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Prognostic significance of preoperative neutrophilia on recurrence-free survival in meningioma

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Abstract

Background. Meningioma is the most common primary intracranial tumor and recurrence is one of the important challenges in patient management. Prognostic factors for tumor recurrences in these patients especially before surgical resection are not fully characterized. Several studies have indicated an association between changes in hematologic laboratory parameters with patient outcomes in solid malignancies. We aimed to assess the association between hematologic parameters and tumor recurrence in patients with meningioma.

Methods. Preoperative complete blood count (CBC) data were analyzed in patients with newly diagnosed meningioma ($n = 222$). Clinical data, including history of corticosteroid therapy, tumor characteristics, and follow-up, were obtained. Recurrence-free survival (RFS) was evaluated using Cox proportional hazards models and log-rank tests.

Results. Using preoperative CBC data from patients prior to any steroid therapy, 51 (23%) patients had neutrophilia. In univariate analysis, neutrophilia was significantly associated with meningioma recurrence (hazard ratio [HR] 2.73; $P < 0.01$). Neither leukocytosis nor lymphocytosis was associated with RFS. In multivariate analysis, after adjusting for tumor grade, tumor size, and extent of resection, neutrophilia remained an independent prognostic factor for RFS (HR 2.23, $P = 0.01$). Forty-six (21%) patients had low hemoglobin levels indicative of anemia, and the presence of anemia showed a trend toward high risk for recurrence (HR 1.83; $P = 0.06$).

Conclusions. The presence of neutrophilia was associated with higher rate of tumor recurrence in patients with meningioma. Validation of these results and the biologic role of neutrophilic inflammatory/immune reaction in meningioma requires further investigation.

Key words

meningioma | preoperative neutrophilia | tumor recurrence

Meningioma is a neoplasm that originates from meningothelial cells. It is the most common primary brain tumor and accounts for 35%–40% of CNS tumors.[1] The World Health Organization (WHO) grading of meningioma is based on histologic subtypes or utilizes histologic features, including mitotic activity, brain invasion, cellularity, growth pattern, and presence of nucleoli.[2,3] Although most meningiomas are WHO grade I (85%–95%) and are considered benign solid tumors, these tumors can recur even after complete resection, and the recurrence rate in these patients has been reported as 7.5% at 10 years and 9.3% at 20 years.[4,5] Furthermore, a subset of meningiomas are well

Importance of the study

A subset of patients with meningioma experience tumor recurrence, which is a major cause of morbidity in these patients. Clinical and pathological factors, including tumor grade, extent of resection, and tumor size, only partially account for recurrence rate. We assessed routinely obtained preoperative, pre-corticosteroid–therapy CBC data from 222 patients with meningioma (World Health Organization [WHO] grades I, II, and III). We observed neutrophilia in 23% of our cases distributed in all grades of meningioma. Using multivariate analysis to adjust for the WHO grade, extent of resection and tumor size showed that neutrophilia was an independent predictor for tumor recurrence in these patients. In addition, we identified anemia in 21% of our cases and univariate analysis indicated that it was marginally significant for worse RFS. If validated, the findings may be useful in the assessment of the biologic role of neutrophils in meningioma.

known to have an aggressive clinical course in a manner that correlates with malignancy grade.[2]

Estimating recurrence risk is an important clinical challenge in therapeutic management of meningioma patients. Previous studies have established that WHO grade, extent of resection, and tumor size are important prognostic factors for tumor recurrence, of which only tumor size can be used to predict tumor recurrence before neurosurgical resection.[2,6–9]

Several studies showed that systemic inflammatory/immunologic reaction before treatment might influence and predict clinical course in cancer patients.[10,11] The prognostic significance of preoperative hematologic parameters has been reported in several solid tumors, including melanoma and cancers of the breast, gastrointestinal tract, lung, bladder, ovary, head and neck, prostate, kidney, and other sites.[12–22]

