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Combination of p53 and Ki67 as a Promising Predictor of Postoperative Recurrence of Meningioma

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Abstract. *Background: Meningioma is a common intracranial tumor originating from arachnoid cap cells. Meningiomas are generally benign tumors curable by one-time resection. However, some meningiomas regrow and invade into the dura mater, and thus frequently require additional treatment. A useful marker to predict the regrowth of meningioma is desired. This study aimed to clarify the significance of p53 and Ki67 for postoperative recurrence of meningioma. Materials and Methods: The expression of p53 and Ki67 in 215 intracranial or intraspinal meningiomas was investigated by immunohistochemistry. Results: Of the 215 meningiomas, 35 cases (16.3%) were p53-positive and 49 cases (22.8%) were Ki67-positive. Multivariate analysis revealed Ki67 and p53 status as being significantly correlated with recurrence. Positivity for either Ki67- or p53 was significantly associated with poor recurrence-free survival. Conclusion: Combined p53 and Ki67 status might represent a useful independent predictive marker for recurrence of meningioma.*

Meningioma is one of the most common types of primary intracranial tumor (1). According to the 2016 World Health Organization (WHO), meningioma is classified WHO grade I, II, or III (2). Microsurgical resection is mostly effective for improving outcomes (3). About 80% of meningiomas are benign, slow-growing tumors that are well controlled by surgical total resection (4, 5). Both the extent of tumor resection and WHO grade are known to influence the recurrence rate (3, 5-7). The rate of meningioma recurrence is around 15-25% after partial resection but relatively low after total resection (5). However, meningioma can recur even after total resection (in about 5%) (8), and sometimes proves life-threatening. Establishment of biological markers to predict meningioma recurrence after total resection is thus important.

Molecular biological research into meningioma has recently progressed, and some studies have reported biological features of meningiomas (9-12). Tumor recurrence is reportedly associated with DNA methylation (13), Telomerase reverse transcriptase (TERT) promoter mutations (14), and gene-expression profiles (15). In particular, a close positive correlation between Ki67 and meningioma recurrence has been reported (16-18), although examination of Ki67 has not yet entered clinical use.

As the product of a well-known tumor-suppressor gene, p53 acts as a transcription factor and is involved in DNA repair, regulation of the cell cycle, and induction of apoptosis. Immunocytochemical detection of p53 is associated with the presence of underlying mutations (19). Correlations between p53 and clinicopathological features in meningioma have been reported (16, 17, 20, 21), but those reports did not include a sufficient number of meningioma cases (16, 17, 19, 20, 22-29). The purpose of this study was to clarify the significance of p53 and Ki67, as a predictive marker of postoperative recurrence in 215 meningiomas.

Materials and Methods

Clinical materials. This retrospective study included 215 patients with intracranial or intraspinal meningiomas who underwent surgical resection at Osaka City University between 2007 and 2018. Patients who needed multiple surgeries because of synchronous multiple meningiomas were excluded from this study. Clinicopathological characteristics of these 215 meningioma cases are summarized in Table I. Length of dural attachment, height from attachment and maximum diameter were measured from preoperative contrast-enhanced magnetic resonance imaging. The resection rate was evaluated according to Simpson grade (30). Gross total resection included Simpson grade 1-3 and subtotal resection

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Key Words: Meningioma, recurrence, p53, Ki67, immunostaining.

Table I. *Clinicopathological data of 215 patients with meningioma.*

Variable	Value
Age, years	
Mean (range)	59 (25-87)
Gender, n (%)	
Male	62 (28.8%)
Female	153 (71.2%)
Location, n (%)	
Skull base	143 (66.5%)
Convexity and falx	57 (26.5%)
Intraventricular	3 (1.4%)
Spinal	12 (5.6%)
Dural attachment, mm	
Mean (range)	30.9 (7-138)
Height from attachment, mm	
Mean (range)	23.3 (7-64)
Max. tumor diameter, mm	
Mean (range)	34.9 (7-79)
Follow-up, months	
Mean (range)	54 (0-136)
WHO grade, n (%)	
I	210 (97.7%)
II	4 (1.9%)
III	1 (0.4%)

included Simpson grade 4. We examined retreatment-free survival to assess recurrence. Retreatment included additional surgical treatment or irradiation for recurrence of meningioma after the initial surgery. All specimens were histologically classified and revised genetically according to WHO criteria [2007 (31) or 2016 (2)] for tumors of the central nervous system by expert neuropathologists. This study was approved by Osaka City University Ethics Committee (approval no. 3084).

