Value of K_i-67 Labeling Index in Predicting Recurrence of WHO Grade I Cranial Base Meningiomas

Jose Gabrielle Matias¹ Ignacio Jusue-Torres² Brendan Martin³ Ankush Bajaj⁴ Ewa Borys⁵
Edward Melian⁶ Kevin Barton⁷ Douglas E. Anderson⁸ Vikram C. Prabhu⁸

¹ Stritch School of Medicine, Maywood, Illinois, United States

² Department of Neurological Surgery, Loyola University Medical Center, Maywood, Illinois, United States

³ Clinical Research Office, Loyola University Chicago, Maywood, Illinois, United States

⁴ Undergraduate Studies Department, Brown University, Providence, Rhode Island, United States

⁵ Department of Pathology, Loyola University Medical Center, Maywood, Illinois, United States

⁶ Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois, United States

⁷ Department of Internal Medicine (Oncology), Loyola University Medical Center, Maywood, Illinois, United States

⁸ Department of Neurological Surgery, Loyola University Medical Center, Maywood, Illinois, United States

Address for correspondence Vikram C. Prabhu, MD, Department of Neurological Surgery and Radiation Oncology, Loyola University Medical Center/Stritch School of Medicine, 2160 S 1st Avenue, Maguire 1900, Maywood, IL 60153, United States (e-mail: vprabhu@lumc.edu).

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Abstract

Objectives Assess impact of K_i-67 labeling index (LI; K_i-67 LI) on risk of recurrence or progression of WHO grade I meningiomas.

Study Design Retrospective study of adult patients who underwent resection of cranial base meningioma between 2004 and 2016.

Results 272 patients fulfilled criteria for inclusion in the study. Average age was 61.8 years; 196 (72%) were females. Simpson's grade 1 resection was noted in 77 patients (32%), grade 2 in 39 (16%), grade 3 in 36 (15%), and grade 4 in 88 (37%). The K_i-67 LI was low (1–4%) in 214 (78.7%), intermediate (5–9%) in 44 (16.2%), and high (>10%) in 14 (5.2%). Median follow-up was 39 months (IQR: 16–71 months); 221 (87.1%) tumors remained stable or did not recur, 19 (7.4%) recurred, and 14 (5.5%) progressed. Compared with tumors with low K_i-67 LI, those with intermediate K_i-67 LI had 2.47 times (2.47 [1.09–5.59], $p = 0.03$), and those with high K_i-67 LI had 3.38 times (3.38 [1.16–9.89], $p = 0.03$) higher risk of recurrence or progression. Tumors with K_i-67 LI > 4% had a shorter time to recurrence or progression ($p = 0.01$). Recurrence or progression-free survival rates at 3, 5, and 10 years for tumors with low K_i-67 LI were 95%, 89%, and 75%, respectively; tumors with intermediate K_i-67 LI, 87%, 69%, and 52%, respectively; tumors with high K_i-67 LI, 78%, 49%, and 49%, respectively.

Conclusions Following surgical resection of a WHO grade I cranial base meningioma, K_i-67 LI > 4% may predict an increased risk of recurrence or progression of residual tumor.

Keywords

- meningioma
- cranial base meningioma
- meningioma recurrence
- K_i-67 labeling index

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Introduction

Meningiomas are the most common primary tumor of the central nervous system (CNS).^{1,2} They comprise 36% of all primary CNS tumors with an incidence of 7.86/100,000 people; the incidence increases with each decade of life.^{1–3} Meningiomas are rare in children and young adults; they represent 1–3% of all intracranial tumors in individuals up to age 20 years and 13.5% of intracranial tumors in the 20–34 age group; both significantly lower than the incidence in patients over the age of 40.³ Sex differences are also evident among the age groups; among patients under the age of 20 years, they are more common in males, while there is a female predominance in patients over the age of 20 years.³