Work from other brain tumor types, including gliomas,[2,23] documents changes in the inflammatory landscape in both low grade glioma and glioblastoma.[24–29] Among these factors, increased neutrophil/lymphocyte ratio (NLR) was associated with poor patient outcome.[24,25] Similarly, neutrophilia at the time of initial diagnosis has been reported in meningioma and vestibular schwannoma.[29] Inflammatory/immunologic reactions in meningioma indicated as peritumoral edema and stromal infiltration of inflammatory cells are also well described.[30–32]

Here, we examined the association of hematologic parameters in routine preoperative complete blood cell count (CBC) with tumor recurrence in patients with meningioma. Given the well-known association of steroid therapy and elevation of white blood cell count, and that a subset of patients with meningioma may receive corticosteroids preoperatively, we limited the cohort to only those patients who had CBC data prior to documented corticosteroid therapy.

Previous studies have shown some relevance of electrolyte imbalance with clinical outcome in cancer patients.[33,34] Hence, we also assessed the prognostic significance of preoperative serum electrolyte levels in patients with meningioma.

Materials and Methods

Patients and Clinical Data

We included patients with newly diagnosed, histologically confirmed meningioma (WHO grades I, II, and III) who underwent craniotomy at Toronto Western Hospital between 2001 and 2015. Appropriate ethics review was approved for this study. We obtained the following clinical information from electronic patient records including demographic information, history of preoperative corticosteroid therapy, and clinical follow-up. Regarding extent of resection (EOR), we reviewed both the operative/clinical notes and postoperative MRI reports from each patient. EOR was categorized as gross total resection (GTR) for complete resection/no residual and as subtotal resection (STR) for incomplete resection/presence of residual tumor, confirmed by postoperative MRIs. Where postoperative imaging was not available in the medical record, we relied on the surgeon's observation based on the operative report. Patients with tumor recurrence/progression and patients with no tumor recurrence with follow-up time >2 years were included in our cohort. Tumor recurrence was defined as appearance of a new enhancing lesion on serial postoperative MRIs that required therapeutic intervention, either second surgery or radiotherapy. Pathology reports and original diagnostic histologic slides were reviewed to confirm the diagnosis and WHO grade. Tumor size was defined as the largest single dimension recorded in the radiology report and/or from the measurement of the MRI/CT preoperative imaging (when the radiology report was not available).

Laboratory Data

The CBC data utilized in our cohort represented the blood draw taken immediately before surgery, unless the patient had documented corticosteroid use, in which case we used CBC data from the last blood draw prior to steroid therapy. The following CBC data were collected: hemoglobin level, packed cell volume, erythrocyte cell count, mean corpuscular volume, total white blood cell count (WBC), and absolute neutrophil, monocyte, lymphocyte, and platelet counts. Normal ranges were obtained based on the clinical laboratory medicine program at the University Health Network, Toronto, Ontario (Supplementary Table S1). We defined leukocytosis as WBC >11.0 billion (bil)/L, neutrophilia as absolute neutrophil count >7.5 bil/L, lymphocytosis as absolute count >4 bil/L, lymphopenia as absolute count <1.5 bil/L, monocytosis as absolute count >0.8 bil/L, and anemia as hemoglobin level <120 g/L for females and <140 g/L for males. We also collected the data on preoperative serum levels of sodium (normal range,

135–145 mmol/L), potassium (normal range, 3.2–5 mmol/L), and chloride (normal range, 100–110 mmol/L).

Statistical Analyses

The primary outcome of interest was recurrence-free survival (RFS), defined as the time from the date of surgery to the date of recurrence or the last known follow-up. Kaplan–Meier curves were performed to evaluate the impact of the following parameters on RFS: malignancy grade (I–III), tumor location (skull base tumor vs non–skull base tumor), maximum tumor size (maximum tumor dimension, dichotomized by median value), extent of resection (GTR vs STR), and hematologic parameters. Associations between clinical and pathological characteristics of interest with time to recurrence were evaluated using multivariate Cox proportional hazards analyses, including the dependent variables that were significant in the univariate analyses.