Immunohistochemical techniques. Immunohistochemical staining was performed using 4-μm sections of formalin-fixed, paraffin-embedded tissue. Immunohistochemical staining for p53 was performed using anti-p53 antibody (clone DO-7; Dako, Carpinteria, CA, USA) with the bond polymer refine detection system (catalogue #DS 9800; Leica Biosystems Newcastle Ltd, UK). Immunohistochemical staining for Ki67 was performed using anti-Ki67 antibody (clone MIB-1; Dako), as follows. Tissue sections were incubated with anti-Ki67 overnight at 4˚C. After washing in phosphate-buffered saline, tissues were incubated with horseradish peroxidase-conjugated anti-rabbit or anti-mouse immunoglobulin polymer as a secondary antibody (Envision kit; Dako) for 30 min at room temperature, according to the instructions from the manufacturer. Slides were treated with streptavidin-peroxidase reagent and incubated in phosphate-buffered saline and diaminobenzidine and 1% hydrogen peroxide v/v, followed by counterstaining with Mayer's hematoxylin. Immunohistochemical determination of positive staining was interpreted by two independent investigators who were blinded to the clinicopathological features of patients. For tissue evaluation, each slide was scored based on the percentage of positively staining nuclei. Both p53 and Ki67 were mainly expressed in tumor cell nuclei (Figure 1). Immunoreactivities of p53 and Ki67 were evaluated according to the intensity of nuclear staining. The cut-off for p53 was ≥1% positive tumor cells with nuclear staining. For Ki67 staining, the number of tumor cells with distinct nuclear staining was recorded after counting 500 tumor cells in consecutive high-power fields in the most reactive areas on the slide. Cells with questionable nuclear staining were discounted. The percentage of positively stained tumor cells was then calculated as the Ki67 labeling index (LI). A Ki67-LI ≥5% was determined to be positive.

Statistical analysis. The chi-square test was used to compare immunohistochemical findings and clinicopathological features. Retreatment-free survival curves were estimated using the Kaplan–Meier method and the log-rank test was used to compare cumulative survival durations among each patient group. In addition, Cox proportional hazards models were used to compute uni- and multivariate hazard ratios for study parameters. Parameters with values of $p<0.05$ in univariate analysis were included in multivariate analysis. For all tests, values of $p<0.05$ were considered statistically significant. SPSS software version 22 (SPSS Japan, Tokyo, Japan) was used for all analyses.

Results

Correlation between clinicopathological features and p53/Ki67 expression. Expressions of p53 and Ki67 in the nucleus of meningioma cells were found in varying proportions (Figure 1). The relationship between p53 and/or Ki67 expressions and clinicopathological variables are summarized in Table II. Among all 215 meningiomas, 35 cases (16.3%) were p53-positive and 49 cases (22.8%) were Ki67-positive. Significant positive correlations were found between p53 expression and WHO grade II/III ($p=0.003$) and high Ki67-LI ($p=0.045$). Positive Ki67 expression also correlated significantly ($p=0.01$) with WHO grade II/III. Positive expression of either p53 or Ki67 was found in 71 cases (33%). Positivity for either p53 or Ki67 correlated significantly ($p=0.004$) with WHO grade II/III (Table II).

