The Ki-67 Proliferation Index as a Marker of Time to Recurrence in Intracranial Meningioma

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BACKGROUND: There are examples of incongruence between the WHO grade and clinical course in meningioma patients. This incongruence between WHO grade and recurrence has led to search for other prognostic histological markers.

OBJECTIVE: To study the correlation between the Ki-67 proliferative index (PI), risk of recurrence, and recurrence rates in meningioma patients.

METHODS: We prospectively collected pathological diagnosis of de novo consecutive meningiomas. In total, we followed 159 patients with clinical controls until recurrence, death, or emigration. We estimated the correlation between risk of recurrence and Ki-67 PI when adjusted for age at diagnosis, sex, WHO grade, extent of surgical resection, and tumor location. We estimated the cumulative incidence of recurrence when considering death without recurrence a competing risk. We report recurrence rates per 100 person-years.

RESULTS: A 1%-point increase of Ki-67 PI yielded a hazard ratio of 1.12 (95% CI: 1.01-1.24) in a multivariate analysis. The cumulative incidence of recurrence was 3% for Ki-67 0% to 4% vs 19% for Ki-67 $>$ 4% meningiomas after 1 yr, but 24% vs 35%, respectively, after 10 yr. There was no significant difference in mean Ki-67 PI between nonrecurrent and recurrent meningioma in a 2-sample *t*-test ($P = .08$). The strongest relationship was detected between Ki-67 PI and time to recurrence: Ki-67 $<$ 4% meningiomas recurred after median 4.8 yr, compared to 0.60 to 0.75 yr for patients with higher Ki-67 PI.

CONCLUSION: Ki-67 PI was a marker for time to recurrence rather than a predictor of recurrence. Ki-67 PI may be utilized for patient tailored follow-up.

KEY WORDS: Ki-67, Meningioma, Recurrence, Proliferative index, Brain tumor

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Meningiomas are the commonest intracranial neoplasms.[1] In clinical series, nonskull base location, male gender, Simpson grade, and peritumoral edema are predictors for recurrence.[2,3] Meningiomas are classified accordingly to the WHO gradings, which is based on the number of mitoses per 10 high-power field along with other subjective criteria.[4] Low-grade meningiomas (WHO-I) primarily display benign behavior, whereas high-grade meningiomas (WHO-II and WHO-III) have higher rates of recurrence and shorter survival.[4] There are examples of incongruence between the WHO grade and clinical course, in which low-grade meningiomas had a worse recurrence-free survival than higher-grade meningiomas[5,6] This incongruence and poor discrimination between WHO grades in relation to recurrence has led to search for other prognostic histological markers.[7]

ABBREVIATIONS: GTR, gross total resection; **PI,** proliferative index; **SD,** standard deviation; **STR,** subtotal resection

The nuclear antigen Ki-67 is expressed by proliferating cells. The MIB-1 antibody detects an epitope on the Ki-67 antigen, which is expressed during the cell cycle but is absent in the quiescent G_0 state. The percentage of immunoreactive meningioma cell nuclei is referred to as the Ki-67 proliferative index (Ki-67 PI). Ki-67 PI is considered a surrogate marker for recurrences and aggressive clinical behavior.[8] Moreover, the Ki-67 PI is frequently employed to dichotomize high and low risks for recurrence, which imply a discrete cutoff value discriminating higher and lower risk.[9] The results from this large review tentatively proposed that 4% may convey such a cutoff.[9]

It is generally accepted that the Ki-67 PI correlates to recurrence, but the belief is not based on consecutive, population-based data with a long-term follow-up. In fact, previous literature is contradictory; several studies report a correlation,[9-11] whereas other studies reject a correlation.[5,12-14] Finally, a third set of studies fail to detect significant differences between the Ki-67 PI of nonrecurrent and recurrent meningiomas.[15-17] Taken together, the prognostic implications of Ki-67 PI remain unestablished, and there is a lack of data from consecutive clinical series with long-term follow-up.

We intended to corroborate (1) if Ki-67 PI is a biomarker for recurrence in a cohort of consecutive meningioma patients with long-term follow-up, and (2) if cutoff values, such as 4%, in fact discriminate between high- and low-risk meningioma patients.

METHODS

Patients and Follow-up

We prospectively collected the pathological diagnosis per the 2007 WHO classification and immunohistochemistry results of 159 consecutive de novo intracranial meningiomas (ICD 10: DD320, intracranial meningioma) surgically removed at the Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden, between January 1, 2005, and April 30, 2008, by the senior author (T.M.).[18] The same senior pathologist (A.O.) evaluated all tumor samples. The cohort has been published in a survey of immunohistochemical markers.[18]

After surgery, the senior author followed the patients with regular visits in the outpatient clinic and MRI examinations at 3 mo and 1, 2, 3, 5, 7, and 10 yr after surgery. We collected data prospectively and followed the 159 patients until recurrence, death, or for a minimum of 10 yr. We lost 2 patients to follow-up, as they emigrated from Sweden, and were methodically right censored. We stored data in a manual patient registry and preserved patient data in clinical charts, which were recovered at each patient follow-up.

We applied antibodies for immunohistochemistry staining (product: "M7240, Ki-67 Antigen"; from supplier: Dako Denmark A/S). The study obtained approval by the regional ethical committee in Stockholm, Sweden (EPN Stockholm), with reference number 2017/1760-31/1. By the ethical committee, it was not required to obtain patient consent.

