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Preoperative hematological inflammatory markers associated with grade and survival in Meningiomas

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Abstract

Meningiomas represent the most frequently diagnosed intracranial tumors. Inflammatory cells present in the tumor can modulate both antitumor and protumor functions, and modify the therapeutic response. Hematological inflammatory parameters have provided prognostic information useful in the treatment and clinical evaluation of several tumors. The aim of this study was to evaluate preoperative hematological markers of patients with meningiomas and to relate them to clinical variables and recurrence-regrowth free survival. Eighty-nine patients without corticosteroid therapy were included. Blood test results and tumor characteristics were collected from medical records. Associations between clinical characteristics and the recurrence-regrowth free survival (RFS) were evaluated using Cox proportional hazard analysis and Kaplan-Meier curves. The receiver operating characteristic (ROC) curves were constructed. Of the 89 cases, 73 (82%) were grade I and 16 (18%) grade II. The mean age was 53 ± 13.9 years, with higher frequency in women. Anemia was observed in 23.6% and neutrophilia in 42% of the patients. In univariate analysis, anemia ($p = 0.04$), neutrophilia ($p = 0.02$) and neutrophil/lymphocyt ratio (NLR) ($p = 0.02$) were associated with an increased risk of recurrence-regrowth and shorter RFS. In multivariate analysis, anemia and NLR > 4.1 represented a higher risk of recurrence-regrowth ($p = 0.003$). The ROC curve analysis showed that only the lymphocyte/monocyte (L/M) > 2.5 was able to predict the tumor grade. The preoperative presence of anemia, neutrophilia, NLR > 4.1 and L/M > 2.5 were associated with a worse prognosis in meningiomas. The use of preoperative hematological inflammatory parameters as prognostic factors can be promissing for evaluation and follow-up of meningiomas.

Keywords: Meningiomas, Grade, Recurrence, Neutrophils, anemia, Survival

Introduction

Meningiomas are tumors that originate from arachnoid meningothelial cells and represent 37% of primary intracranial tumors. More prevalent in women, with an incidence of 8.3 cases per 100.000 inhabitants, increasing these values after 65 years of age (Abbritti et al. 2016). Despite the high prevalence of benign cases and slow progression, meningiomas recur even after complete resection, demonstrating aggressive behavior and poor prognosis (Ostrom et al. 2018).

According to World Health Organization (WHO), the tumor grade and type of surgical resection remain important predictors of recurrence (Abbritti et al. 2016). Besides the preoperative imaging exams, few parameters showed influence in the outcome of meningiomas, including male gender and young age (Balasubramanian et al. 2017; Zhao et al. 2018). Thus, preoperative markers

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able to predict tumor recurrence or regrowth are considered important instruments for clinical practice.

Inflammation is related to carcinogenic processes, being considered a relevant epigenetic factor, as it allows the formation of a tumor microenvironment favorable to the occurrence of mutations (Quail and Joyce 2013; Wang et al. 2018). Studies describe that inflammatory cells present in the tumor can perform a dual function, anti and protumor, and may modify the therapeutic responses (Mantovani et al. 2008; Shiao et al. 2011). In several tumor types, such as intracranial, pulmonary, gastrointestinal, among others, hematological inflammatory markers were able to provide prognostic information useful in the management or therapeutic evaluation (Templeton et al. 2014; Kozak et al. 2017).

Meningiomas often present peritumoral edema and cell stroma infiltration, related to the immune and inflammatory response, with a consequent poorer prognosis (Domingues et al. 2016). The evaluation of hematological inflammatory markers in meningiomas showed promising, allowing the identification of more aggressive cases (grade II and III) and worse clinical evolution (Karimi et al. 2017; Liang et al. 2019; Lin et al. 2019).

This study aimed to evaluate preoperative hematological inflammatory markers in blood count and leukogram in patients with meningiomas and to relate them to clinical, tumoral variables and recurrence-regrowth free survival.

Patiens and methods

This cross-sectional study involved 102 patients above 18 years, undergoing transcranial resection by single surgeon (NPF) in a neurosurgical reference hospital in southern Brazil diagnosed with meningioma. The study sample was for convenience and the patients were included between 2016 and 2019. All patients signed the free and informed consent form, the study was approved by the Institutional Ethics Committee (Report n° 1.446.130 and 1.509.852) and conducted in accordance with the Helsinki Declaration.

The slides, with tissue from surgery, were stained with hematoxylin and eosin (HE) to confirm the presence of tumor, tumor grade and subtypes and analyzed by an experienced pathologist (LBC).

The medical records were reviewed to obtain clinical (age, gender, tumor size and location, the extension of resection, recurrence-regrowth) (Tables 1 and 2 – Supplementary material) and preoperative hematological parameters (blood count and leukogram), including 89 patients without preoperative use of corticosteroids and no history of radiotherapy or chemotherapy.

