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Long-term surgical outcome and biological prognostic factors in patients with skull base meningiomas

Clinical article

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Object. Although gross-total resection (GTR) is a preferable treatment for skull base meningiomas, subtotal resection (STR) with or without radiation therapy can be considered as an alternative treatment for patients at considerable surgical risk. The long-term prognosis of such patients might be related to the biological activity of the tumor. This study examined predictors of progression-free survival (PFS) and sought to determine the optimal treatment strategies, focusing on the pathobiological findings of skull base meningiomas.

Methods. This study included 281 patients with skull base meningiomas (mean follow-up period 88.4 months). Risk factors for tumor progression were examined using a multivariate analysis. The PFS and overall survival (OS) rates were evaluated using the Kaplan-Meier method. The functional outcomes of the patients were measured using the Karnofsky Performance Scale (KPS).

Results. The 10-year PFS and OS rates were 66.4% and 97.4%, respectively. Overall, 83.3% of patients achieved a favorable outcome, that is, an improved or unchanged KPS score. The extent of resection, additional radiotherapy, histological grade, MIB-1 index, and p53-positive rate were significantly associated with PFS. The PFS of patients undergoing STR without radiation therapy was significantly shorter than that of either those undergoing STR with radiation therapy or GTR, while no statistical difference was observed between the latter 2 groups. Among the patients undergoing STR with pathobiological risk factors (histological grade, MIB-1 index, and p53-positive rate), the PFS of the patients who received radiation therapy was better than that of those who did not receive radiation therapy. Among the patients undergoing STR without such risk factors, the PFS was not significantly different between patients who received radiation therapy and those who did not.

Conclusions. For patients with skull base meningiomas, a GTR is desirable and additional radiation therapy after STR may contribute to a longer PFS. Additional radiation therapy should be recommended, especially for patients with pathobiological risk factors, but not necessarily for those without such risks.
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Key Words • MIB-1 index • progression • p53 • radiation therapy • skull base meningioma

Meningiomas are among the most common brain tumors, accounting for 13%–26% of primary intracranial tumors;[4,5] approximately 25% of these tumors arise in the skull base region.[8] Surgery, radiation therapy, and a combination of such treatments have been the major strategies for the treatment of meningiomas. A GTR is a logical, optimal treatment for meningiomas,[30,58] although aggressive resection may lead to severe morbidity, especially in patients with skull base meningiomas, because of the various critical surrounding structures. An STR or PR can be selected as an alternative treatment to preserve neurological function; additional radiation therapy for residual tumor tissue should be considered in such cases. Several reports have suggested that a conservative, incomplete resection followed by radiosurgery may benefit the quality of life of patients who have tumors located in the cavernous sinus or close to the brainstem and who exhibit minimal symptoms.[1,7,56,65] Radiation therapy, however, is not always a completely safe procedure and may not be necessary for all patients with residual tumors.

One of the most influential factors affecting the progression of meningiomas might be the extent of tumor resection,[58] which is not always completely achieved for

Abbreviations used in this paper: CPA = cerebellopontine angle; GTR = gross-total resection; KPS = Karnofsky Performance Scale; OS = overall survival; PFS = progression-free survival; PR = partial resection; STR = subtotal resection.

skull base meningiomas. Other factors influencing the progression of meningiomas have been reported, such as the skull base location, tumor size, calcification, cavernous sinus invasion, tumor grade, MIB-1 index, and loss of 1p.[15,16,18,39,41] Such prognostic factors, however, have not been sufficiently analyzed for skull base meningiomas. To establish optimal treatment strategies, an evaluation of the risk factors for tumor progression in skull base meningiomas is essential. In this study, we investigated the factors influencing PFS, OS, and the KPS among patients with skull base meningiomas who underwent surgery at our institution between 1980 and 2004 so as to establish an optimal management strategy for skull base meningiomas.

Methods

Patient Population

Between 1980 and 2004, 325 patients with skull base meningiomas underwent surgery at our institution. This retrospective study included 281 patients who had undergone follow-up for more than 6 months at our institution or affiliated hospitals. Of these patients, 266 (94.7%) had undergone their initial surgery at our institution. The patient population comprised 68 men and 213 women with a mean age of 51.5 years (range 6–81 years). The mean follow-up period was 88.4 months (median 76 months).

Radiological Evaluation of Tumors

The tumor size was calculated using MR imaging or CT scanning and the image processing and analysis software ImageJ (http://rsb.info.nih.gov/ij/).[39] Briefly, the results of MR imaging or CT scanning were scanned into a personal computer. The areas of the tumor were drawn on each image using free-hand tools, and the tumor volume was calculated using the slice thickness of the images. The locations of the tumors were categorized into 3 groups (anterior, middle, and posterior fossae) (Table 1).