Classification

We constructed groups composed of different Ki-67 PI intervals: first, we constructed Ki-67 PI subgroups that comprise ascending percentages as follows: Ki-67 0% to 4%, Ki-67 5% to 9%, and Ki-67 $\geq$ 10% meningiomas, which corresponded to a Ki-67 PI ranging from 0% to 4%, from 5% to 9%, and $\geq$10%, respectively; and second, we dichotomized 2 groups based on the median Ki-67 PI of 4% and to corroborate previous suggestions of this cutoff value.[9] Thus, we included Ki-67 0% to 4% vs Ki-67 > 4% meningiomas for subgroup analysis.

Statistical Analysis

We computed a model that predicts the correlation between risk of recurrence and Ki-67 PI when adjusted to age at diagnosis, sex, WHO grade, location, and extent of surgical resection. Two patients received radiosurgery after subtotal removal of a meningioma; we did not correct for this variable because a preliminary sensitivity analysis (not shown) indicated negligible impact.

We tested nonlinear effects for the continuous covariates Ki-67 PI and age at diagnosis with restricted cubic splines and found that that a linear relationship was adequate in both cases. We defined the extent of surgical resection according to the EANO guidelines: gross total resection (abbreviated GTR and corresponding to Simpsons grades I-III) and subtotal resection (abbreviated STR and corresponding to Simpsons grade IV).[19]

In addition, we applied a Cox regression analysis including the beforementioned covariates. We reported first, univariate estimates; and second, the multivariate estimates, which was adjusted to the covariates as described above.

We used time since diagnosis as underlying time scale. End of follow-up was either the date of death or date of loss to follow-up or end of study, whichever came first. We evaluated the assumption of proportionality by inspection of Schoenfeld residuals and found all covariate effects to be proportional.

We estimated the cumulative incidence of recurrence for the entire cohort and for the subgroups Ki-67 0% to 4% vs Ki-67 > 4% meningiomas. We considered death without recurrence a competing risk and applied the Aalen-Johansen method to estimate the cumulative incidence and Gray's[21] test to compare the curves.[20,21]

We estimated recurrence rates per 100 person-years for the subgroups Ki-67 0% to 4%, Ki-67 5% to 9%, and Ki-67 $\geq$ 10% meningiomas and compared them as recurrence rate ratios. We applied a likelihood ratio test (chi-squared) to test whether the effect of Ki-67 PI on recurrence was modified by (1) age at diagnosis or (2) WHO grade. We considered *P*-values below .05 significant.

We performed all analyses in R version 3.6.0[22] (The R Project for Statistical Computing) with the packages "rms," "etm," and "survival."[23-25] We visualized data using ggplot2 and metafor.[26,27]

RESULTS

We followed the cohort for 1173 person-years, with a median radiological follow-up of 7 yr (range: 0-10 yr). Radiological follow-up comprised time since diagnosis to recurrence, death, emigration, or termination of patient follow-up after 10 yr. The female (n = 126, 79%) to male (n = 33) ratio was 3.82. The median age at diagnosis was 57 yr (range: 19-88). Of the 159 patients, a total of 142 (89%), 16 (10%), and 1 (<1%) had a WHO-I, -II, and -III meningioma, respectively. The Ki-67 PI ranged between 0% and 25%. The tumor location was at the anterior skull base in 36% (n = 57) of the cases, the posterior skull base in 18% (n = 29) of the cases, and nonskull base in 46% (n = 73) of the cases. There were 127 (80%) GTR and 32 STR.

In total, 29 patients (18%) of the 159 de novo meningioma experienced a recurrence. The median time to recurrence was 38.5 mo (range: 2-124 mo). We listed cohort characteristics in Table 1.

WHO Gradings and Distribution of Ki-67 PI

We visualized and listed the frequency of each individual Ki-67 PI and its prevalence stratified for WHO grades in Figure 1 and Table 2, respectively.

TABLE 1. Patient and Meningioma Characteristics

	Total, n = 159 (100%)	WHO-I (n = 142)	WHO-II (n = 16)	WHO-III (n = 1)
Male	33 (21%)	29 (20%)	4 (25%)	0
Female	126 (79%)	113 (80%)	12 (75%)	1 (100%)
Mean age (±SD)	56 (±13)	55 (±13)	60 (±13)	72 (±NA)
Mean Ki-67 PI (±SD)	4.7% (±3.8)	4.0% (±2.7)	9.3% (±6.2)	20% (±NA)
Ki-67 (0-4%)	108 (68%)	105 (74%)	3 (19%)	0
Ki-67 (5-9%)	34 (21%)	28 (20%)	6 (38%)	0
Ki-67 (≥10%)	17 (11%)	9 (6%)	7 (44%)	1 (100%)
Gross total resection	127 (80%)	112 (79%)	14 (88%)	1 (100%)
Subtotal resection	32 (20%)	30 (21%)	2 (12%)	0
Anterior skull base	57 (36%)	52 (37%)	5 (31%)	0
Posterior skull base	29 (18%)	27 (19%)	2 (13%)	0
Non-skull base	73 (46%)	63 (44%)	9 (56%)	1 (100%)

SD: standard deviation. NA: Not available.