Blood tests were conducted by a specialized laboratory of clinical analysis in reference hospital, considering

Table 1 Univariate analysis of clinical, tumor and hematological characteristics

Characteristics	Total (%)	P-valor	HR	IC 95%
Gender				
Male	27 (30.3%)		1	
Female	62 (69.7%)	0.22	1.85	0.6–5.0
Age				
> 50 years	40 (44.9%)		1	
≤ 50 years	49 (55.1%)	0.78	1.13	0.4–2.7
WHO grade				
I	73 (82%)		1	
II	16 (18%)	0.27	1.77	0.6–5.0
Localization				
Peripheral	57 (62,8%)		1	
Central	32 (37.2%)	0.66	1.24	0.4–3.3
Extent of resection				
Complete	49 (55.1%)		1	
Parcial	40 (44.9%)	0.50	1.34	0.5–3.3
Anemia				
Absence	68 (76.4%)		1	
Presence	21 (23.6%)	0.02*	3.4	1.1–10.1
Leukocytosis				
Absence	18 (25.7%)		1	
Presence	52 (74.3%)	0.26	1.74	0.6–4.6
Neutrophilia				
Absence	52 (58.4%)		1	
Presence	37 (41.5%)	0.04*	2.6	1.0–6.4
Lymphopenia				
Absence	67 (76.1%)		1	
Presence	21 (23.9%)	0.77	1.17	0.3–3.5
Monocytosis				
Absence	75 (85.2%)		1	
Presence	13 (14.8%)	0.65	0.71	0.1–3.1
Ratio N/L				
Median	4.12		1	
		0.02*	2.79	1.1–7.0

* $p < 0.05$; *HR* Hazard Ratio, *IC* Confidence Interval

Table 2 Multivariate analysis of hematological parameters anemia and N/L > 4.1 with tumor recurrence-regrowth

Hematological parameters	P-valor	HR	IC (95%)
		1	
Presence of anemia	0.490	2.12	0.2–18.0
Presence of N/L > 4.1	0.127	2.27	0.8–6.5
Presence of anemia and N/L > 4.1	0.003*	7.13	2.0–25.9

* $p < 0.05$; *HR* Hazard Ratio, *IC* Confidence Interval

normal ranges: erythrocytes (4–5,6 million/μL), hemoglobin (11,6–15,6 g/dL), leukocytes (3600–11,000/μL), neutrophils (1500–7000/μL), lymphocytes (1000–4500/μL), monocytes (100–1000/μL), basophils (0–220/μL), eosinophils (0–500/μL), platelets (150000–440,000/μL). Meningiomas were classified according to tumor grade in benign (grade I), atypical (grade II) and anaplastic (grade III) and according to histological subtype, following the WHO.

Tumor size was defined by the larger dimension at preoperative imaging (magnetic resonance or computed tomography). Tumors with a size greater than 3 cm were considered large (Oya et al. 2011; Karsy et al. 2016). Regarding location, tumors were divided according to central or peripheral regions (Splavski et al. 2017).

The surgical extension was determined by Simpson's classification, based on the surgical description and postoperative imaging analysis. Considering complete resection: Simpson grade I-II, absence of tumor residue visible in surgical description and absence of lesion in image performed 3 months after surgery and, partial resection: Simpson grade III-V, presence of tumor residue visible in surgical description and/or presence of lesion in image performed 3 months after surgery (Simpson 1957; Splavski et al. 2017). Recurrence was defined as the appearance of a new tumor after complete surgical resection and regrowth as an increase of tumor residue after partial resection. Follow-up included patients with at least 6 months of medical monitoring after surgery.

Statistical analyses

The data were presented by frequency and percentage, mean and standard deviation. The correlations between the quantitative variables were verified by the Spearman correlation test. The Chi-square or Fisher's exact test were used for qualitative variables when necessary. The clinical outcome evaluated was recurrence-regrowth free survival, considering the time elapsed between the date of surgical removal and the date of disease progression or the last follow-up record. The Kaplan-Meier curves were used to estimate the recurrence-regrowth free survival time.

Associations between clinical and tumor characteristics with recurrence-free survival time or regrowth were evaluated using multivariate Cox proportional hazards analysis (HR), the multivariate analysis included the dependent variables that were significant in the univariate analysis ($p < 0.20$). The receiver operating characteristic (ROC) curves were constructed, and the areas under the curve (AUCs) were calculated to assess the diagnostic value of each biomarker. The optimal cutoff values were determined using the Youden's index. The statistical significance adopted was 5% ($p < 0.05$) and the analysis were performed with the Software SPSS version 25 (SPSS Inc., IBM Company, Chicago, IL, USA).

Results

We evaluated 89 patients with confirmed diagnosis of meningioma, of these 73 (82%) were grade I and 16 (18%) grade II. The mean age was 53 ± 13.9 years, ranging from 18 to 82 years, with higher frequency in women (69.7%) in the proportion 2:1. The most frequent subtypes were meningothelial (40.4%), transitional (23.5%) and atypical (17.9%). As for location, the more common was the peripheral (64%) and most tumors (64%) were larger than 3 cm with a mean of 3.52 ± 2.13 cm. Tumor characteristics and univariate analysis are described in Table 1.