The surgeries were performed by several skull base neurosurgeons. An independent experienced neurosurgeon without knowledge of the intraoperative findings and patients' clinical data evaluated the extent of the tumor resections based on the postoperative radiological images. Gross-total resection, STR, and PR indicate macroscopic complete removal, tumor removal at or more than 80% of the initial volume, and tumor removal of less than 80%, respectively. Tumor recurrence was defined as the presence of any new lesion after GTR. Tumor regrowth was defined as an increase of at least 25% in the enhanced tumor volume and/or the significant progression of tumor-associated neurological symptoms after STR or PR.[14] The intensities of the T2-weighted images of the tumors were evaluated, compared with those of the gray matter, and the presence of calcification was also evaluated radiographically.

Tumor Histology

All the specimens were diagnosed according to the WHO classification. Immunohistochemical evaluation was performed using anti–Ki 67 antibody (DakoCytomation) or anti–p53 antibody (Santa Cruz Biotech). The MIB-1 index is the percentage of cells reactive for Ki 67. The MIB-1 index and the p53-positive rate were determined by counting more than 1000 tumor cell nuclei in more than 3 screens and averaging the results. The cutoff values for the MIB-1 index and the p53-positive rate were defined as 3% and 5%, respectively, based on the results of our data (Table 2, see below) and previous reports.[5,31]

Evaluation of Clinical Outcomes

The PFS (period from diagnosis to first evidence of recurrence or regrowth) and the OS (period from diagnosis until death) were measured based on the clinical and radiographic records. The objective functional status of each patient was evaluated using the KPS score before surgery and at the most recent follow-up. The patients' functional outcomes were categorized into 2 groups: favorable, when the KPS assessment improved or remained unchanged, and unfavorable, when the KPS assessment worsened.[43]

Statistical Analysis

To evaluate predictors of PFS, OS, and KPS, the following items were examined: sex, age (> 60 years), extent of resection, radiotherapy following initial surgery, histological grade, intensity of T2-weighted images, presence of calcification, tumor size, tumor location, MIB-1 index, and p53-positive rate. The intensity of the T2-weighted images was classified as high or not high (low or isointensity), comparing the intensities of the tumors with those of the gray matter. The presence of calcification was determined using CT scans. Because all these factors were evaluated in 176 of the 281 cases enrolled in this study, the multivariate analysis evaluated data from 176 cases. The OS and PFS rates were estimated using the Kaplan-Meier method and a log-rank test. The Cox proportional hazards model and a stepwise regression analysis were used to evaluate possible predictors of the risk of progression or death. To estimate the prognostic factors for favorable KPS score, a univariate analysis was performed using the chi-square test or the Mann-Whitney U-test, and a multivariate analysis was also done using a stepwise regression analysis. To compare the MIB-1 index and the p53-positive rate between primary and subsequent operative groups, between benign and malignant groups, and between progression and progression-free groups, the paired t-test and the Mann-Whitney U-test were performed, respectively. The association of the MIB-1 index or the p53-positive rate with malignant transformation was evaluated using a chi-square test. Differences were considered significant at probability values of less than 0.05.

Results

Overall Clinical Outcome

A GTR was performed in 152 patients (54.1%), while an STR and a PR were performed in 120 and 9 patients, respectively (129 patients [45.9%]). Thirty of the 129 patients subsequently underwent additional radiation

TABLE 1: Tumor location*

Location	No. of Cases (%)
ant fossa	
tuberculum sellae	26 (9.3)
orbita	10 (3.6)
olfactory groove	8 (2.8)
optic nerve sheath	8 (2.8)
other ant fossa	13 (4.6)
total	65 (23.1)
middle fossa	
sphenoid wing	49 (17.4)
parasellar	7 (2.5)
cavernous sinus	5 (1.8)
other middle fossa	8 (2.8)
total	69 (24.6)
pst fossa	
petroclival	77 (27.4)
CPA	44 (15.7)
foramen magnum, lower clivus	11 (3.9)
jugular foramen	5 (1.8)
other pst fossa	10 (3.6)
total	147 (52.3)

* ant = anterior; pst = posterior.

therapy. Stereotactic radiosurgery was performed in 23 patients. The median marginal and maximal doses delivered to the tumor were 13 Gy (range 10–18 Gy) and 24 Gy (range 19–45 Gy), respectively. The tumor volumes were enclosed by the 40%–75% isodose lines (median 50%). For the remaining 7 patients, stereotactic radiotherapy (35 Gy with 10 fractions) was performed in 1 patient, conventional radiation therapy (38–50 Gy with 19–25 fractions) was performed in 3, a combination of conventional radiation and stereotactic radiosurgery was performed in 2, and heavy particle radiotherapy was performed in 1 patient. The median period from surgery to additional radiotherapy was 9.5 months (range 2–125 months). The number of patients in the PR group was relatively small, and the results of the statistical analysis did not change when the PR group was included in the STR group and when it was analyzed separately. Consequently, the PR group was included in the STR group for the statistical analysis in the present study.