Retreatment-free survival for patients with meningioma. The Kaplan–Meier curve for retreatment-free survival of 215 patients with meningioma is shown in Figure 2. The retreatment-free rate of 215 cases with meningioma was 75% ($p=0.018$, Figure 2A). Kaplan–Meier curves for retreatment-free survival according to Ki67 expression showed that retreatment-free survival was significantly worse for Ki67-positive patients than for Ki67-negative patients ($p=0.018$, Figure 2B). Kaplan-Meier curves for retreatment-free survival according to p53 expression showed that retreatment-free survival did not differ significantly between p53-positive and -negative cases ($p=0.135$, Figure 2C). Retreatment-free survival was significantly worse for patients with positivity for Ki67 or p53 than for cases negative for both Ki67 and p53 ($p=0.033$, Figure 2D). Retreatment-free survival was significantly worse in cases with gross total resection

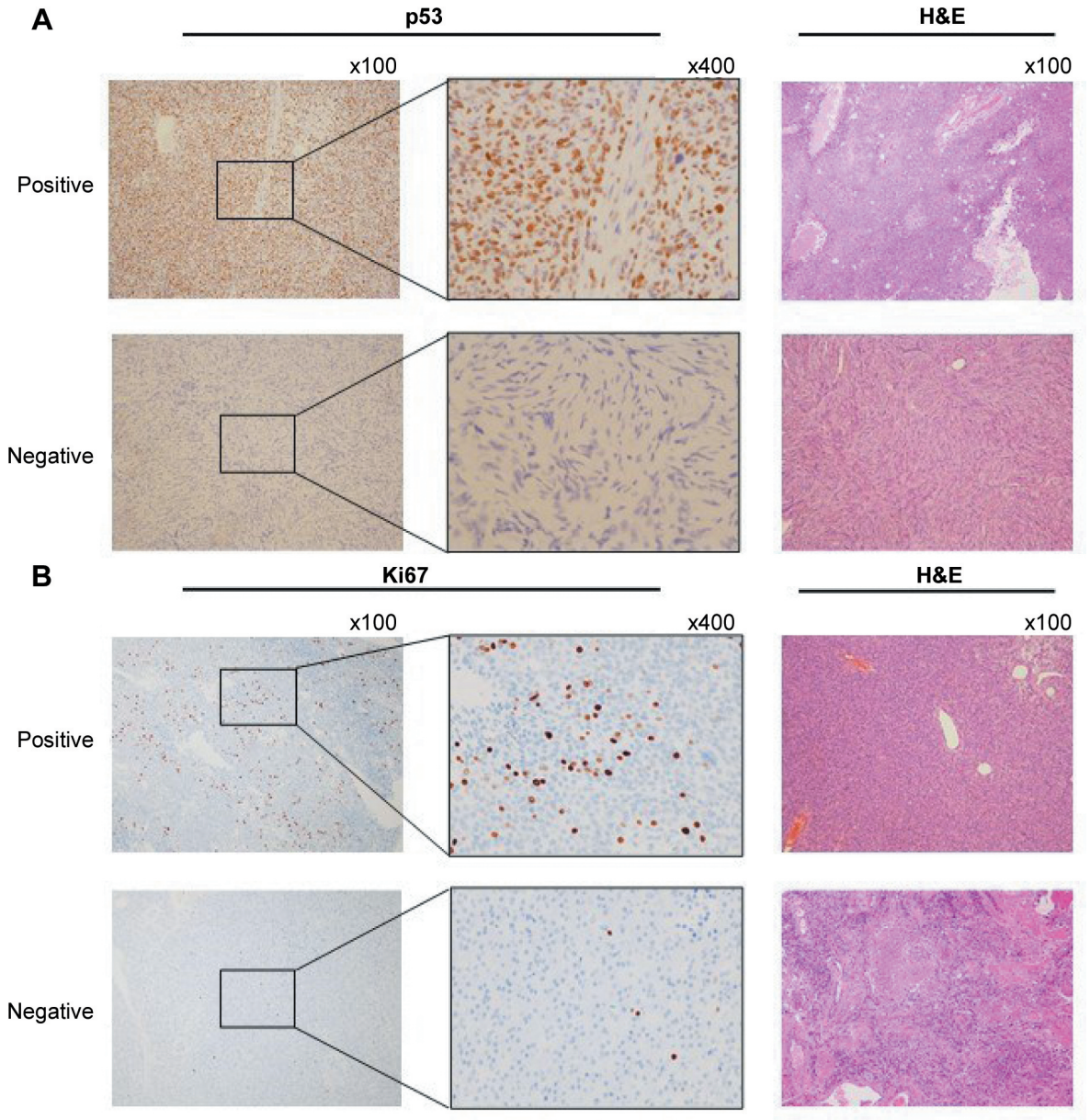

Figure 1. *Representative images of p53 and Ki67 expression in meningioma. Expression of Ki67 and p53 was evaluated as the percentage of stained tumor cells. A: Expression of p53 was found mainly in the nuclei of meningioma cells. The upper row shows a positive result of staining for p53 (80%), and the lower row shows a negative case (0%). B: Ki67 immunostaining produced discernible diffuse or granular, brown nuclear staining, more accentuated in nucleoli, with relatively uniform intensity. The upper row shows a positive result of staining for Ki67 (26%), and the lower row shows a negative case (2.8%). HE: Hematoxylin and eosin.*

(n=132) than in those with subtotal resection (n=83) (p<0.001, Figure 2E). In patients with gross total resection (n=132), retreatment-free survival was significantly worse in patients with positivity for Ki67 or p53 than in patients negative for both Ki67 and p53 (p=0.035, Figure 2F). In patients with subtotal resection, no significant associations with retreatment were seen (p=0.083, Figure 2G).

Correlation between retreatment for meningioma and p53/Ki67 expression. Univariate analysis for the retreatment of meningioma (Table III) revealed that retreatment correlated significantly with age <50 years (p=0.016), dural attachment ≥40 mm (p=0.014), subtotal resection (p<0.001), and positivity for Ki67 or p53 (p=0.004). Multivariate logistic regression analysis (Table III) showed that gross total