Meningiomas are found in any area of the CNS, but are most common over the cerebral convexities or at the cranial base.^{1,2} They may occur sporadically or as part of a familial syndrome, such as neurofibromatosis 2 (NF2), meningioangiomatosis (MA), or Gorlin's syndrome.^{1,4,5} The most common histological subtypes of meningioma are meningothelial and fibroblastic; however, numerous other subtypes exist suggesting complex origins of this tumor.^{4–7} Genetic studies suggest meningiomas are clonal outgrowths from a single mutated cell and are associated with chromosomal abnormalities, which increase in frequency and complexity with increasing histological grade.⁸ Deletion or inactivation of the NF2 gene on chromosome 22 is frequently seen in sporadic meningiomas, although 1p, 6q, 14q, and 18q deletions have also been reported.⁹ Location may also have an impact; convexity meningiomas have a high incidence of NF2 mutations on chromosome 22, which confers a more aggressive phenotype. On the other hand, cranial base meningiomas have a higher incidence of TRAF-7, SMO, and AKT mutations and behave in a less aggressive manner.⁹

A complete surgical removal of the tumor and its dural base with any involved bone is considered the best therapeutic option for patients with intracranial meningiomas.^{10–14} Other options include single fraction radiosurgery, or fractionated radiation for symptomatic or enlarging tumors in surgically inaccessible locations, or in patients in whom surgery is contraindicated or not feasible due to medical comorbidities.^{15–18} Meningiomas are classified into 3 grades of ascending anaplasia by the World Health Organization (WHO) based largely on their appearance on hematoxylin & eosin stained slides. Grade II and III meningiomas have anaplastic features that portend a worse prognosis. Clear cell and chordoid meningiomas are considered grade II tumors, while papillary and rhabdoid meningiomas are considered grade III tumors.⁷ The WHO and Simpson's grades have the most significant impact on the risk of recurrence or progression of a meningioma, although location of the tumor and the presence of a preoperative neurological deficit may also have an impact on this.^{10,13,14} A higher WHO grade (II or III) or incomplete tumor removal risks higher rates of progression of residual tumor or regrowth. Among grade I meningiomas, some atypical features, such as necrosis or prominent nucleoli, also correlate with a higher risk of recurrence.^{13,14} On the other hand, positive progesterone receptor (PR) staining represents a good prognostic indicator of tumor behavior.^{1,19,20}

The nuclear antigen K_i-67, found in all active phases of the cell cycle, is an excellent marker of neoplastic cell proliferative capacity.^{21,22} It is routinely assessed in meningioma specimens but not used to determine the WHO grade.²³ However, it does progressively increase with each grade; grade I meningiomas generally have a low K_i-67 LI (< 4%), grade II tumors 7 to 10%, and grade III > 10%.^{24,25} Variability in the K_i-67 LI among cranial base grade I meningiomas may also be observed without obvious radiological or histopathological clues. The purpose of this study was to ascertain whether varying levels of K_i-67 LI among resected (complete or incomplete) WHO grade I cranial base meningiomas had an impact on their recurrence or progression following surgery.

Materials and Methods

Patient Population

We conducted a retrospective cohort study of all adult patients who underwent resection for an intracranial meningioma at Loyola University Medical Center between January 2004 and December 2016. Inclusion criteria were: adult patients over age 18 with confirmed WHO grade I meningioma of the cranial base and with a minimum of 1 year of radiological imaging follow-up following initial surgery. We excluded WHO grade II or III meningiomas, convexity and spinal meningiomas, patients with a known diagnosis of a syndrome, such as neurofibromatosis 2, predisposing to meningioma or intracranial tumors, patients who had received preoperative or postoperative radiation treatment, and patients that expired secondary to postoperative complications or from undisclosed causes. Only the data from the patient's first surgery were used for patients that underwent multiple surgeries.

Data Collection

The records of patients with meningiomas were identified based on the Current Procedural Terminology (CPT) codes for cranial base tumors, supratentorial, and infratentorial meningiomas. Convexity, intraventricular, or other noncranial base meningiomas were then excluded along with WHO grade II and III tumors. Other inclusion and exclusion criteria are listed above. Demographic data, including age and sex, and detailed clinical information for each patient was recorded. Length of follow-up was calculated as the time from the date of surgery to the last reported clinical follow-up. Presurgical radiographic images; computed tomography (CT) and magnetic resonance imaging (MRI) were analyzed. Radiological variables recorded included: tumor location (anterior, middle, posterior skull base), tumor diameter (anterior–posterior and transverse), presence or absence of contrast enhancement, description of tumor margins (distinct, intermediate, or infiltrative), presence or absence of calcifications, degree of hyperostosis (mild, moderate, or severe), presence or absence of a dural tail, and extent of vasogenic edema (mild, moderate, or severe).