During the follow-up period, tumor progression was observed in 63 patients; 28 of these patients underwent repeated surgery, and 26 underwent further radiotherapy 3–93 months after the initial surgery. The overall 5- and 10-year PFS rates were 79.5% and 66.4%, respectively (Fig. 1 left). The 5-year PFS rates for the GTR and STR groups were 88.3% and 70.0%, respectively. Nine patients died during this period, and the 5- and 10-year OS rates were 98.3% and 97.4%, respectively (Fig. 1 right). Five patients died of tumor progression 1–205 months after the initial surgery, and the other 4 patients died of other causes such as meningitis or suicide.

The KPS scores before surgery and at the latest follow-up were 90.6 ± 6.3 and 88.2 ± 18.1, respectively. In 47 patients (16.7%), the KPS score at the latest follow-up was lower than that before surgery, while 172 (61.2%) and 62 (22.1%) patients showed equal and better scores, respectively. Thus, 83.3% of the patients had a favorable KPS score, while 16.7% had an unfavorable KPS score. The percentage of GTR and the 5- and 10-year PFS rates for meningiomas in various locations are summarized in Table 3.

TABLE 2: The MIB-1 indices, p53-positive rates, and 5-year PFS

Parameter	5-Yr PFS (%)
MIB-1 index (%)	
<1	87.7
1–3	86.9
3.1–5	61.7
>5	69.9
p53-positive rate (%)	5
<1	91.5
1–3	89.1
3.1–5	88.9
>5	57.5

Pathological Findings

Histopathologically, most of the patients (97.5%) were classified as having WHO Grade I meningiomas, of which 73.0% had meningothelial meningioma. Five (1.8%) and 2 (0.7%) patients were diagnosed as having WHO Grade II and III meningiomas, respectively. The overall mean MIB-1 index was 2.28 (range 0.2–19.7), and the mean p53-positive rate was 2.98 (range 0.1–35.4). The mean MIB-1 index of the benign group (WHO Grade I) was 2.27 and that of the malignant group (WHO Grades II and III) was 2.60. The mean p53-positive rates of the benign and malignant groups were 2.88 and 5.43, respectively. No significant difference in the MIB-1 index or the p53-positive rate was observed between the benign and malignant groups.

On the other hand, the MIB-1 indices and the p53-positive rates of the patients with tumor progression were significantly greater than those of the patients with PFS, that is, the mean MIB-1 indices of the patients with and without tumor progression were 3.06 and 2.11, and the mean p53-positive rates were 6.69 and 2.26, respectively.

Table 2 shows the PFS for various ranges of the MIB-1 indices and p53-positive rates. The PFS decreased remarkably at an MIB-1 index value of 3% and a p53-positive rate of 5%, demonstrating that the cutoff values of the MIB-1 index and the p53-positive rate were appropriate for the analysis performed in this study, as reported previously.[5,31]

Among the 63 patients with tumor progression, 28 underwent additional surgeries. According to histopathological examinations, 7 patients exhibited malignant transformation from their previous WHO grade. The MIB-1 index and the p53-positive rate were measured in 14 and 13 patients, respectively. According to the statisti-

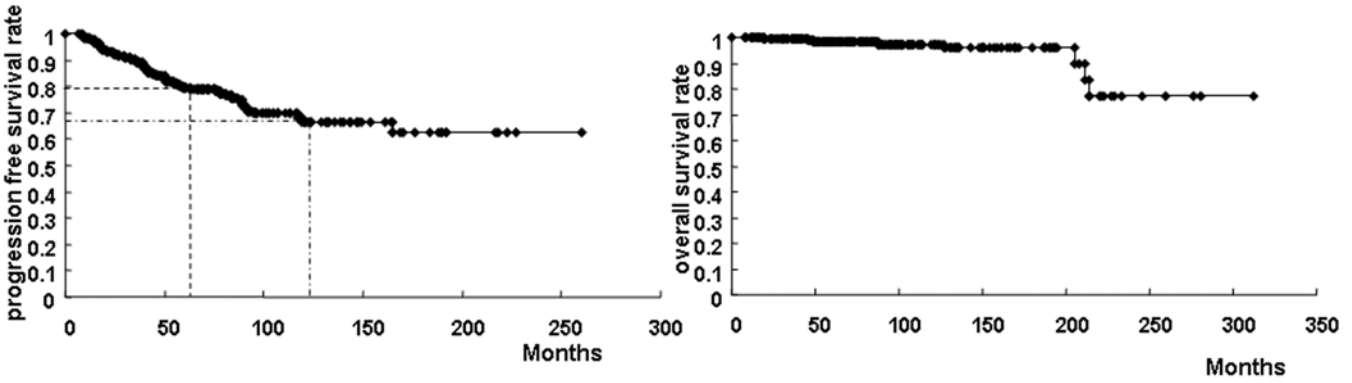

Fig. 1. Kaplan-Meier survival plots showing the PFS **(left)** and OS **(right)** rates. The 5- and 10-year PFS rates were 79.5% and 66.4%, respectively. The 5- and 10-year OS rates were 98.3% and 97.4%, respectively.

cal analysis, however, no significant subsequent increases in the MIB-1 indices and p53-positive rates were observed among the patients who underwent additional surgeries. No significant correlation was observed between malignant transformation and the MIB-1 index ($p = 0.22$) or the p53-positive rate ($p = 0.14$).

