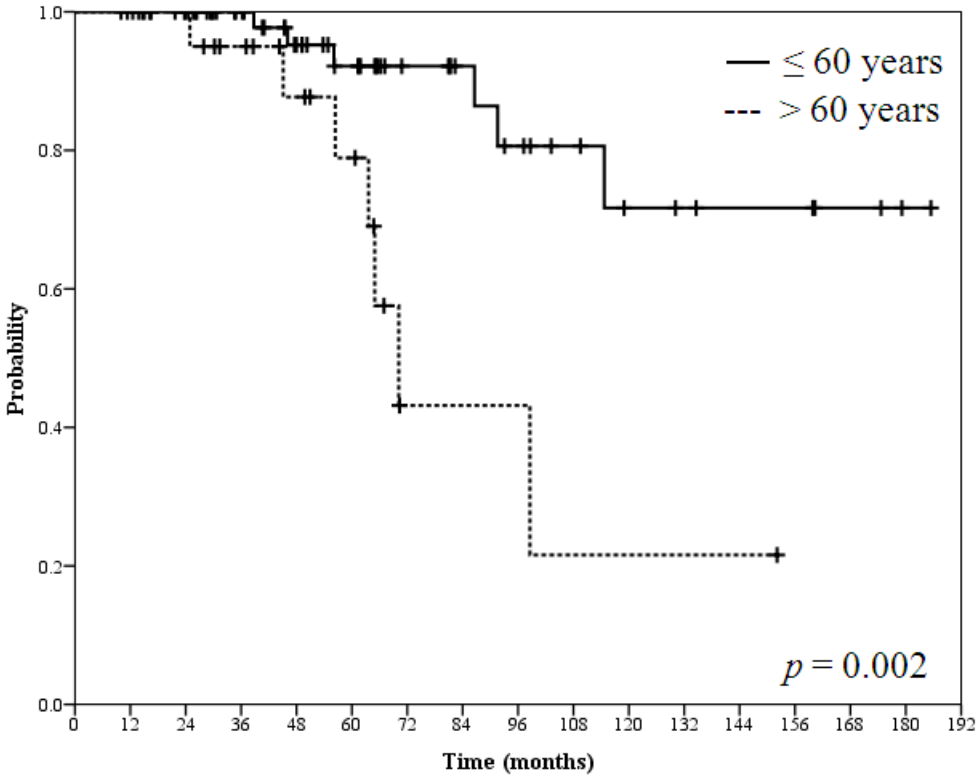
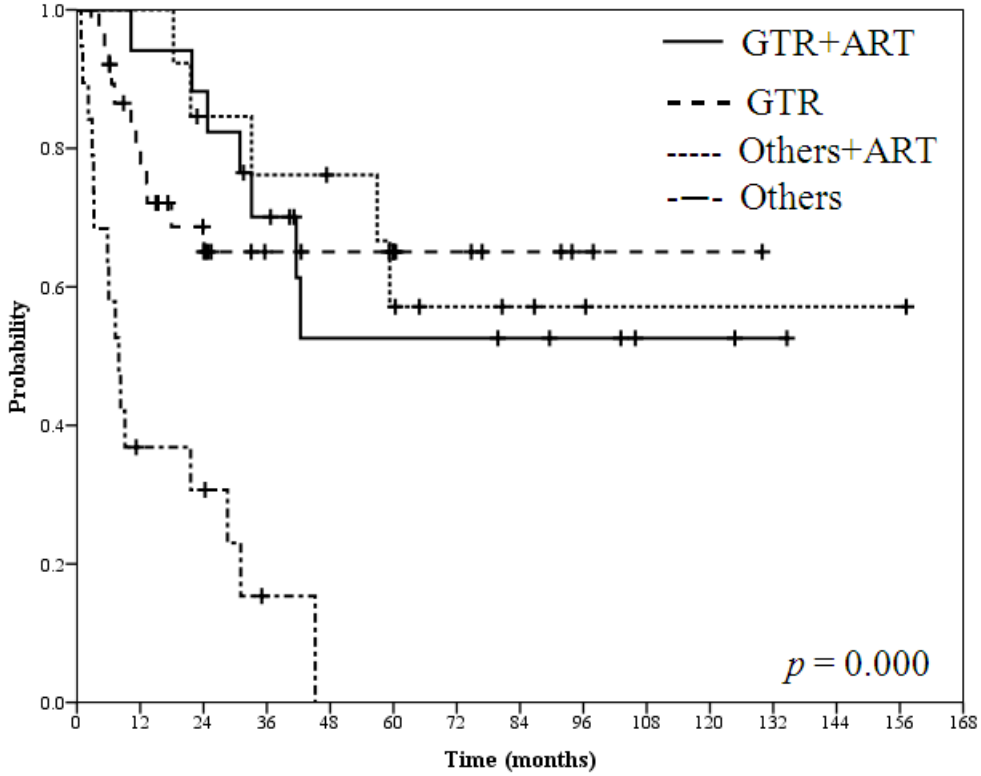


Figure 4. Progression-free survival rate according to resection status and adjuvant radiotherapy



received salvage therapy. The salvage treatment option related details are summarized in Table 4. Six patients had more than 3 courses of treatment after disease recurrence with various combinations of modalities. Chemotherapy was used in one patient.