The Simpson's grade of resection was determined by meticulous review of the surgeon's operative report and correlated with the postoperative imaging study. Pathology reports were reviewed and the tumor's histological type, WHO grade, K_i-67 LI, progesterone receptor status (present

or not present), and mitotic index (per 10 high power field) were recorded. Pathological diagnoses were made at our institution based on the 2000 and 2007 versions of the WHO Classification of tumors of the CNS.¹¹ The K_i-67 LI was calculated using the highest labeling index method in areas of maximum density via visual analysis.

Among this cohort of WHO grade I cranial base meningiomas, we defined 3 groups: *Group 1* tumors had a low K_i-67 LI (1–4%), *Group 2* tumors had an intermediate K_i-67 LI (5–9%), and *Group 3* tumors had a high K_i-67 LI (> 10%). Postoperative imaging studies were reviewed and the date of recurrence or progression of any residual tumor was recorded. Recurrence was defined as evidence of a new enhancing tumor in follow-up imaging after gross total resection (Simpson's grades 1 and 2); progression was defined as evidence of any growth of a residual tumor after Simpson's grade 3–5 resection. Recurrence free survival (RFS) was defined as the time from the date of the first postoperative MRI documenting complete removal of the tumor to the date of the last MRI study, when tumor recurrence is observed. Progression free survival (PFS) was defined as the time from the date of the first postoperative MRI showing the residual tumor to the date of the last MRI study, when any tumor progression was observed.

Statistical Analysis

Descriptive statistics included a baseline analysis of patients' demographic and clinical characteristics. Categorical variables were summarized using frequencies and percentages, while continuous variables were expressed as means and standard deviations (SD), or medians and interquartile ranges (IQR), based on the underlying distribution of each variable. Univariable and multivariable Cox's proportional hazards models were then used to estimate the hazard of recurrence at any given time as a function of select risk factors. For these models, the proportional hazards assumption for each predictor was assessed using Martingale residuals as described by Lin, Wei, and Ying.²⁶ The linearity assumption between K_i-67 LI, age, and (the natural logarithm of) each outcome was assessed using a Hosmer and Lemeshow goodness of fit test. A *p*-value less than or equal to 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Between 2004 and 2016, over a 12-year-span, a total of 289 patients underwent surgical resection of a WHO grade I cranial base meningioma at our institution and fulfilled all criteria for inclusion in the study. Of these, 7 patients expired from postoperative complications or from undisclosed causes; 10 patients did not meet the required postoperative radiological follow-up. The demographic and clinical data, preoperative imaging, surgical and histological characteristics, along with the clinical outcomes for the remaining 272 patients, are summarized in **Table 1**. The average age ($\pm$ SD) of a patient in this group was 61.8 $\pm$ 14.1 years; the cohort had 196 (72%) females and 76 (28%) males. In terms of location, 85 (31%) tumors were located in the anterior cranial fossa, 79 (29%) in

Table 1 Demographic and operative information for WHO grade I cranial base meningioma's resected between 2004 and 2016 at Loyola University Medical Center

	Total (n = 272)
Age (mean, SD)	61.8 (14.1)
Sex	
Female	196 (72%)
Male	76 (28%)
Tumor location	
Anterior	85 (31%)
Middle	79 (29%)
Posterior	108 (40%)
Size (mm) (n = 254)	
Anterior-posterior (mean, SD)	32.5 (14.8)
Transverse (mean, SD)	31.1 (13.1)
Simpson's grade (n = 240)	
1	77 (32%)
2	39 (16%)
3	36 (15%)
4	88 (37%)
Progesterone receptor (n = 234)	
Expressed	225 (96%)
Not expressed	9 (4%)
K _i -67 labeling index (%)	
(median, IQR)	2 (1–4)
≤ 4	214 (78.7%)
$5 \leq 9$	44 (16.2%)
≥ 10	14 (5.2%)
Recurrence/progression	
No	239 (88%)
Yes	33 (12%)
Recurrence	19 (7%)
Progression	14 (5.1%)

Abbreviations: IQR, Interquartile range; MM, millimeters; SD, standard deviation.