Clinical Outcomes and Prognostic Factors

The results of the statistical analyses to identify prognostic factors are summarized in Table 4. In the univariate analyses, the extent of resection, a high histological grade, a high MIB-1 index (> 3%), and a high p53-positive rate (> 5%) were significantly associated with the PFS. A high histological grade and the MIB-1 index were associated with the OS. A high histological grade, MIB-1 index, and p53-positive rate were also significantly associated with an unfavorable KPS.

In the multivariate analysis of the PFS, the extent of resection, a high histological grade, a high MIB-1 index, a high p53-positive rate, and the absence of radiation therapy were also statistically associated with a poor PFS. On the other hand, no factors were associated with a poor OS in the multivariate analysis. The multivariate analysis for the KPS showed that female sex and a higher histological grade and p53-positive rate were statistically associated with poor performance.

To investigate the effect of radiation therapy, the PFS was compared among 3 groups: GTR, STR with radiation therapy, and STR without radiation therapy (Fig. 2). The 5-year PFS rates of the GTR, STR with radiation therapy, and STR without radiation therapy groups were 88.3%, 92.3%, and 63.7%, respectively. The PFS rate of the STR without radiation therapy group was significantly shorter than that of the STR with radiation therapy and the GTR groups, while no statistical difference was detected between the GTR and STR with radiation therapy groups.

To examine whether additional radiotherapy is necessary for residual tumors, the PFS rates were analyzed by dividing the patients into 2 groups with or without the following pathological or biological risk factors: histological malignancy, a high MIB-1 index, or a high p53-positive rate. Among the patients with at least 1 of these factors (58 patients), the 5-year PFS rates of the GTR, STR with radiation therapy, and STR without radiation therapy groups were 65.2%, 85.7%, and 44.5%, respectively, while those of the groups without these factors were 100%, 100%, and 87.4%, respectively. Tumor recurrence was observed even in some patients in the GTR group with at least 1 of the pathobiological risk factors, but no recurrences occurred among the patients without such risk factors (Fig. 3A). Among the STR group with pathobiological risk factors, the PFS of the patients with radiation therapy tended to be higher than that for those without radiation therapy; however, the difference did not reach statistical significance ($p = 0.07$), probably because of the small number of patients (Fig. 3B). On the other hand, in the STR group without any of these factors (55 patients), no significant difference in PFS was observed between patients with and those without radiation therapy (Fig. 3C).

TABLE 3: The percentages of GTR and the rate of PFS in each meningioma*

Location	% GTR	PFS Rate	
		5-Yr	10-Yr
ant fossa			
tuberculum sellae	57.7	0.955	0.818
orbita	70.0	0.556	0.556
olfactory groove	87.5	0.875	0.700
optic nerve sheath	50.0	0.571	0.571
other ant fossa	100.0	0.900	0.900
middle fossa			
sphenoid wing	63.3	0.827	0.732
parasellar	28.6	0.857	0.857
cavernous sinus	0.0	0.400	0.400
other middle fossa	75.0	0.700	NA
pst fossa			
petroclival	33.8	0.764	0.591
CPA	70.5	0.870	0.816
foramen magnum, lower clivus	36.4	0.788	NA
jugular foramen	40.0	0.750	NA
other pst fossa	40.0	0.648	0.162

* NA = not applicable.

TABLE 4: The results of statistical analyses for prognostic factors*

	PFS				OS	KPS			
	Univariate		Multivariate		Univariate	Univariate		Multivariate	
Factor	p Value	HR	p Value	95% CI	p Value	p Value	OR	F Value	95% CI
sex (female)	0.35		NA		0.26	0.61	0.103	2.787	−0.019 to 0.224
age (≥60 yrs)	0.25		NA		0.073	0.14		NA	
location	0.80		NA		0.99	0.55		NA	
pst/middle	0.87				0.99				
ant/middle	0.72				0.92				
tumor size	0.90		NA		0.69	0.10		NA	
high T2-weighted image	0.99		NA		0.17	0.48		NA	
calcification	0.53		NA		0.64	0.60		NA	
resection (STR)	<0.0001	3.706	0.0018	1.626–8.448	0.15	0.40		NA	
radiation (absent)	0.12	4.693	0.0429	1.050–20.967	0.35	0.10		NA	
higher histological grade	<0.0001	6.928	0.0014	2.120–22.646	<0.001	0.0037	0.453	12.208	0.197–0.709
MIB-1 index (>3%)	0.0005	3.003	0.0072	1.347–6.694	0.029	0.040		NA	
p53-positive rate (>5%)	<0.0001	3.058	0.0054	1.392–6.718	0.074	0.011	0.161	6.145	0.033–0.289

* HR = hazard ratio.