Significance was determined as $P < 0.05$ on all univariate and multivariate analyses. Hazard ratios (HRs) were reported with 95% CIs. All statistical analyses were performed using Med Calc. To assess the robustness of the association between RFS and hematologic variables, we used these factors as continuous variables in both univariate and multivariate Cox proportional hazards models.

Results

Study Population

Our initial cohort included 226 patients with newly diagnosed meningioma who underwent surgical resection (WHO grades I, II, and III). We excluded 4 patients due to lack of CBC data prior to the administration of corticosteroid therapy. Of the 222 patients, the final cohort included 169 grade I, 47 grade II, and 6 grade III tumors. Demographics, tumor characteristics, and the results of univariate analyses are included in Table 1, showing an expected preponderance of female patients (F/M ratio = 2.5), with a median age of 58 years (range, 20–88 y). The maximum tumor diameters were available for 205 patients, and the median tumor diameter was 3.5 cm (range, 0.5–8.4). Twenty-eight (13%) patients had a history of corticosteroid use prior to the surgery. Regarding EOR, 158 patients had GTR, 63 patients had STR, and data for EOR was not available for 1 patient. Of the cohort of 222 patients, EOR data were obtained by analysis of the presence of residual tumor in all patients for whom postoperative imaging was available, comprising 215 patients (97%), and by the surgeon's observation (from the operative note) in 6 patients (3%), with the remaining patient having unavailable EOR data. The patient median follow-up time was 6.0 years (range, 0.6–14 y). In total, 48 (22%) patients had a documented tumor recurrence. As expected, Kaplan–Meier survival analysis showed that both WHO grade and EOR correlated with poor RFS ($P < 0.01$ for each, log-rank test) (Fig. 1A, B). Also, tumor size, as a continuous parameter, was predictive for tumor recurrence ($P < 0.01$), and when we dichotomized this factor at the 3.5 cm median value, it remained prognostic for poor RFS (Fig. 1C). Tumor location was not prognostic for tumor recurrence in our cohort ($P = 0.3$).

Table 1 Patient characteristics and univariate analyses

Characteristic	Total Number (%)	*P*-value	HR	95% CI
WHO grade		<0.01	2.98	1.95–4.56
I	169 (76)			
II	47 (21)			
III	6 (3)			
Gender		0.10	0.61	0.34–1.10
Female	158 (71)			
Male	64 (29)			
Tumor location		0.59	1.17	0.65–2.11
Skull base	70 (32)			
Non–skull base	152 (68)			
Max. tumor size, cm		<0.01	1.49	1.24–1.78
>3.5	123 (55)			
<3.5	99 (45)			
Extent of resection		<0.01	2.63	1.50 to 4.65
GTR	158(71)			
STR	63(29)			
Anemia		0.06	1.83	0.97–3.48
Present	46 (21)			
Absent	176 (79)			
Leukocytosis		0.10	1.74	0.90–3.36
Present	42 (19)			
Absent	180 (81)			
Neutrophilia		<0.01	2.73	1.52–4.88
Present	51 (23)			
Absent	171 (77)			
Lymphocytosis		0.31	2.82	0.38–20.82
Present	4 (2)			
Absent	218 (98)			
Lymphopenia		0.26	1.4	0.78–2.46
Present	83 (37)			
Absent	139 (63)			
Monocytosis		0.25	1.6	0.72–3.56
Present	24 (11)			
Absent	198 (89)			

WBC Count and Differential in CBC: Neutrophilia Is a Prognostic Factor for High Rate of Tumor Recurrence in Patients with All Grades of Meningioma

Leukocytosis

We identified leukocytosis in 42 (19%) patients. Univariate analysis of WBC as a continuous parameter was prognostically significant for tumor recurrence ($P = 0.01$) (Supplementary Table S1); however, univariate analysis showed that leukocytosis was not associated with worse RFS in meningioma patients ($P = 0.1$) (Table 1).