Note: Percentages are within parentheses.

the middle cranial fossa, and 108 (40%) in the posterior cranial fossa. Adequate radiological imaging studies were available in 254 patients; among these, the mean ($\pm$ SD) anterior-posterior and transverse diameters were 32.5 $\pm$ 14.8 mm and 31.1 $\pm$ 13.1 mm, respectively.

In terms of completeness of the surgical resection, 77 (32%) patients underwent Simpson's grade 1 resection, 39 (16%) grade 2, 36 (15%) grade 3, and 88 (37%) grade 4. Thus, 116 (48%) of patients had a complete or near complete resection of the tumor and its dural base and involved bone. Progesterone receptor status was available in 234 patients; of these, 225 (96%) expressed progesterone receptors (PR+). The median K_i-67 LI

for the entire cohort was 2% (IQR: 1–4%); 214 (78.7%) had a low K_i-67 LI (1–4%), 44 (16.2%) intermediate (5–9%), and 14 (5.2%) high (> 10%). The median follow-up was 39 months (IQR: 16–71 months). Among the 254 patients with adequate radiological imaging at follow-up, 221 (87.1%) remained stable or did not recur, 19 (7.4%) tumors recurred, and 14 (5.5%) progressed.

Independent Association of Risk Factors with Time to Recurrence

The association of several independent risk factors with recurrence/progression (HR [95%, confidence interval (CI)], *p*-value) for this cohort of cranial base meningiomas is summarized in ►Table 2. For every percent increase in the K_i-67 LI score, there was an increased risk of recurrence/progression at any given time (*p* = 0.02). Compared with tumors with low K_i-67 LI (*Group 1*), those with intermediate K_i-67 LI (*Group 2*) had 2.47 times (2.47 [1.09–5.59], *p* = 0.03) higher risk, and those with high K_i-67 LI (*Group 3*) had 3.38 times (3.38 [1.16–9.89], *p* = 0.03) higher risk of recurrence or progression. Using log-ranked analyses, tumors with K_i-67 LI > 4% had a significantly shorter time to recurrence (*p* = 0.01) compared with tumors that had K_i-67 LI < 4% (►Fig. 1). For *Group 1* tumors (K_i-67 LI: 1–4%), the RFS or PFS rates at 3, 5, and 10 years were 95%, 89%, and 75%, respectively (►Figs. 2 and 3). For *Group 2* tumors (K_i-67 LI: 5–9%), the RFS or PFS rates at 3, 5, and 10 years were 87%, 69%, and

52%, respectively. For *Group 3* tumors (K_i-67 LI: > 10%), the RFS or PFS at 3, 5, and 10 years were 78%, 49%, and 49%, respectively (►Fig. 4).

For every 1-year-increase in patient age, the risk of recurrence/progression decreased by 2% (0.98 [0.96–0.99], *p* = 0.04). In contrast, patient sex (*p* = 0.30), Simpson's grade (*p* = 0.44), PR status (*p* = 0.76), anterior–posterior tumor size (*p* = 0.28), and transverse tumor size (*p* = 0.48) were not independently associated with a risk of recurrence or progression.

Multivariable Relationship of Risk Factors with Time to Recurrence

The results for the multivariable adjusted hazard model involving age, Simpson's grade, PR status, and K_i-67 LI are summarized in ►Table 3. On multivariable analysis, adjusting for age, Simpson's grade, and PR status, an increase in the K_i-67 LI > 4% had an impact on the risk of recurrence or progression but failed to reach statistical significance (*p* = 0.19). Similar results emerged for patient age (*p* = 0.11) and PR status (*p* = 0.95). However, controlling for age, PR status, and K_i-67 LI, the Simpson's grade was a powerful predictor of recurrence or progression; the instantaneous hazard of recurrence/progression for patients with a Simpson's grade of 3, 4, or 5 was 4.12 (4.12 [1.45–11.72], *p* = 0.01) times higher compared with patients with a Simpson's grade of 1 or 2.