Discussion

Literature Review

Considering the benign nature of the majority of meningiomas, the long-term outcome after resection should be investigated to determine the optimal treatment strategy. Mathiesen et al.[30] investigated the long-term outcome of whole skull base meningiomas after resection and demonstrated 5-year recurrence rates of 4% and 25%–45% for patient groups treated with GTR and STR, respectively; these outcomes were better than our present data. However, their recurrence rates were evaluated based only on clinical symptoms in an era without CT or MR imaging (between 1947 and 1982); thus, the recurrence rates may have been underestimated. In our study in which we analyzed 281 patients, 9 died during the follow-up period; however, only 5 patients died of tumor growth, and the 10-year OS rate was 97.4%. The mortality rate in our study was much lower than that reported by Mathiesen et al.[30] who reported a perioperative mortality rate of 10.8% and an additional mortality rate of 9.7% within 10 years; these results reflect the recent advances in microsurgical techniques for skull base surgery.

Other studies have reported long-term outcome data for meningiomas at specific skull base locations, such as the sphenoid wing, anterior clinoid, CPA, tuberculum sellae, and petroclival region.[9,24–26,37,38,42–44,49,55,61] Table 5 summarizes these reports and shows that their results were almost similar to those in our study and that GTR contributes to longer tumor control. The PFS rates, however, seem to be reduced in studies with longer follow-up periods, indicating the importance of long-term observation for patients with these tumors.

Predictors of Tumor Progression

Several predictors of meningioma recurrence have been reported, such as the extent of resection,[19,58] tumor histology,[6] patient sex,[59] age,[33] tumor location,[6] tumor size,[16,41] the presence of calcification,[39,41] the proliferation rate,[19,52] and p53 expression.[20] In our study, a multivariate analysis revealed that resection, histological grade, MIB-1 index, p53-positive rate, and additional radiotherapy were associated with the PFS. While these factors were reported in previous studies with meningiomas in other locations, our study has provided robust and essential data regarding the long-term outcome and prognostic factors for skull base meningiomas, with the analysis of the largest number of patients (281 cases) with the longest mean follow-up period (88.4 months) among recent studies (Table 5). Indeed, all the prognostic factors detected in our study can only be evaluated during or after resec-

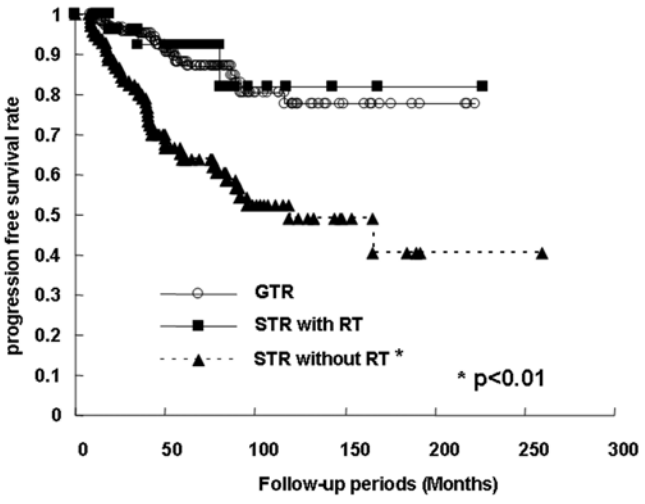

Fig. 2. Kaplan-Meier survival plot showing the PFS rates in the GTR, STR with radiation therapy (RT), and STR without radiation therapy groups. The 5-year PFS rates of the GTR, STR with radiation therapy, and STR without radiation therapy groups were 88.3%, 92.3%, and 63.7%, respectively. The PFS of the STR without radiation therapy group was significantly shorter than those of the other 2 groups ($p < 0.01$).