TABLE 2. Frequency of the Ki67 Proliferative Index Among the Different WHO Grades

	Ki-67 (0%-4%)	Ki-67 (5%-9%)	Ki-67 (≥10%)	Total
WHO-I	105	28	9	142
WHO-II	3	6	7	16
WHO-III	0	0	1	1
Total	108	34	17	159

The mean Ki-67 PI of 4.0% (standard deviation [SD]: 2.7) and 9.3% (SD: 6.2) in WHO-I (range: 0-20) and WHO-II (range: 2-25) meningiomas, respectively, was significantly different in a 2-sample *t*-test ($P = .005$) (Figure 1). The single case of WHO III had a Ki-67 PI of 20% and recurred after 2 mo.

Recurrence-Free Survival

We adjusted a prediction model (age at diagnosis, sex, WHO grade, location, extent of surgical resection). The model predicts the correlation between recurrence and the Ki-67 PI (Figure 2). We chose the median Ki-67 PI of 4.0% as reference (equivalent to a hazard ratio equal to 1), meaning that all Ki-67 PI values must be interpreted in reference to 4.0%. We observed that increasing the Ki-67 PI yielded a correspondingly higher risk of recurrence. We noted that the confidence bands became very wide toward higher indices because of the decreasing number of patients with high Ki-67 PI.

Cox Regression Analysis

In the univariate model, the effect of the Ki-67 PI, WHO grade, and extent of surgical resection was significantly associated to recurrence. The hazard ratio was 1.14 (95% CI: 1.06-1.22, $P = .0004$) for 1%-point increase of the Ki-67 PI, meaning that risk of recurrence increased by 14% per 1%-point increase of Ki-67 PI. With WHO-I as reference, WHO-II had a hazard ratio of 2.89 (95% CI: 1.10-7.63). The one case of WHO-III was omitted from the model. The hazard ratio was 2.25 (95% CI:

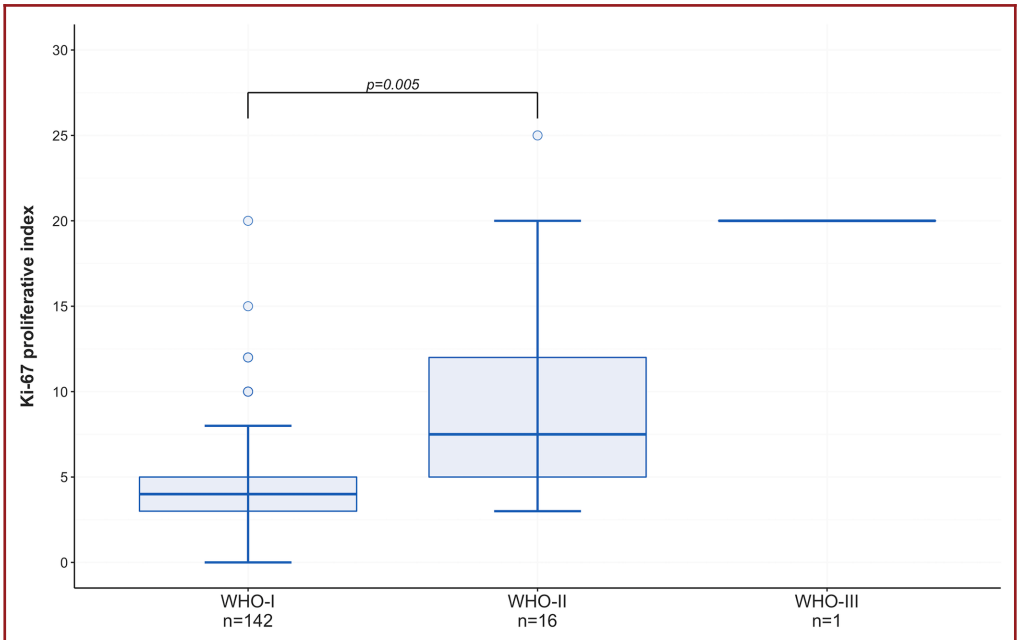

FIGURE 1. *The frequency of Ki-67 PI among WHO-I, -II, and -III meningiomas.*

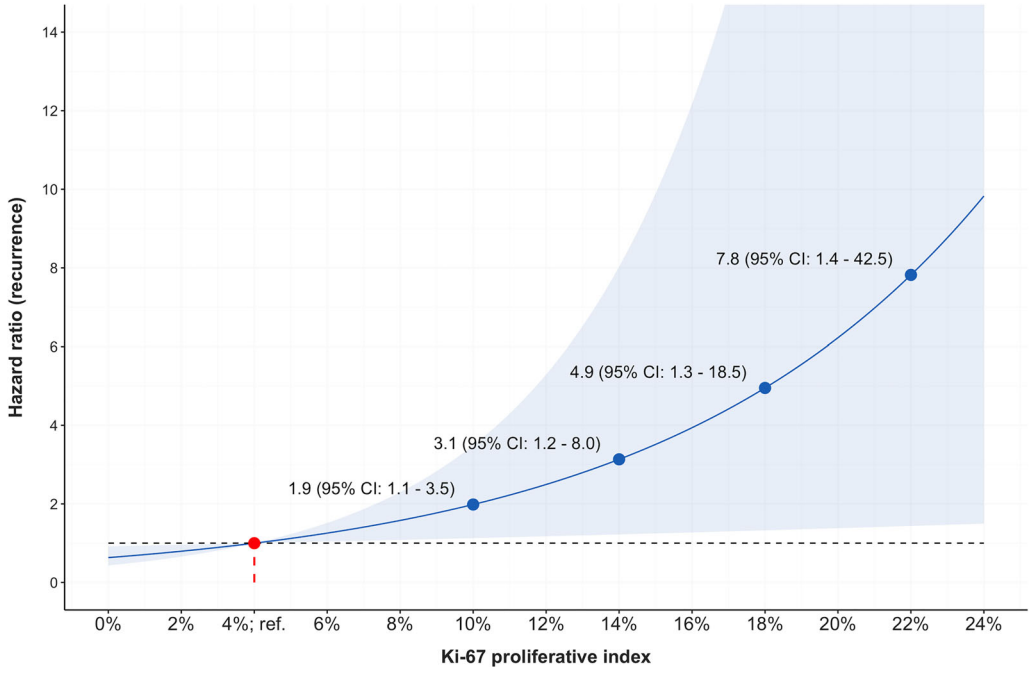

FIGURE 2. *The correlation between the Ki-67 proliferative index and recurrence. We adjusted the model to age, sex, WHO grade, location, extent of resection.*

TABLE 3. Unadjusted and Adjusted Cox Regression Analysis: Recurrence-Free Survival

	Univariate		Multivariate	
Covariate	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age at diagnosis, per 5-yr increase	1.07 (0.93-1.23)	.3	1.10 (0.94-1.29)	.2
Female	Ref	Ref	Ref	Ref
Male	0.98 (0.40-2.41)	1.0	0.93 (0.35-2.43)	.9
WHO-I	Ref	Ref	Ref	Ref
WHO-II	2.89 (1.10-7.63)	.03	1.88 (0.54-6.49)	.3
WHO-III	NA	NA	NA	NA
Ki-67, per 1%-point increase	1.14 (1.06-1.22)	.0004	1.12 (1.01-1.24)	.03
Anterior skull base	Ref	Ref	Ref	Ref
Posterior skull base	1.08 (0.36-3.24)	.9	0.87 (0.28-2.70)	.8
Nonskull base	1.34 (0.59-3.06)	.5	1.00 (0.43-2.32)	1.0
Gross total resection	Ref	Ref	Ref	Ref
Subtotal resection	2.25 (1.04-4.84)	.04	3.54 (1.49-8.43)	.004

1.04-4.84, $P = .04$) for STR, with GTR as reference. The effect of age at diagnosis, sex, and location on recurrence was not significant (Table 3).

In the multivariate model, the effect of the Ki-67 PI and extent of surgical resection was significantly associated to recurrence. A 1%-point increase of Ki-67 PI yielded a hazard ratio of 1.12 (95% CI: 1.01-1.24, $P = .03$), meaning that the risk of recurrence increased by 12% per 1%-point increase of Ki-67 PI. With GTR as reference, STR had a hazard ratio of 3.54 (95% CI: 1.49-8.43, $P = .004$). The effect of age at diagnosis, sex, WHO grade, and location on recurrence was not significant (Table 3).

We estimated the cumulative incidence of recurrence when considering death without recurrence a competing risk. We compared the 2 subgroups of Ki-67 0% to 4% vs Ki-67 > 4% meningiomas. We observed that the cumulative incidence of recurrence was slightly significant (Gray's[21] test, $P = .04$) (Figure 3). We noted that the curve was much steeper for