Table II. *Correlation between clinicopathological features and p53 and Ki67 expression in 215 meningiomas.*

Variable	p53 Expression, n (%)			Ki67 Expression, n (%)			p53/Ki67 Expression, n (%)					
	Negative (n=180)	Positive (n=35)	*p*-Value	Negative (n=166)	Positive (n=49)	*p*-Value	Both negative (n=144)	Either positive (n=71)	*p*-Value	Either negative (n=202)	Both positive (n=13)	*p*-Value
Age												
<50 Years	44 (83.0%)	9 (17.0%)	0.834	43 (81.1%)	10 (18.9%)	0.572	38 (71.7%)	15 (28.3%)	0.501	49 (92.5%)	4 (7.5%)	0.740
≥50 Years	136 (84%)	26 (16.0%)		123 (75.9%)	39 (24.1%)		106 (65.4%)	56 (34.6%)		153 (94.4%)	9 (5.6%)	
Gender												
Male	47 (75.8%)	15 (24.2%)	0.065	47 (75.8%)	15 (24.2%)	0.858	38 (61.3%)	24 (38.7%)	0.267	56 (90.3%)	6 (9.7%)	0.204
Female	133 (86.9%)	20 (13.1%)		119 (77.8%)	34 (22.2%)		106 (69.3%)	47 (30.7%)		146 (95.4%)	7 (4.6%)	
Dural attachment												
<40 mm	129 (82.2%)	28 (17.8%)	0.666	125 (79.6%)	32 (20.4%)	0.433	106 (67.5%)	51 (32.5%)	>0.999	148 (94.3%)	9 (5.7%)	0.519
≥40 mm	43 (86.0%)	7 (14.0%)		37 (74%)	13 (26%)		34 (68%)	16 (32.0%)		46 (92.0%)	4 (8.0%)	
Height from dural attachment												
<25 mm	106 (83.5%)	21 (16.5%)	0.851	100 (78.7%)	27 (21.3%)	0.482	84 (66.1%)	43 (33.9%)	0.648	122 (96.1%)	5 (3.9%)	0.138
≥25 mm	66 (82.5%)	14 (17.5%)		62 (77.5%)	18 (22.5%)		56 (70.0%)	24 (30.0%)		72 (90%)	8 (10.0%)	
Max. tumor diameter												
<40 mm	111 (84.7%)	20 (15.3%)	0.567	104 (79.4%)	27 (20.6%)	0.495	88 (67.2%)	43 (32.8%)	>0.999	127 (96.9%)	4 (3.1%)	0.020
≥40 mm	64 (81.0%)	15 (19.0%)		59 (74.7%)	20 (25.3%)		53 (67.1%)	26 (32.9%)		70 (88.6%)	9 (11.4%)	
Height-dural attachment ratio												
<0.77	97 (84.3%)	18 (15.7%)	0.709	91 (79.1%)	24 (20.9%)	0.738	77 (67.0%)	38 (33%)	0.882	111 (96.5%)	4 (3.5%)	0.084
≥0.77	75 (81.5%)	17 (18.5%)		71 (77.2%)	21 (22.8%)		63 (68.5%)	29 (31.5%)		83 (90.2%)	9 (9.8%)	
Resection												
Gross total	112 (84.8%)	20 (15.2%)	0.575	98 (74.2%)	34 (25.8%)	0.243	88 (66.7%)	44 (33.3%)	>0.999	122 (92.4%)	10 (7.6%)	0.379
Subtotal	68 (81.9%)	15 (18.1%)		68 (81.9%)	15 (18.1%)		56 (67.5%)	27 (32.5%)		80 (96.4%)	3 (3.6%)	
WHO grade												
I	179 (85.2%)	31 (14.8%)	0.003	165 (78.9%)	45 (21.4%)	0.010	144 (68.6%)	66 (31.4%)	0.004	196 (95.1%)	10 (4.9%)	0.002
II/III	1 (20%)	4 (80%)		1 (20%)	4 (80%)		0 (0.0%)	5 (100%)		2 (40.0%)	3 (60.0%)	
Ki67												
<5%	144 (86.7%)	22 (13.3%)	0.045									
≥5%	36 (73.5%)	13 (26.5%)										