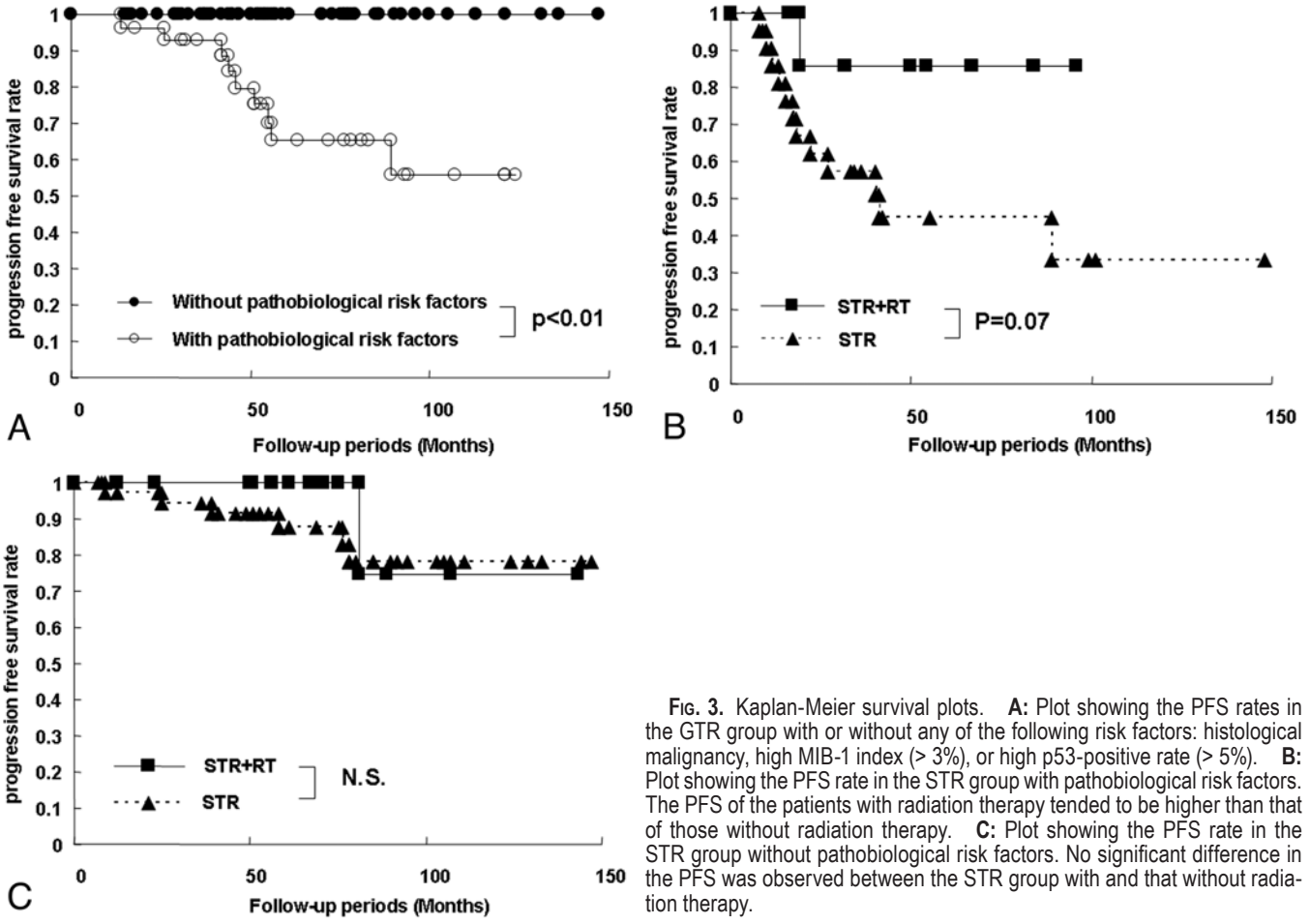

Fig. 3. Kaplan-Meier survival plots. **A:** Plot showing the PFS rates in the GTR group with or without any of the following risk factors: histological malignancy, high MIB-1 index (> 3%), or high p53-positive rate (> 5%). **B:** Plot showing the PFS rate in the STR group with pathobiological risk factors. The PFS of the patients with radiation therapy tended to be higher than that of those without radiation therapy. **C:** Plot showing the PFS rate in the STR group without pathobiological risk factors. No significant difference in the PFS was observed between the STR group with and that without radiation therapy.

tion, but not before surgery. However, our study confirms the efficacy of radiation therapy for residual skull base meningiomas and also suggests indication criteria for additional radiation therapy. A GTR, which is the optimal surgical result, cannot always be achieved for skull base meningiomas. Thus, additional radiationtherapy may be beneficial to patients with residual tumors, even though stereotactic radiosurgery can cause adverse effects during the long-term follow-up of skull base meningiomas. Consequently, histological and immunohistochemical analyses to evaluate pathological or biological risk factors after surgery but before radiation therapy would provide essential information for the treatment of skull base meningiomas needed to determine the optimal strategy for subsequent treatment and follow-up.

Several recent reports have shown that there are several factors predicting the extent of tumor removal and neurological complications of surgery for skull base meningiomas.[1,53] These factors consist of tumor involvement with neurovascular structures, brainstem contact, tumor location along the central axis, the extent of tumor attachment, and so on. In our study, we did not examine all of these factors because they have been reported as factors predicting the extent of tumor resection and surgical complications, and the extent of resection had already been identified as a possible prognostic factor in our analysis. However, among these factors, the tumor involvement of critical neurovascular structures would be an important and critical factor predicting the long-term prognosis before surgery, as it would affect the resection as well as the possible complications of postoperative radiation therapy.