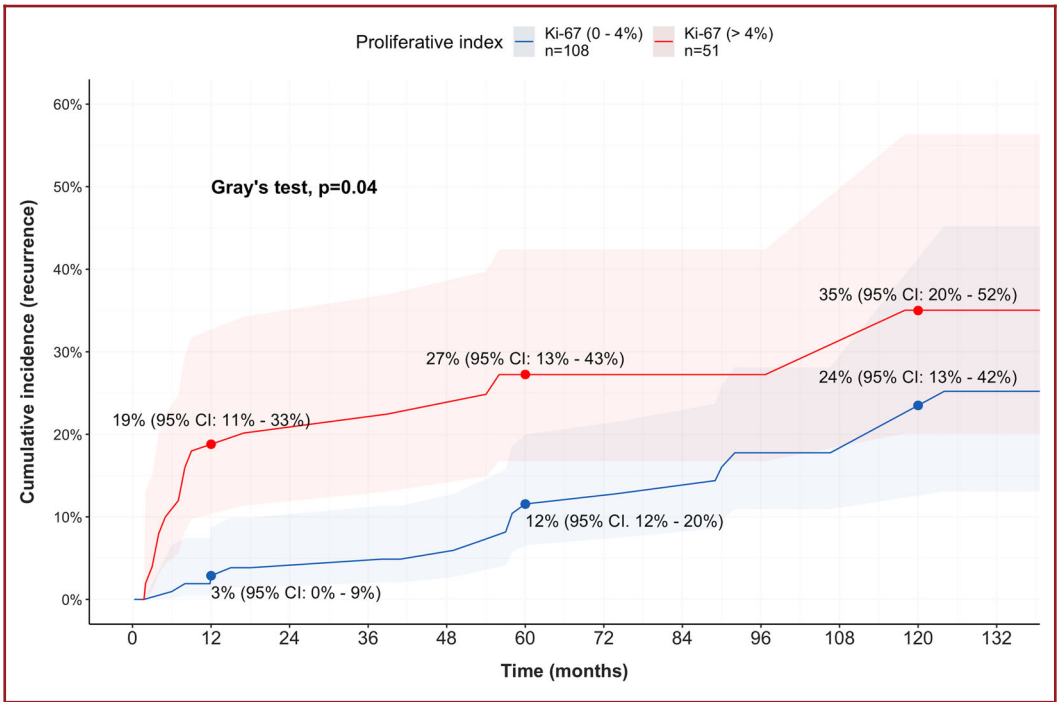

FIGURE 3. *Cumulative incidence for recurrence for Ki-67 (0%-4%) vs Ki-67 (>4%) when considering death without recurrence as a competing risk.*

Ki-67 > 4% than Ki-67 0% to 4% meningiomas during the initial 1 yr. Thus, the 1-yr cumulative incidence of recurrence was 19% (95% CI: 11-33) for Ki-67 > 4% vs 3% (95% CI: 0-9) for Ki-67 0% to 4% meningiomas. However, the 10-yr cumulative incidence of recurrence was 35% (95% CI: 20-52) vs 24% (95% CI: 13-42), respectively. Based on the confidence bands, the cumulative incidence of recurrence was significantly different after 1 yr which was reduced after 10-yr follow-up. This indicates that Ki-67 PI might correlate better to time to recurrence rather than predicting recurrence in a long-term follow-up (Figure 3).

There were no significant interactions between the Ki-67 PI and (1) age at diagnosis (chi-sq., $P = .26$) or (2) WHO grade (chi-sq., $P = .91$), meaning that the effect of the Ki-67 PI was not modified by (1) age at diagnosis or (2) WHO grade.

Recurrence Rates

Recurrence was most likely to occur between 3 and 7 yr after surgery for the Ki-67 0% to 4% meningiomas (median: 4.8 yr), during the first 2 yr after surgery for the Ki-67 5% to 9% meningiomas (median: 0.75 yr), and within the first year for the Ki-67 ≥ 10% meningiomas (median: 0.60 yr) (Figure 4).

In total, there occurred 16/108 (15%), 8/34 (24%), and 5/17 (29%) recurrences during follow-up for Ki-67 0% to 4%, Ki-67 5% to 9%, and Ki-67 ≥ 10% meningiomas, respectively. We followed the recurrent meningioma patients (n = 29) for 253 person-years.

We estimated recurrence rates as recurrences per 100 person-years for each Ki-67 meningioma subgroup. We observed that meningiomas with the lowest Ki-67 PI associated to the lowest recurrence rate, ie, recurrences per time unit, again indicating the correlation to time. We found that Ki-67 0% to 4%, Ki-67 5% to 9%, and Ki-67 ≥ 10% meningiomas had 2.4, 4.9, and 9.7 recurrences per 100 person-years, respectively (Figure 5A).

Subsequently, we compared recurrence rates between beforementioned subgroups as ratios. We also included Ki-67 0% to 4% vs Ki-67 > 4% meningiomas for this analysis. The recurrence rate was significantly 75% lower (95% CI: 37-90, $P = .003$) in Ki-67 0% to 4% compared with Ki-67 ≥ 10% meningiomas. Similarly, the recurrence rate was significantly 62% lower (95% CI: 22-81, $P = .009$) in Ki-67 0% to 4% compared with Ki-67 > 4% meningiomas. There was no significant difference between Ki-67 0% to 4% vs Ki-67 5% to 9% meningiomas or Ki-67 5% to 9% meningiomas vs Ki-67 ≥ 10% meningiomas (Figure 5B).

Recurrent vs Nonrecurrent Meningioma

We followed nonrecurrent meningiomas (n = 129) for 920 person-years, which comprised 118 WHO-I and 11 WHO-II meningioma patients with Ki-67 PI ranging from 0% up to 25% (mean 4.3%, SD: 3.3). We visualized the Ki-67 PI in nonrecurrent vs recurrent meningioma for the individual WHO grades and for all WHO grades combined (Figure 6).

We found that the mean Ki-67 PI of 4.4% in nonrecurrent meningiomas was not significantly different from the mean 6.0%