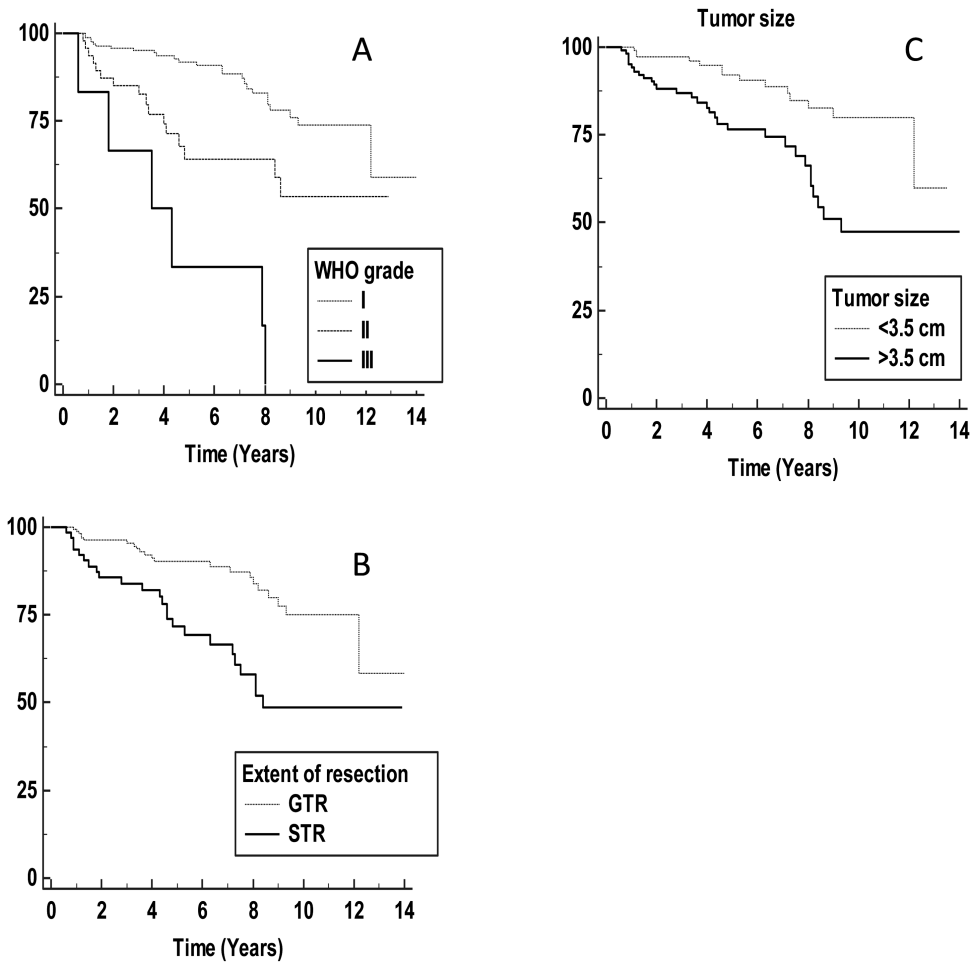

Fig. 1 (A) Kaplan–Meier analysis of the association of WHO grade ($P < 0.01$); (B) extent of resection—gross total resection (GTR) versus subtotal resection (STR) ($P < 0.01$); and (C) tumor size (maximum tumor dimension) dichotomized at 3.5 cm ($P < 0.01$) with recurrence-free survival.

Neutrophilia

The median of neutrophil count in the cohort was 4.55 (bil/L) (range, 0.6–21.5 bil/L). Interestingly, absolute neutrophilia (defined in our clinical laboratory as a neutrophil count >7.5 bil/L) was observed in 51 (23%) and was distributed among all grades of meningioma, including grade I: 34 (15%), grade II: 12 (5%), and grade III: 5 (2%) tumors (Fig. 2A). Kaplan–Meier analysis indicated that the presence of neutrophilia was a significant predictor of poor RFS ($P < 0.01$) (Fig. 3A). In addition, when neutrophil count was used as a continuous variable, we found that it remained a statistically significant parameter for tumor recurrence (HR 1.10, $P < 0.01$, 95% CI: 1.03–1.17) (Supplementary Table S1). This finding suggested that a unit increase in neutrophil count was associated with a 10% increase in the rate of tumor recurrence. Using the Cox proportional hazards model, when adjusting for WHO grade, maximum tumor size, and EOR, the presence of neutrophilia remained as an independent factor for predicting tumor recurrence ($P = 0.01$) (Table 2).