Extent of Tumor Resection and Radiation Therapy

Among the GTR, STR with radiation therapy, and STR without radiation therapy groups, the PFS of the STR without radiation therapy group was significantly shorter than that of the other 2 groups. Interestingly, no statistical difference in the PFS of the GTR and STR with radiation therapy groups was observed, indicating that STR followed by radiation therapy could be an alternative to GTR.

Meningiomas are considered to be suitable for stereotactic radiosurgery for the following reasons: 1) they are well encapsulated; 2) they rarely invade the brain; 3) the steep radiation falloff can be conformed to fit the irregular tumor margin; 4) they can be easily defined using contrast-enhanced MR imaging and CT scanning; 5) they are often recognized even when they are relatively small in size; and 6) the high radiation dose induces the delayed obliteration of the supplying blood vessel.[27] Excellent tumor control rates after stereotactic radiosurgery, ranging

TABLE 5: Summary of previous studies

Location	Authors & Year	No. of Patients	Rate of GTR (%)	Mean Follow-Up	Recurrence Rate (%)
petroclival	Couldwell et al., 1996	109	68.8	6.1 yrs	13.0
	Little et al., 2005	137	40.1	29.8 mos	17.6
	Park et al., 2006[43]	49	20.4	86 mos	22.4
sphenoid wing	Nakamura et al., 2006[37]	39*	92.3	79.0 mos	7.7
		69†	14.5		27.5
	Pamir et al., 2008	43	90.7	39 mos	9.3
	Puzzilli et al., 1999	33	54.5	53.7 mos	15.2
CPA	Leonetti et al., 2006	29	65.5	4.6 yrs	13.8
	Sekhar & Jannetta, 1984	22	63.6	GTR, 5 yrs; STR, 4 yrs	9.1
	Voss et al., 2000	40	82	3 yrs	7.5
tuberculum	Li et al., 2007	43	74.4	5.4 yrs	4.7
	Nakamura et al., 2006[38]	72	91.7	45.3 mos	2.8
	Park et al., 2006[44]	30	76.7	75.9 mos	13.3

* These patients had tumors without cavernous sinus involvement.
† These patients had tumors with cavernous sinus involvement.

from 82% to 98%, have been reported in previous studies, contributing to a longer PFS and a better KPS score.[2,17,35,57] Stereotactic radiosurgery, however, continues to be associated with long-term risks for radiation-induced adverse effects such as peritumoral edema, radiation necrosis, and secondary neoplasms, although the incidence of such effects is less than 7%.[10,23,27,34,64]

Therefore, determining the indications for additional prophylactic radiation therapy for residual tumor tissue after the resection of a skull base meningioma is of considerable importance. According to our study, additional radiotherapy should be considered for patients who have undergone STR and have any of the following pathobiological risk factors: histological malignancy, a high MIB-1 index (> 3%), or a high p53-positive rate (> 5%) (Fig. 3B). On the other hand, prophylactic radiation therapy might not always be necessary for patients who have undergone STR but do not have any risk factors, since the tumor progression rates of the patients undergoing STR with radiotherapy and those without radiotherapy were almost equivalent (Fig. 3C). Even after GTR, tumor recurrence was observed in some patients with the aforementioned pathobiological risk factors (Fig. 3A). Together with the results of the multivariate analysis, these findings suggest that patients with these risk factors, even those who have undergone GTR, should be closely observed.

Histology and Biological Markers

According to a report by the WHO in 2007,[45] almost all meningiomas are classified as benign, while 4.7%–7.2% are classified as atypical and 1.0%–2.8% are classified as anaplastic. In the present study, however, 97.5% were classified as Grade I meningiomas, and only 1.8% and 0.7% were classified as Grades II and III, respectively. Other studies have also reported that atypical and anaplastic meningiomas are relatively rare in the skull base region.[30,33,54] The reasons for the rare occurrence of high-grade meningiomas at the skull base are not clear, but a few hypotheses can be considered. First, the meninges covering the brainstem may differ from those covering the convexity.[54] Second, skull base meningiomas located close to the cranial nerves and brainstem may cause clinical symptoms during a relatively early period of growth, leading to an earlier diagnosis and fewer additional molecular alterations, compared with other meningiomas.[54]

In our study, malignant transformation from the previous histological findings was found in 7 cases, accounting for 2.5% of all 281 skull base meningiomas and 28.0% of the 25 patients who underwent additional surgery for recurrent benign meningiomas. These data are comparable with those of previous reports, including meningiomas in other locations, indicating that 0.16%–2% of all meningiomas and 14%–28.5% of recurrent benign meningiomas transform into malignant variants.[3,22,51] Thus, malignant skull base meningiomas are relatively rare, but the risk of malignant transformation may be similar or even relatively higher than that of meningiomas in other locations.