Table 2 Univariate association of independent risk factors of WHO grade I cranial base meningioma with recurrence or progression

	Hazard ratio (95 CI)	<i>p</i>
Sex		
Female	1.56 (0.68–3.59)	0.30
Male (ref)	–	
Age	0.98 (0.96–0.99)	0.04
Size (mm)		
Anterior–posterior	1.01 (0.99–1.04)	0.28
Transverse	1.01 (0.98–1.04)	0.48
Simpson's grade		0.44
1 (ref)	–	
2	1.18 (0.35–4.03)	
3	1.19 (0.35–4.05)	
4	1.97 (0.80–4.84)	
Progesterone receptor		
Expressed	1.36 (0.19–9.99)	0.76
Not expressed (ref)	–	
K _i -67 labeling index (%)		0.02
≤ 4 (Ref)	–	
5 ≤ 9	2.47 (1.09–5.59)	0.03
≥ 10	3.38 (1.16–9.89)	0.03

Abbreviations: CI, confidence interval.

Discussion

The risk of recurrence or progression of residual cranial base meningiomas following surgery is generally predicated by the Simpson's grade of resection and the WHO grade of the tumor.^{10,11,13,14} Other factors, such as the presence of a neurological deficit prior to surgery, parasagittal location or involvement of the venous sinuses, a “mushroom” shape of the tumor, or a thick dural tail, may also be predictive of a higher risk of tumor recurrence.^{13,14,18,25} A higher WHO grade (II or III) or incomplete tumor removal risks higher rates of progression of residual tumor or regrowth.^{13,14} These are the parameters used by most clinicians when making decisions for adjuvant treatment, following surgical removal of a meningioma.^{27–32} A WHO grade I meningioma that has been completely resected along with its dural base and any involved bone (Simpson's grade 1) has a very low risk of recurrence and requires no adjuvant treatment. Routine clinical and radiological follow-up is the norm for these patients. A WHO grade I meningioma that has been incompletely resected (Simpson's grade 2–5) may also be followed carefully if there are signs of progression of the residual tumor; repeat surgery or radiation therapy (RT) may be considered.^{27–32} For WHO grade II meningiomas that have been completely resected (Simpson's grade 1), a similar watchful approach may be followed, reserving adjuvant RT, only in the event there is tumor regrowth that is not amenable to repeat surgical removal.^{27–32} WHO grade II meningiomas that have been incompletely resected (Simpson's grades 2–5) are always treated with adjuvant RT.^{27–32} All WHO grade III meningiomas regardless of the Simpson's

Fig. 1 Kaplan–Meier curve for WHO grade I cranial base meningioma divided between *Group 1* (K_i-67 LI: 4% or less), *Group 2* (K_i-67 LI: 5–9%), and *Group 3* (K_i-67 LI: 10% or greater). The 3-, 5-, and 10-year RFS/PFS rates for *Group 1* were 95%, 89%, and 75%, respectively. The 3-, 5-, and 10-year RFS/PFS rates for *Group 2* were 87%, 69%, and 52%, respectively. The 3-, 5-, and 10-year RFS/PFS rates for *Group 3* were 78%, 49%, and 49%, respectively. Abbreviations: WHO, world health organization, LI, labeling index, RFS, recurrence free survival, PFS, progression free survival.

grade of resection are also treated with adjuvant RT.^{27–32} For WHO grade I meningiomas, there is a recurrence risk of 7 to 25% with a mean time to recurrence of 60.5 months.^{25,33} Significant variability among WHO grade I tumors may be noted in terms of their histological subtypes; however, these rarely have an impact on the risk of recurrence or the decision whether to administer adjuvant RT. Other factors may be important predictors of the behavior pattern of a WHO grade I meningioma include the PR (and estrogen receptor) status. PR positive tumors tend to be more benign

and have a lower risk of recurrence. However, PR receptor status is not used to determine the need for adjuvant RT.³⁴

For recurrent meningiomas, a complete surgical removal of the tumor and its dural base with any involved bone is considered the best therapeutic option.¹³ Other options include single fraction radiosurgery or fractionated radiation for symptomatic or enlarging tumors in surgically inaccessible locations, or in patients in whom surgery is contraindicated or not feasible due to medical comorbidities.^{27–32} The use of stereotactic RT either single fraction or

Fig. 2 WHO grade I olfactory groove meningioma, K_i-67 1%. (A) Preoperative axial T1-weighted postgadolinium MRI. (B) Immediate postoperative MRI and (C). Follow-up MRI at 6 years without recurrence. Abbreviations: MRI, magnetic resonance imaging.