Complications

During the treatment period, no severe acute side effects were observed. Transient mild side effects, such as fatigue, headache, intermittent nausea, dizziness and skin irritation at portals were observed in most patients. Late toxicity was categorized according to the Common Terminology Criteria for Adverse Events v3.0 score. Cognitive disturbance and motor neuropathy were the most common late side effects. Others including memory disturbance, speech impairment, encephalopathy, seizures, and hemorrhage were also observed.

Table 4. Details of first-salvage treatment according to primary therapy

Salvage options	Resection only (n = 28)	ART addition (n = 12)
Resection alone	2	3
Resection + ART	4	0
EBRT (IMRT)	1	0
Gamma Knife Radiosurgery	18	5
None	3	4

Abbreviations: ART = adjuvant radiotherapy; EBRT = external radiotherapy; IMRT = intensity modulated radiotherapy

DISCUSSION

The purpose of this study was to analyze long-term treatment outcomes in patients with atypical meningioma treated with surgical resection with or without postoperative adjuvant radiotherapy at a single institution. To the best of our knowledge, the present work is one of the largest series ever published dealing with only atypical histology and with a focus on the usefulness of ART in this group of patients.

Survival outcomes of the current study are comparable to those of recent other atypical meningioma series (Table 5)(6, 7, 9, 14-16). The results from the current study demonstrated a significant benefit of ART by showing reduced tumor progression following surgery, especially for the patients who underwent less than GTR, as these patients achieved similar PFS with the addition of postoperative radiotherapy covering gross residual disease and tumor bed. While the use of ART after incomplete resection in atypical meningiomas has been accepted as a standard treatment, the optimal treatment after complete tumor resection still remains uncertain. Studies shown in Table 5 have presented inconsistent outcomes in relation to the effects of ART. Mair *et al*. represented that radiotherapy after first-time resection was beneficial only for patients who had undergone subtotal resection and favored radiosurgery after tumor progression rather than early ART after surgery(9). On the contrary, Aghi *et al.* reported high recurrence rates without postoperative radiation although all their patients underwent GTR(6). Nevertheless, they could not evaluate the influence of ART on tumor progression because only 7.4% patients had ART. Komotar *et al.* also included

Table 5. Summary of recent atypical meningioma studies

Authors	Year	Median f/u	Pts No.	A-MNG (%)	GTR (%)	ART (%)	5Y PFS (%)	Progression ART (+) vs. (-)
Pasquier(16)	2008	49 mo	119	68.9	NR	79.7	58*	NR
Gabeau-Lacet(15)	2009	29 mo	47	100	74	23	48	$p = 0.83$
Aghi(6)	2009	39 mo	108	100	100	7.4	59	not significant
Mair†(9)	2011	NR	114	100	57.9	26.3	47	not significant
Komotar(7)	2012	44 mo	45	100	100	28.9	65	$p = 0.085$
Adeberg†(14)	2012	73 mo	85	72.9	41.2	60.0	50	NR
Current study	2012	43 mo	88	100	63.6	34.1	46	$p = 0.032$

*Analysis of atypical and malignant histology together

†2000/2007 updated WHO classification adopted

Abbreviations: A-MNG = Atypical histology; NR = not reported; GTR = gross total resection; ART = adjuvant radiotherapy; 5Y PFS = 5-year progression-free survival

only GTR cases in their study and presented that there was no recurrence in 92% patients who received postoperative radiotherapy whereas in 59% patients who did not (p=0.085), demonstrating a strong trend toward improved local control with ART(7). The virtue of postoperative radiotherapy, especially covering the entire tumor bed, could be reasonably inferred from these two studies, because they excluded the most powerful confounding factor, the completeness of resection.

The present study failed to demonstrate that improvement of local control obtained with the addition of ART could lead to an increase in the overall survival rate. Nevertheless, it is important to put efforts into preventing local tumor progression because recurrence causes additional treatment burden to patients, both emotionally and economically, and multiple re-treatments including craniotomies possibly give rise to morbidity.

Despite growing evidence that postoperative radiotherapy helps to lower local recurrence, some clinicians still advocate to offer salvage treatments only after local failure is evident. The main argument against early ART is the concern about possible late neurotoxicity. However, Nieuwenhuizen *et al.* demonstrated that radiotherapy following surgery did not have additional deleterious effects on impaired long-term neurocognitive functioning in meningioma patients(17). In the subsequent study, it was suggested that neurocognitive deficits could be partly attributed to the use of antiepileptic drugs and tumor location but not to the use of radiotherapy(18). Therefore, deferring ART for the fear of radiotherapy-induced neurotoxicity should not be done.

An interesting finding of this study was that surgical resection without ART showed better OS than resection with ART ($p = 0.045$). However, cautious interpretation is needed as the median age was 10 years older in the ART group and only 2 deaths, out of total 13, occurred in the surgery only group.