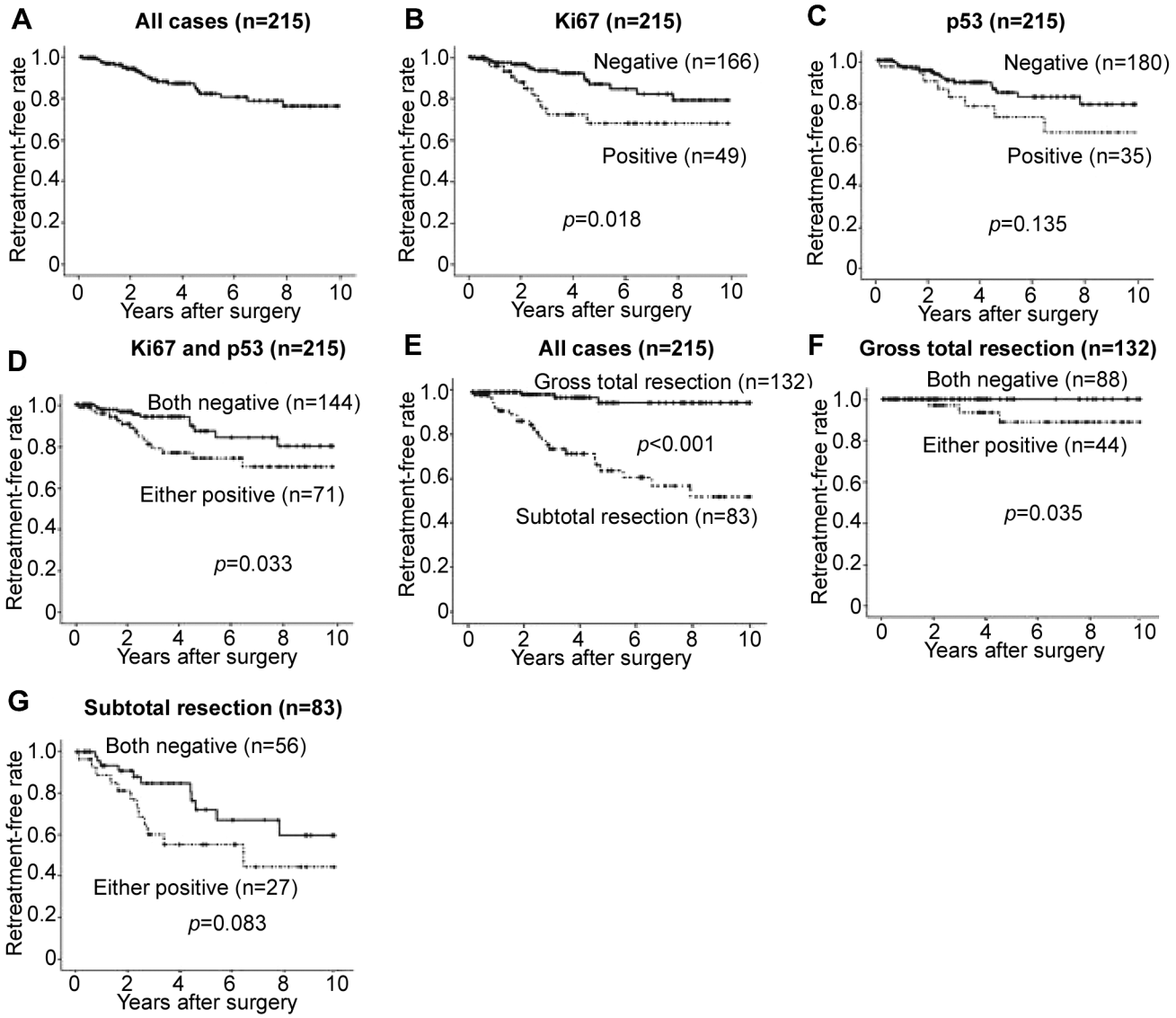

Figure 2. *Kaplan–Meier curve for retreatment-free survival in patients with meningioma. A: Retreatment-free survival for the whole cohort of 215 patients with meningioma. B: Retreatment-free survival according to Ki67 expression. Survival was significantly worse for Ki67-positive than for Ki67-negative cases (p=0.018). C: Retreatment-free survival according to p53 expression. Survival did not differ significantly between p53-positive and p53-negative cases (p=0.135). D: Retreatment-free survival according to Ki67 and p53 expression. Retreatment-free survival for patients with positivity for either Ki67 or p53 was significantly worse than that for patients with negativity for both Ki67 and p53 (p=0.033). E: Retreatment-free survival according to type of resection. Survival was significantly worse in cases which underwent gross total resection (n=132) rather than subtotal resection (n=83) (p<0.001). F: Retreatment-free survival according to Ki67 and p53 expression in patients after gross total resection. Positivity for either Ki67 or p53 was significantly associated with retreatment for meningioma (p=0.035). G: Retreatment-free survival according to Ki67 and p53 expression in patients after subtotal resection. Ki67- and p53 status were not significantly associated with retreatment (p=0.083).*

resection ($p<0.001$) and positivity for either p53 or Ki67 ($p<0.001$) were significantly associated with retreatment for meningioma.