Fig. 3 WHO grade I left medial sphenoid wing meningioma, K_i-67 1%. (A) Preoperative axial T1-weighted postgadolinium MRI; (B) Immediate post-operative MRI shows residual tumor. This was treated with fractionated RT; (C) Follow-up MRI 10 years later showing further decrease of residual tumor. Abbreviations: RT, radiation therapy.

fractionated in the management of meningiomas continues to evolve. Technical advances have enabled precise, intensity modulated stereotactic administration of RT by linear accelerator (LINAC), Leksell Gamma Knife or CyberKnife radiosurgery with excellent results in terms of tumor control and minimization of neurological morbidity. Long-term local control rates approach 90% for cranial base WHO grade I meningiomas treated with these modalities.^{27–32} Fractionated doses of 45 to 54 gray or single fraction doses of 12 to 16 gray for small (< 35 mm) meningiomas for recurrent, or partially resected WHO grade I meningiomas, or as primary therapy in surgically inaccessible tumors or in patients deemed poor surgical candidates because of advanced age or medical comorbidities.^{27–32}

The nuclear antigen K_i-67, found in all active phases of the cell cycle, is an excellent marker of neoplastic cell proliferative capacity and predictive of the risk of recurrence.^{21–23} It was first identified through the isolation of a monoclonal antibody derived from mice immunized with the nuclei of the L428 Hodgkin's lymphoma cell line.²³ The antibody corresponding to K_i-67 was only present during the active phases of the cell cycle (G1, S, G2, M) and not during the quiescent (G0) phase.^{21–23} The antibody MIB-1 (Molecular Immunology Borstel) was subsequently developed to allow antigen reassessment in paraffin sections and study K_i-67 in different mammals. The utility of the MIB-1 antibody to consistently stain K_i-67 expressing cells provided a robust

and reproducible methodology to assess the proliferative capacity of neoplastic cells. To quantify the degree of positive staining, an index was developed. The K_i-67 LI is calculated through a subjective assessment of 10 high-power fields to estimate the number of positively staining cells.^{21–23} The K_i-67 LI correlates well with cell proliferation and prognosis in neoplasms such as non Hodgkin's lymphoma, cervical and uterine cancer, bladder cancer, mucosal malignant melanoma, gastrointestinal stromal tumor, and, breast cancer.^{21–23} However, a limitation of this study is that the K_i-67 LI was calculated in a subjective semiquantitative manner by a single neuropathologist; interobserver variability in the K_i-67 LI has been reported and recent reports suggest an advantage to doing this using digital image analysis software and in a more rigidly defined automated manner to reduce the risk of error.^{35,36}

The K_i-67 LI is routinely assessed in meningioma specimens, but not used to determine the WHO grade.^{24,25} However, it does progressively increase with each grade and has significant correlative value with recurrence or progression of meningiomas; A K_i-67 LI > 4% correlates with decreased recurrence-free survival, higher mitotic indices, and more histological atypia and invasion; 97% of meningiomas with a K_i-67 LI > 10% are reported to recur within 10 years.^{24,25} The predictive capacity of the K_i-67 LI for risk of recurrence is noted even when correcting for the Simpson's grade of resection.³⁷ While the variability of K_i-67 LI among different

Fig. 4 WHO grade I Right medial sphenoid wing and cavernous sinus meningioma, K_i-67 10%. (A) Preoperative coronal T1-weighted postgadolinium MRI; (B) Immediate postoperative MRI shows residual tumor; (C) Follow-up MRI 4 months later shows tumor progression with increase in size of residual tumor, this was treated with fractionated RT; (D) Follow-up MRI 1 year later shows no further progression of tumor.

Table 3 Multivariate analysis of independent risk factors of WHO grade I cranial base meningioma with recurrence or progression

	Adj. hazard ratio (95 CI)	P
Age	0.98 (0.95–1.01)	0.11
Simpson's grade		0.03
1 (ref)		
2	1.18 (0.21–6.54)	0.85
3	1.66 (0.44–6.26)	0.45
4	4.12 (1.45–11.72)	0.01
Progesterone receptor		
Expressed	0.93 (0.12–7.20)	0.95
Not expressed (ref)		
K _i -67 labeling index (%)		0.19
≤ 4 (ref)		
5 ≤ 9	2.21 (0.90–5.43)	
≥ 10	1.83 (0.39–8.54)	

Multivariable Note: 12.8% (or 26 patients) of the 203 patients in the model sample experienced a tumor recurrence/progression.

grades of meningiomas is evident, variability among just WHO grade I meningiomas may also be observed.³⁸ In other words, a tumor that fulfilled all the histological criteria for a WHO grade I meningioma, may have a K_i-67 LI > 4%. This would not alter its classification; it would remain a grade I meningioma. However, there may be an increase in the risk of recurrence or progression and should prompt closer clinical and radiological follow-up and consideration for additional surgery, or RT as the situation would warrant.