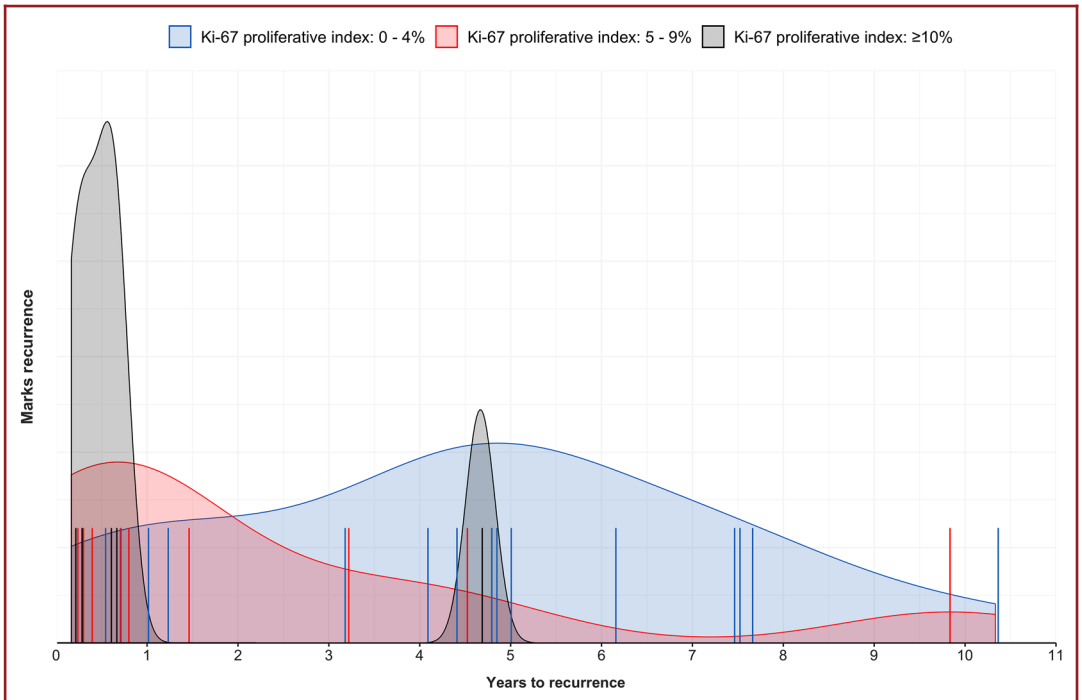

FIGURE 4. *A histogram of the 3 Ki-67 subgroups plotted with density lines.*

Ki-67 PI in recurrent meningioma (*t*-test, $P = .08$). Similarly, nonrecurrent vs recurrent WHO-I demonstrated a mean Ki-67 PI of 3.9% and 4.5%, respectively, which was not significantly different (*t*-test, $P = .4$). Further, nonrecurrent vs recurrent WHO-II demonstrated a mean Ki-67 PI of 8.6% and 10.6%, respectively, which too was not significantly different (*t*-test, $P = .6$) (Figure 6).

DISCUSSION

We did find a correlation between Ki-67 PI and recurrence in this prospective, long-term, consecutive series on the Ki-67 PI, but could not confirm it as a suitable biomarker to predict recurrence.

The effect of increasing Ki-67 PI correlated to an increased risk of recurrence in the multivariate analysis; however, we did not find any significant difference in the Ki-67 PI between nonrecurrent and recurrent when stratifying for WHO grade, which complicates translation into clinical practice and thus its utilization.

Instead, we found a particularly strong correlation between Ki-67 PI and time to recurrence: first, the cumulative incidence of recurrence differed significantly at the 1-yr follow-up for the dichotomized group at 4%, but was reduced at the 10-yr follow-up; and second, the median time to recurrence differed extensively at 4.8, 0.75, and 0.60 yr for Ki-67 0% to 4%, Ki-67 5% to 9%, and Ki-67 $\geq$ 10% meningiomas, respectively.

The most precise description of extent of resection is the Simpson classification.[28] Tumor progression is the rule after subtotal (Simpson grade IV) resection.[28-31] Yet, long-term meningioma follow-up shows substantial recurrence following presumed Simpson grade I resection, indicating that small amounts of tumor may remain even after presumed complete resection.[29-31] Previously, we have found that only 41% of patients with presumed Simpson grade I surgery of parasagittal meningiomas in fact had free resection margins.[31]

Strength and Limitations

One important strength is that we collected data consecutively at a single center and followed the patients comprehensively. This approach ensures a validated, long-term-followed cohort with limited possible bias from lost to follow-up and selection of patients from available specimens. We successfully adjusted for several important parameters such as extent of surgical resection. The strength of a comprehensive long-term follow-up must be weighed against the limitation of having a relatively limited cohort; thus, it is probable that a larger cohort would have allowed detection of additional statistical associations, eg, most cases had relatively low Ki-67 PI. Therefore, we observed increasingly broad confidence bands toward higher Ki-67 PI. This limitation induces an increasing uncertainty for effect size estimates of higher Ki-67 PI, which correlates directly to the small sample size comprising high Ki-67 PI. The limited cohort restricted the numbers of categories for statistically meaningful analysis of the extent of resection. Simpson grade carries more prognostic information than the EANO GTR/STR definition.[18,19] Because of