To examine the effect of neutrophilia in grade I meningioma, we used the Cox proportional hazards model, which showed that in this subset alone, neutrophilia lacked prognostic significance for prediction of tumor recurrence (Supplementary Table S3). We observed that the number and proportion of events (tumor recurrence) were lower in patients with grade I meningiomas (26/169, 15%) compared with grades II–III meningiomas combined (21/53, 40%), which may account for this finding.

Additional clinical laboratory data

While lymphocytosis was detected in only 4 patients (2%), lymphopenia was noted in 83 (37%). Univariate analysis showed that lymphopenia was not a predictor for poor RFS ($P = 0.26$). Twenty-four patients (11%) showed absolute monocytosis, distributed among all grades of meningioma, including 16 (7%) grade I, 5 (2%) grade II, and 3 (1%) grade III; however, the univariate analysis suggested that it was not associated with higher risk for

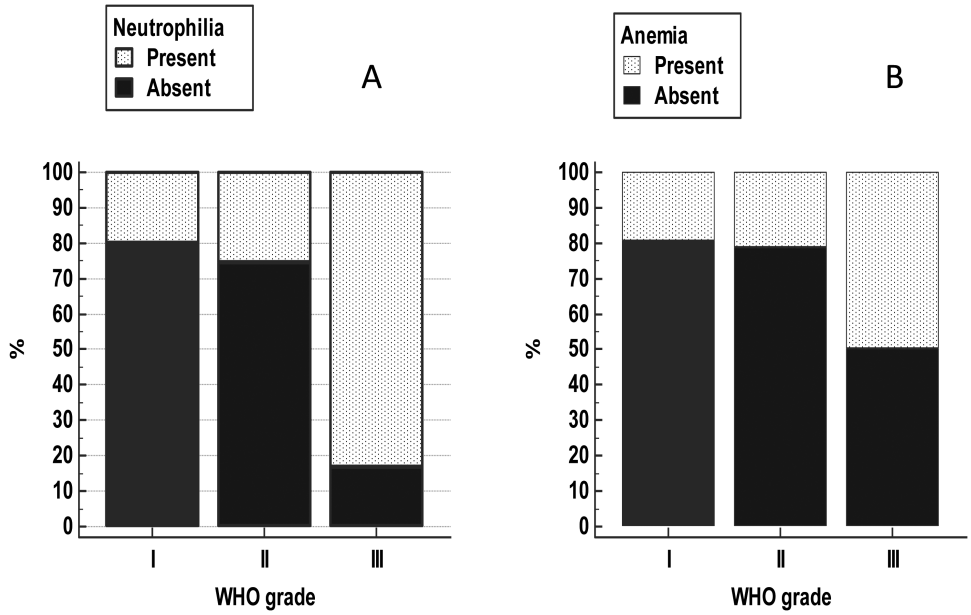

Fig. 2 (A) Distribution of neutrophilia. (B) Anemia in preoperative, pre-steroid complete blood cell count among WHO grades I, II, and III meningiomas.

tumor recurrence ($P = 0.25$). Preoperative serum levels of sodium, potassium, and chloride were not prognostically significant for tumor recurrence in our cohort (data not shown).

Preoperative anemia and recurrence-free survival

Preoperative anemia was present in 46/222 (21%) patients (Table 1). Thirty-three of 46 anemic patients (71%) had grade I meningioma, while the remainder had atypical meningioma (10; 5%) and malignant meningioma (3; 1%) (Fig. 2B). Regarding the type of anemia, 37/46 patients (80%) of the anemic cases had normocytic anemia, with the remaining 9 (20%) having macrocytic ($n = 5$) and microcytic anemia ($n = 4$). Overall, for all types of anemia, Kaplan–Meier analysis showed that the presence of preoperative anemia was marginally significant ($P = 0.06$) for predicting unfavorable RFS in meningioma patients (Fig. 3B).