The variability in the K_i-67 LI among cranial base WHO grade I meningiomas may be observed without obvious radiological or histopathological clues. Our study had a specific goal to ascertain whether these different levels of K_i-67 LI conferred a different risk of recurrence, or progression of residual tumors among adult patients, who had undergone surgical resection of a cranial base WHO grade I meningioma. Given the impact of age, sex, PR receptor status, and Simpson's grade, these variables were also recorded and used in the multivariable analyses. There was a clear and reproducible effect of increasing K_i-67 LI in terms of recurrence of completely resected tumors and progression of residual tumors in this cohort. A K_i-67 LI > 4% appeared to be the critical marker. In other words, patients with a WHO grade I cranial base meningioma with a K_i-67 LI > 4% form a specific subpopulation of patients with a higher risk of recurrence or progression. Compared with tumors with K_i-67 LI < 4%, those with intermediate K_i-67 LI (5–9%) had a 2.47 times higher risk, and those with high K_i-67 LI (> 10%) had a 3.38 times higher risk of recurrence or progression. For *Group 1* tumors (K_i-67 LI: 1–4%), the RFS or PFS rates at 3, 5, and 10 years were 95%, 89%, and 75%, respectively. This was significantly better than for *Group 2* tumors (K_i-67 LI: 5–9%), wherein the RFS or PFS rates at 3, 5, and 10 years were 87%,

69%, and 52%, respectively. And significantly better than for *Group 3* tumors (K_i-67 LI: > 10%), wherein the RFS or PFS at 3, 5, and 10 years were 78%, 49%, and 49%, respectively.

The predictive strength of the K_i-67 LI fared less well on multivariable analysis, in which we adjusted for age, Simpson's grade, and PR status. Although, a K_i-67 LI > 4% did predict a higher risk of recurrence or progression it failed to reach statistical significance ($p = 0.19$). Similar results emerged for patient age and PR status. This was not surprising; these are all WHO grade I cranial base tumors; there is abundant literature that substantiates the impact age, Simpson's grade, and PR receptor status have on tumor recurrence.^{39–41} Our cohort was reflective of the usual reported pattern of WHO grade I cranial base meningiomas; 72% of the patients were female and the average age was 61.8 years. The PR receptor status was also consistent with that reported for WHO grade I cranial base meningiomas; among the 234 patients, in whom this information was available, 96% were PR+.

The Simpson's grade in particular remains a powerful predictor of recurrence or progression; the instantaneous hazard of recurrence/progression for patients with a Simpson's grade of 3, 4, or 5 was 4.12 (4.12 [1.45–11.72], $p = 0.01$) times higher compared with patients with a Simpson's grade of 1 or 2. This substantiates recommendations for a maximal safe resection of the tumor along with its dural base and involved bone. Our cohort of patients reflected a surgical resection profile consistent with the literature on cranial base meningiomas: 32% were categorized as Simpson's grade 1 resections, 16% as grade 2, 15% as grade 3, and 37% as grade 4.

Thus, our patients were an excellent representation of WHO grade I cranial base meningiomas and we found the K_i-67 LI to be a significant independent risk factor. In other words, a K_i-67 LI elevation > 4% in a patient with a cranial base meningioma without any other atypical features is a caution sign; these patients may have a higher risk of recurrence or progression of residual tumor. This population of patients requires close radiological and clinical follow-up and consideration for repeat surgery or other treatments, such as SRS (stereotactic radiosurgery) or SRT (stereotactic radiotherapy) if surgery is not feasible or safe.

Conclusion

Following surgical resection of WHO grade I cranial base meningiomas, a K_i-67 LI > 4% may be predictive of an increased risk of recurrence or progression of residual tumor; accurate estimation of the K_i-67 LI is essential and automated processes may be advantageous. This information is valuable in planning radiological and clinical follow-up for these patients and determining the need for adjuvant therapies.

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