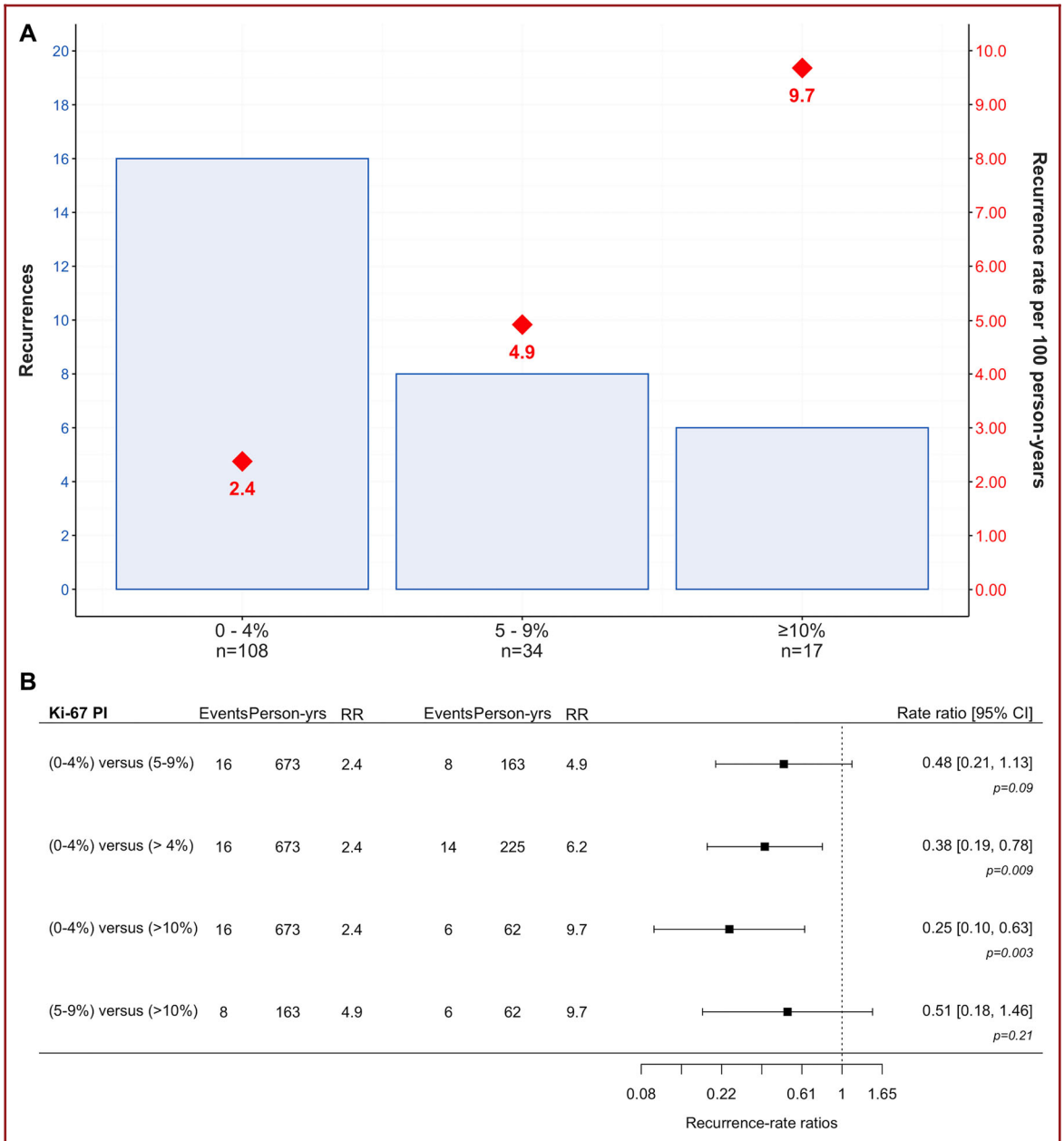

FIGURE 5. **A**, *Recurrence rates for each Ki-67 subgroup. The recurrence rate was calculated as recurrences per 100 person-years.* **B**, *Recurrence rate ratios for different Ki-67 subgroup comparisons. RR: recurrence rate per 100 person-years. PI: proliferative index.*

the limited sample size, a dichotomized group of patients yielded 2 finer proportioned groups and subsequent conclusive results compared with results of 4 relatively disproportioned Simpson grade subgroups.

Diagnostic criteria for WHO classification have evolved since we started the study, and WHO-II meningiomas is a wider class with the 2016 classification in comparison with the 2007 edition; however, in this context, the updated WHO classification would not alter these presented results. This was because the single histopathological finding that would lead to grade migration to WHO-II is "brain invasion," a feature that was not detected in any of our WHO-I meningiomas.

Ki-67 PI and Cutoff Values?

An emerging, but essential, question is whether a Ki-67 PI cutoff value would convey legitimate risk stratification of meningioma patients? Numerous investigators have attempted such dichotomization, and the intention seems to utilize Ki-67 PI to