Table 2 Multivariate analysis of clinical and pathological characteristics with tumor recurrence in meningioma patients

Covariate	*P*-value	Hazard Ratio	95% CI
Neutrophilia	0.01	2.23	1.20–4.20
WHO grade	0.04	1.68	1.01–2.78
Extent of resection	0.002	2.55	1.40–4.70
Tumor size	0.01	1.3	1.10–1.60

Discussion

Estimating recurrence risk is an important clinical problem in meningioma. A subset of patients will experience tumor recurrence, and efforts to estimate this risk include assessment of WHO grade, along with EOR and other metrics, such as tumor size. With these parameters, there remains uncertainty for individual patients as to their individual recurrence risk, which is of importance when considering different treatment options such as neurosurgical resection, adjuvant radiation therapy, and clinical follow-up. In an effort to identify pretreatment clinical parameters that predict recurrence of meningioma, we examined routinely collected laboratory data from patients assessed preoperatively. Our study identifies an elevated neutrophil count as correlated with recurrence. We identified the presence of preoperative neutrophilia in 23% of the patients in our cohort, distributed among all grades of meningioma. Multivariate analyses, adjusting for WHO grade, maximum tumor size, and EOR, indicated that this parameter was an independent prognostic factor for worse RFS in our cohort. We also accounted for 2 important confounding factors for neutrophilia in these patients, including surgical resection and corticosteroid therapy. Preoperative hematologic testing for CBC is routine in all patients and inexpensive and can be widely used to predict risk of tumor recurrence in meningioma before surgical resection.

Our results align with previous findings regarding the prognostic role of inflammatory changes in other tumor types.[29,35] The prognostic role of tumor-infiltrating neutrophils, neutrophilia, and elevated blood NLR in predicting poor clinical outcome has been shown in several

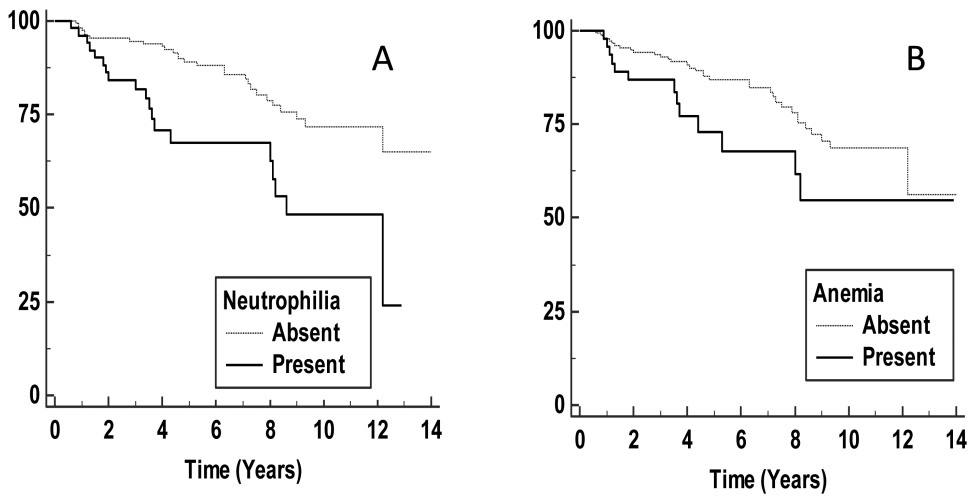

Fig. 3 Kaplan–Meier analysis of the association of (A) preoperative neutrophilia ($P < 0.01$) and (B) anemia ($P = 0.06$) with recurrence-free survival.

cancers.[15,21,22,36] The definition for cutoffs for neutrophilia across these studies varied between 3.5–7.5 10^9/L. The cutoff of 7.5 bil/L, defined by the laboratory at our hospital, is set at the high end of cutoffs relative to other studies, and it has been used in at least 2 previous studies that examined neutrophilia and prognosis in renal cell carcinoma and malignant melanoma.[37,38] Among brain tumors, previous studies showed that elevated NLR and overall neutrophilic activation are associated with worse outcome in glioblastoma.[24,25,27] In our cohort of meningiomas, we observed lymphopenia in 83 (37%) of our cases, but this finding was not associated with worse RFS. Therefore it appears that neutrophil count alone might be a more relevant parameter in meningioma rather than NLR. Future studies may prove useful for further elucidation.