Associations between histological grades and tumor progression have been reported in many studies, with recurrence rates of 7%–25%, 29%–52%, and 50%–94% for WHO Grades I, II, and III, respectively.[6,21,28,45–47,54] While histological grading is important for the prediction of tumor progression, it is sometimes difficult to determine the exact grading in some cases. Even meningiomas with the same histological grading do not necessarily grow at a similar rate. Thus, the identification of useful markers that can predict the risk of tumor progression is important. In our study, the MIB-1 indices and p53-positive rates were examined in addition to the histological grades. As shown in Table 2, the PFS decreased considerably at the cutoff values of these parameters, and both factors were clearly associated with the PFS for skull base meningiomas.

The MIB-1 index represents the ratio of cells that are

reactive for the Ki 67 protein, which is expressed during the G_1, S, G_2, and M phases of the cell cycles but not in the G_0 phase or the early G_1 phase.[12] This index is one of the most frequently used values for assessing the proliferative activities of various tumors.[13] A correlation between the MIB-1 index and the earlier recurrence of meningiomas has been reported in several reports, in agreement with the present study,[29,48] and a correlation with the neuroradiological growth rate has also been observed for meningiomas.[52] Although the MIB-1 index is a valuable prognostic marker for meningiomas, as shown above, a few concerns exist regarding its clinical application. The reported cutoff values for the MIB-1 indices vary from 3% to 12%[19,31,48] because of the various staining and counting methods used in different institutions. A cutoff point identified at one institution may not be applicable at other institutions. Furthermore, there are 2 different methods for measuring the MIB-1 index: counting the cells in the area with the highest MIB-1 label and in randomly selected fields.[40,50] Previous reports comparing these different methods have indicated that both methods detect significantly higher MIB-1 values in recurrent cases than in nonrecurrent cases.[40,50] Nakasu et al.[40] reported that the randomly selected method was a better predictor of recurrence and tumor growth, while the counting of a large number of tumor cells and proper processing of the specimen were necessary to maintain the same reproducibility.[40] Rezanko et al.,[50] on the other hand, pointed out that the MIB-1 values obtained by 2 pathologists counting the highest labeled areas agreed perfectly, indicating a good reproducibility. Residual tumors that invade the surrounding structures and recur shortly would have aggressive features, which could be highlighted by counting in the highest labeled areas. In our study, we measured the index in the highest MIB-1–labeled areas to ensure reproducibility and demonstrated a significant correlation between the MIB-1 index and the clinical outcomes of skull base meningiomas.

Mutation of the *p53* gene is extremely rare in meningiomas,[4,11,36,62] and immunohistochemical reactivity for p53 has been shown to be caused by wild-type p53 in meningiomas.[36] While the mechanism responsible for the accumulation of wild-type p53 has not been elucidated, DNA damage may lead to the accumulation of wild-type p53 or the stabilization of the wild-type p53 protein through complex formation with several cellular and viral proteins, leading to the accumulation of p53 protein.[11,36] Several studies have reported a correlation between the p53-positive rate and the tumor progression of meningiomas.[20,32,59,63] Konstantinidou et al.[20] reported that p53 expression was a significant predictor of the recurrence of totally resected meningiomas, and Yang et al.[63] reported that p53 overexpression was associated with malignant progression. Terzi et al.[60] reported that the expression of p53 was associated with a shortened event-free survival period. Our results, which are consistent with these studies, once again emphasized the significance of the evaluation of p53 expression in skull base meningiomas.

The histological classification of some cases cannot be clearly diagnosed, and even meningiomas with the same WHO grade do not always manifest similar biological behaviors. The assessment of the MIB-1 index and p53 expression should be recommended in the management of skull base meningiomas to determine subsequent treatment and follow-up care.

Conclusions

Our results have once again confirmed that a total resection is the optimal treatment for skull base meningioma and that a subtotal resection followed by radiation therapy is a reasonable strategy in cases in which aggressive resection is expected to lead to severe complications. In particular, radiation therapy for residual tumors should be considered in cases in which there are pathological or biological risk factors, such as a high histological grade, MIB-1 index, or p53-positive rate. For cases without any of these risk factors, additional radiation therapy might not be necessary if the residual tumor tissue is closely observed. Even after GTR, close observation is recommended for patients with these risk factors.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ohba. Acquisition of data: Ohba, Horiguchi. Analysis and interpretation of data: Ohba. Drafting the article: Ohba. Critically revising the article: Kobayashi, Kawase. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Ohba, Kobayashi. Administrative/technical/material support: Kobayashi, Horiguchi. Study supervision: Kawase.

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