Accuracy of Ki67 and p53 relative to retreatment for meningioma after initial surgery. Sensitivity, specificity for estimating retreatment after initial surgery for meningioma are shown in Table IV. Ki67 alone and p53 alone predicted retreatment at relatively high specificity (0.80 and 0.85) after initial surgery of meningioma but low sensitivity (0.42 and 0.30). On the other hand, positivity for either p53 or Ki67 predicted retreatment at high specificity and specificity

Table III. *Univariate and multivariate correlations between clinicopathological parameters and retreatment.*

Variable	Comparison	Risk ratio	95% CI	*p*-Value	Risk ratio	95% CI	*p*-Value
Age	<50 *versus* ≥50 years	2.445	1.223-4.889	0.016	2.686	0.985-7.323	0.053
Gender	Male *versus* female	1.452	0.704-2.992	0.364			
Dural attachment	<40 mm *versus* ≥40 mm	0.398	0.200	0.014	0.453	0.168-1.223	0.118
Height from dural attachment	<25 mm *versus* ≥25 mm	0.678	0.336-1.368	0.295			
Max. tumor diameter	<40 mm *versus* ≥40 mm	0.482	0.238-0.977	0.054			
Height-dural attachment ratio	<0.77 *versus* ≥0.77	1.360	0.654-2.826	0.534			
Resection	Gross total *versus* subtotal	0.109	0.39-0.305	<0.001	0.076	0.024-0.248	<0.001
WHO classification	Grade I *versus* grade II/III	0.619	0.103-3.706	0.492			
p53 and Ki67 expression	Both negative *versus* either positive	0.339	0.166-0.692	0.004	0.165	0.060-0.454	<0.001

(sensitivity=0.57, specificity=0.70) after initial surgery for meningioma.