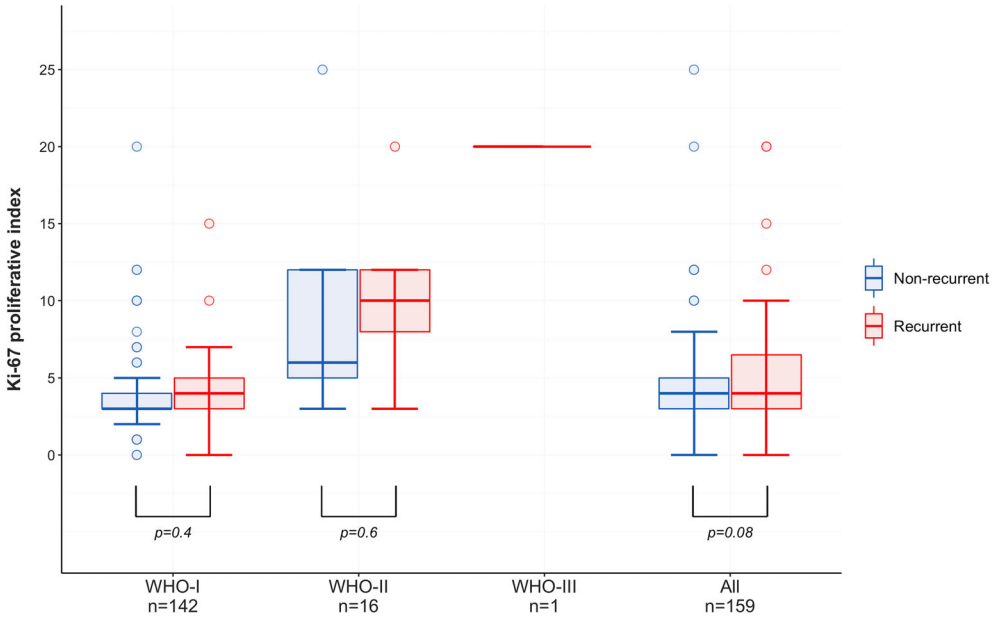

FIGURE 6. *Distribution of the Ki-67 proliferative indices in recurrent vs non-recurrent meningioma.*

stratify the meningioma population into "high-" or "low-risk" groups by a predetermined cutoff value.

A large systematic review of 53 articles published up to 2010 concluded that Ki-67 PI correlated to the meningioma grade.[9] Of 53 papers, 21 addressed or suggested a specific cutoff value for Ki-67 PI, and a Ki-67 PI cutoff at 4% was suggested to differentiate between high and low risk by the authors. Subsequently, we applied the dichotomization based on the 4% cutoff but did not find the expected differences between high and low risk. The specific 10-yr cumulative incidence of recurrence was not different between the dichotomized groups; in fact, the cumulative incidence of recurrence was barely significantly different in a time span of 10 yr. Contrarily, the 1- and 5-yr cumulative incidences of recurrence were significantly different between the dichotomized groups. Hence, a short patient follow-up terminated at 5 yr would erroneously have confirmed that 4% potentially was a legitimate cutoff for risk stratification. Importantly, this emphasizes that time to recurence must be realiasticlly considered to avoid type-II errors and bias from differetial growth rate in different meningioma tumors. Ki-67 PI may legitimately convey such a metric.

We subsequently applied 3 Ki-67 PI categories of 0% to 4%, 5% to 9%, and ≥10%, which we considered arbitrary in relation to our hypotheses. They were chosen for practical reasons in relation to statistical modeling. The Ki-67 PI categories represent proportioned groups of ascending Ki-67 percentages, which were suitable for the statistical analysis.

Retrospective dichotomized analyses of continuous variables carry a high risk of overestimation and confounding with subsequent problems of reproducibility and have been discouraged in biostatistical literature.[32-35] Any cutoff values for continuous covariates based on a given set of data are universally applicable only if future patients are assumed to display an exactly identical clinical course as the patients on which the dichotomization was established. Cutoff values for dichotomization of a population are human constructs, typically for pragmatic treatment algorithms, which may not be equivalently suitable or appropriate for all continuous covariates. We believe that is the case for the Ki-67 PI.

Implications on Clinical Practice and Future Research

Our findings add to the mounting literature of conflicting conclusions regarding Ki-67 PI and its correlation to recurrence. We suggested that some of the confusion may reflect bias that may have been introduced into series in which selection criteria may have included availability of samples, in which clinical continuity and information has been lacking and in which patients have been lost to follow-up for unknown reasons. We did not find that the Ki-67 PI is an appropriate predictor of recurrence but found a strong relation to time to recurrence. Hence, much of the previous conflicting findings may have reflected that analyses have failed to consider the impact of residual tumor after resection and the need to have a long-term follow-up that would allow small residual volumes of slowly growing tumors to become detectable. Follow-up of meningioma patients can be better tailored with the knowledge that slowly growing tumors need to have a longer follow-up than more rapidly growing tumors. Moreover, a better distinction than GTR or STR would allow further stratification of risk for recurrence.

Our findings reflect a small cohort, but it is clear that recurrences must be viewed as a consequence of 2 variables: first, surgical-related factors, ie, residual tumor cells; and second, growth rate determined by intrinsic tumor properties. For growth rate, Ki-67 PI is useful, but more comprehensive surrogate markers for growth might become available with proteomics, genome-wide sequencing, and methylation analyses.[36]

CONCLUSION

We did not find Ki-67 PI an appropriate predictor for recurrence. Our comprehensive, long-term follow-up indicated that the Ki-67 PI is a marker for when a recurrence is likely to occur and not if a meningioma will recur. Long-term strategy of follow-up needs to consider (1) extent of resection and (2) growth rate. Our analyses indicated that Ki-67 PI reflected growth rate well. We do not support dichotomization of Ki-67 PI to define risk groups for recurrence.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors' study adds an important nuance to the interpretation of the Ki-67 labeling index as it applies to meningioma. Their novel finding is that the Ki-67 labeling index, rather than predicting the occurrence of a recurrence is more an indicator of time to recurrence, with lower indices predicting a longer time to recurrence. The Ki-67 data needs to be used in conjunction with the extent of resection, which is the primary driver of the likelihood of recurrence. This study has significant clinical implications as it can help in guiding the need, frequency, and duration of clinical and radiological follow-up of patients following resection of their meningioma.

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