In the 2000/2007 WHO classification, a mitotic rate >4 per 10 high-power fields was considered as the most important factor defining atypical meningioma. In patients with a lower mitotic rate, the presence of at least three of the following variables is necessary: 1) increased cellularity, 2) macronuclei, 3) prominent nucleoli, 4) a sheet-like growth pattern, and 5) necrosis. The diagnosis of atypical meningioma in the present work was made according to this updated WHO criteria. Considering that most publications predated the 2000 WHO grading change and only two studies in Table 5 have adopted the new WHO classification(9, 14), our study is valuable in that it can set up the indications for ART according to the newly defined atypical meningioma. Moreover, we are anticipating the results of two ongoing phase II trials (NCT00626730 and RTOG 0539), which are examining the role of radiotherapy following resection in the management of these patients. However, the results will not be available in the near future. We believe this makes the present study more relevant to current clinical practice for the time-being.

It is important to recognize the limitations of this study. Firstly, due to the retrospective nature, conclusions drawn from our study need further validation through prospective trials. Secondly, the decision to undergo postoperative ART was at the discretion of referring surgeons rather than objective

parameters, such as the extent of residual disease. This may hamper appropriate evaluation of the efficacy of ART in local control. Thirdly, retrospective grading of treatment complications had its inborn limitations including difficulty in distinguishing disease related symptoms from treatment related symptoms.

CONCLUSION

Surgical resection followed by ART led to lower local tumor progression in patients with atypical meningioma defined by the updated 2000/2007 WHO classification. This result would contribute to a growing number of series that support routine ART as an adjuvant treatment for these lesions, especially after incomplete resection.

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국문초록

비정형 뇌수막종에서의 보조적 방사선치료의 역할

목적: 본 연구는 비정형 뇌수막종의 치료성적을 후향적으로 분석하고, 질병 진행을 예측하는 예후 인자 중 특히 방사선치료의 역할을 밝히고자 하였다.

대상환자 및 방법: 1997 년 5 월부터 2011 년 12 월까지 서울대학교병원에서 조직학적으로 진단된 비정형 뇌수막종 환자들 중 수술적 종양절제 이후 수술 후 방사선치료를 받거나 받지 않은 환자는 모두 88 명이었다. 그 중에서 처음 진단받을 당시에는 양성 뇌수막종(WHO grade I)이었으나, 비정형 뇌수막종(WHO grade II)으로 재발한 환자는 4 명이었다. 비정형 뇌수막종 진단 후 첫 치료로서 30 명의 환자들이 수술적 치료와 이에 뒤이은 수술 후 방사선치료를 받았고, 58 명의 환자들은 수술 후 보조적 치료를 받지 않았다. 분석 가능한 88 명의 환자들 중, 56 명, 29 명의 환자에서 각각 종양의 완전절제, 불완전 절제가 이루어졌고, 3 명의 환자에서는 종양절제의 범위를 확인 할 수 없었다. 수술 후 방사선치료량의 중앙값은 61.2 Gy(범위, 40-61.2 Gy)이었다. 진단

당시 연령의 중앙값은 51 세(범위, 16–78 세)였으며, 남:여 비율은 35:53 이었다.

결과: 중앙 추적관찰 기간 42.8 개월(범위, 2.7–160.0 개월)에, 5 년 전체생존율과 10 년 전체생존율은 각각 88.7%, 59.5%였다. 질병의 진행은 모두 5 년 이내에 발생하여 무진행생존율은 5 년, 10 년 모두 46.2%였다. 질병 진행까지의 중앙 기간은 24.7 개월(범위, 0.8–57.2 개월)이었다. 다변량분석을 시행하였을 때, 수술 후 방사선치료의 시행(p = 0.011)과 종양의 완전 절제(p = 0.001)가 우월한 무진행생존율을 예측할 수 있는 인자로 나타났고, 진단 당시의 나이(p = 0.028)가 전체생존율에 영향을 미치는 유일한 인자였다. 종양 절제의 범위와 수술 후 방사선치료 여부에 따라 네 군으로 나누어 분석하였을 때, 종양의 불완전 절제 후 수술 후 방사선치료를 추가하지 않은 군에서 다른 세 군에 비하여 월등히 낮은 무진행생존율을 보였다 (p = 0.000). 질병의 진행이 발생하였던 40 명의 환자들 중 33 명(82.5%)의 환자가 구체치료를 받았다. 첫 번째 구제치료의 대부분은 이전의 방사선치료 여부와 관련 없이 감마나이프를 이용한 방사선수술이었다.

결론: 2000/2007 년 개정된 WHO 분류에 따른 비정형 뇌수막종 환자에서, 종양의 수술적 절제에 뒤이어 보조적 방사선치료를 추가하는 것이 종양의 진행을 유의하게 낮추었다. 이러한 본 연구의 결과는 현재 진행중인 전향적 연구의 결과들이 발표될 때까지

비정형 뇌수막종 환자군, 특히 불완전 절제가 이루어진 환자에서 수술 후 방사선치료가 보조적 치료로서 이용되는 것에 대한 근거를 제공할 수 있다.

주요어: 뇌수막종, 비정형 뇌수막종, 방사선치료, 수술 후 방사선치료, 보조적 방사선치료
학번: 2010-21799