The local inflammatory/immune response in meningioma has been described, including peritumoral edema, which is a predictor of tumor recurrence in meningioma.[31] Interestingly, one of the important contributing mediators for peritumoral edema in meningioma is interleukin-6,[39] which has also been implicated as an activated mediator for neutrophils in glioblastoma.[27] Stromal infiltration of lymphocytes and macrophages has been largely studied in meningioma.[30,40–42]

While this requires further investigation, several large-scale studies indicated that neutrophils are the most important prognostic factors in the biology of cancer,[43,44] with possible roles of angiogenesis, migration, invasion, metastasis, mutagenesis, or immunosuppression.[36] Prior studies on meningioma point to roles of an intratumoral inflammatory response, including biological roles of T lymphocytes, macrophages, and microglia, as well as programmed cell death ligand 1 expression in meningioma.[41,45,46] As these studies did not specifically investigate changes in circulating neutrophils or intratumoral neutrophils, the biologic role of these inflammatory cells in meningioma remains unclear.

We also identified anemia in 21% of the patients in our cohort, the majority of whom were normocytic, with smaller proportions showing microcytic and macrocytic anemia. Univariate analysis showed borderline significance of anemia for predicting tumor recurrence ($P = 0.06$). While this exploratory analysis precludes a definitive conclusion regarding the role of anemia as a robust predictor for tumor recurrence, this finding warrants further study for cause and possible correlation of anemia with worst outcome in meningioma. Pre-radiotherapy anemia has been studied in brain tumors and is reported as a poor prognostic factor in patients with malignant gliomas.[47] A prior study noted pretreatment low hemoglobin levels in patients with meningioma and vestibular schwannoma compared with a normal control group.[29] Interestingly, anemia has been implicated in chordoid meningioma and lymphoplasmacytic meningioma[48,49] (perhaps in relation to associated comorbidities), and our findings suggest that further investigations may be warranted for all meningioma subtypes.

Limitations of our study design include its retrospective nature in a single center, its exploratory nature, and presence of possible confounding factors for neutrophilia. We could not collect CBC data in a defined time period before surgery because the time of starting steroid therapy varied in our patients. Our sample size was limited by the availability of preoperative and pre-steroid CBC in the medical records. In addition, we required patients with clinical follow-up, and excluded meningioma patients with less than 2 years follow-up (assuming no evidence of recurrence). While we addressed steroid use and surgical resection as possible confounders for neutrophilia in our patients, we could not exclude other possible causes of neutrophilia in them, including infectious, inflammatory, immunologic, smoking, seizure, and stress induced adrenalin release before surgery. Future

studies will attempt to monitor the changes in neutrophil count after resection; in the current cohort we were unable to follow up these changes due to missing data: absence of systematic CBC collection at follow-up and possible confounding factors after surgery including steroid therapy.

In conclusion, our study indicated a prognostic association of preoperative neutrophilia in meningioma patients. If our results are validated in an independent cohort, they could potentially be used as one of the preoperative predictors for risk of tumor recurrence in these patients. This exploratory study may serve to stimulate additional prospective studies to investigate whether routinely assessed hematologic parameters might help predict tumor recurrence in meningioma patients. In addition, there is a need for future research studies to better understand the biologic role of tumor-associated inflammation in meningioma. New perspectives learned from immunologic characteristics of meningioma may help us to tailor new therapeutic approaches for these patients.

Supplementary material

Supplementary material is available at *Neuro-Oncology* online.

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Conflict of interest statement. None.

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