Discussion

Since around 5% of meningiomas reportedly recur after total resection (5, 30), long-term follow-up is performed even after total resection. Useful markers to predict meningioma regrowth are desired but none have yet become clinically available. Recently, it was reported that DNA methylation profiling (32, 33) or *TERT* gene alternations (32, 33) might be predictive markers for the recurrence of meningioma. However, the examination of DNA methylation profiling or *TERT* gene alternations would only be possible at a limited number of institutions. This study aimed to identify a useful predictive marker(s) for the postoperative recurrence of meningioma. We included a total of 215 patients who underwent initial resection of meningioma at Osaka City University in this study.

According to the fourth edition of the WHO Classification of Tumors of the Central Nervous System, meningiomas are classified by morphological features of mitotic cells and atypical pathological features (2). The atypical features are significantly associated with recurrence and Ki67-LI (4). In this study, p53 expression correlated significantly with a high Ki67-LI. A previous study reported that p53 plays a role in tumor progression by regulating the cell cycle, with which Ki67 is also associated (22). In fact, our study showed that p53 expression correlated significantly with WHO grade II/III. A positive correlation has been reported between p53 and high WHO histological grade (21, 28). Expression of p53 protein was found in 10.8% of benign meningiomas, 50% of atypical meningiomas, and 77% of anaplastic meningiomas (17). These findings suggest that p53 expression correlates closely with a high degree of meningioma anaplasia. Expression of p53 may be related to these atypical features leading to malignant characteristics. As a result, p53 might be closely associated with high regrowth activity of meningioma cells.

Table IV. *Accuracy of Ki67 and p53 tests relative to retreatment after initial surgery for meningioma.*

Variable	Sensitivity	Specificity
Ki67-positive	0.42	0.80
p53-positive	0.3	0.85
Both Ki67- and p53-positive	0.15	0.95
Either Ki67- or p53-positive	0.57	0.70

Previous reports have associated p53 reactivity with recurrent meningioma (16, 34). Our results indicated that p53 is associated with meningioma recurrence, even in cases of benign meningioma. Univariate analysis of retreatment for meningioma found that retreatment for meningioma correlated with p53-positive status, age <50 years, greater tumor size, subtotal resection, and p53- or Ki67-positive status. Multivariate logistic regression analysis indicated that p53-positive status, gross total resection and positive Ki67-LI were significantly associated with retreatment for meningioma. Since the gross total resection rate was closely associated with meningioma recurrence, we evaluated predictive factors related to retreatment for meningioma after gross total resection. Kaplan–Meier curves for retreatment-free survival showed that positivity for Ki67 or p53 was significantly associated with retreatment in patients with gross total resection, while no significant association with retreatment was found in patients with subtotal resection. These findings suggested that the combination of p53 and Ki67 might provide a promising predictive marker for postoperative recurrence in meningioma after total resection, while recurrence after total resection is relatively rare (5).

Next, we compared the accuracy of Ki67 and p53 in predicting retreatment for meningioma after initial surgery. The sensitivity of the combination with Ki67 was higher than those of p53 alone or Ki67 alone. These findings support the notion that the combination of Ki67 and p53 might provide a useful predictive factor for recurrence after gross total resection.

Our study has a limitation, as follows. In this study, the retreatment-free-survival was evaluated, but the recurrence-free-survival was not. Since the timing of treatment against recurrence differs among the location of meningioma or patient background, it might be better to evaluate the recurrences. However, no standardized definition of recurrence of meningioma was established so far. It will be necessary to establish the definition of recurrence of meningioma in future.

In conclusion, p53 expression might represent a useful predictive marker for recurrence of meningioma, especially in patients treated by gross total resection.

Conflicts of Interest

The Authors have no financial or other interests with regard to this article that might be construed as a conflict of interest.

Authors' Contributions

N.A. performed the experiments of this study, interpreted the data and wrote the article; Y.M., designed the experiments of this study, interpreted the data and edited the article; K.T., contributed to the immunohistochemical analysis; M.H., N.K., U.T., I.T., T.T., O.K., and G.T collected the meningioma specimen; G.T. helped draft the article.

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