Regarding surgical extension, 49 (55.1%) underwent complete resection, 40 (81.6%) remained without lesion and 9 (18.3%) presented tumor recurrence. Forty patients underwent partial resection (44.9%), 29 (72.5%) remained with stable lesion and 11 (25%) had tumor regrowth. In total, 20 (22.4%) cases of recurrence-regrowth were observed. The median follow-up at the time of data analysis was 22 months, ranging from 6 to 96 months. Gender, age, grade, location, size and extent of surgical resection were not predictive factors for shorter RFS. The mean RFS was 62 months (95% CI: 52.2 to 72.0) and, according to Kaplan-Meier, survival rates were 96.1% at 1 year, 67.4% by 3 years and 51.2% in 5 years (Fig. 1).

The presence of anemia was observed in 23.6% of the sample, 18 (85,7%) grade I and 3 (14,3%) grade II. Neutrophilia was present in 41.5%, 28 (75.6%) grade I and 9 (23,4%) grade II. There was no statistically significant difference between anemia, neutrophilia and tumor grade.

The preoperative presence of anemia or neutrophilia was related to the increased risk of recurrence by 3.4 times ($p = 0.02$) and regrowth by 2.6 times ($p = 0.04$) (Table 1). The Kaplan-Meier curve demonstrated that the median time to RFS in patients with anemia was 38 months ((95% CI 25–50) and in patients without anemia was 66 months (95% CI: 55–76). In patients with neutrophilia, the RFS was 50 months (95% CI 35–65) and patients without neutrophilia was 69 months (95% CI: 57–81) (Fig. 2).

A significant association was found between lymphopenia and neutrophilia ($p = 0.004$) and lymphopenia and anemia ($p = 0.018$). Leukocytosis, lymphopenia and monocytosis were not predictive factors associated with shorter RFS.

The ratio between neutrophils and lymphocytes (N/L) was 4.1 (range 0.9–28.4), which was considered the cutoff point for the other analysis. The N/L > 4.1 was related to a 2.79-fold increased risk of recurrence-

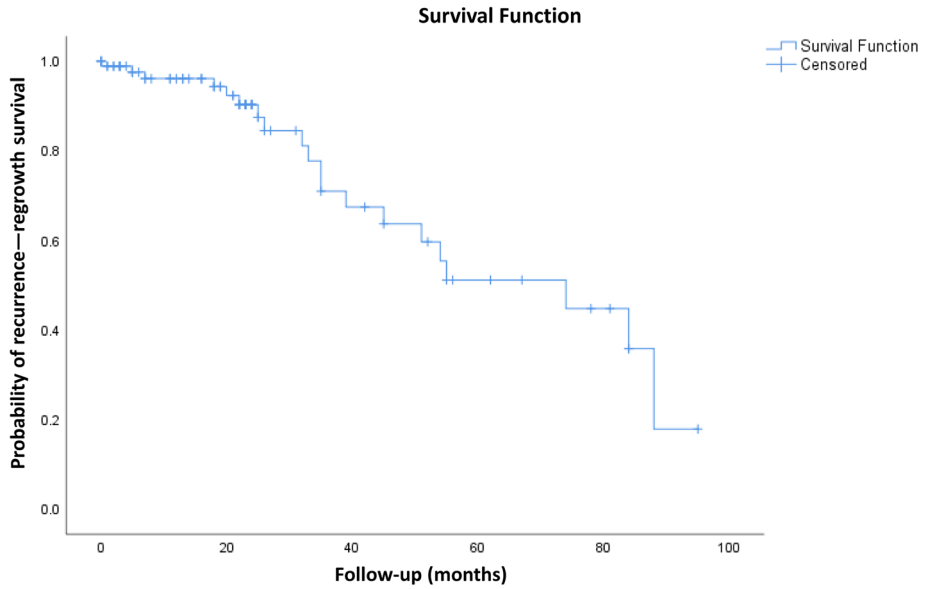

Fig. 1 Kaplan-Meier curve demonstrating recurrence-regrowth free survival rate in meningiomas

regrowth ($p = 0.02$) (Table 1), the Kaplan-Meier curve demonstrated that the RFS in patients with N/L > 4.1 was 48 months (95% CI: 32–64) and with N/L < 4.1 was 70 months (95% CI: 58–81) .

Positive correlations were found between neutrophils and leukocytes ($r = 0.95$; $p < 0.001$) and neutrophils and N/L > 4.1 ($r = 0.78$; $p < 0.001$). We found negative correlation between lymphocytes and N/L > 4.1 ($r = -0.70$; $p < 0.001$).

The relationship between platelets and N/L > 4.1, platelets and lymphocytes, and lymphocytes and monocytes in the preoperative period were not predictive factors associated with shorter RFS. A statistical trend was observed between N/L > 4.1 and the male gender ($p = 0.06$).

In the multivariate analysis, only patients with anemia and N/L > 4.1 had an increased risk of tumor recurrence-regrowth by 7.13 times ($p = 0.003$) (Table 2).

After univariate and multivariate analyzes, the ROC curves and their areas were constructed. The cutoff values were established using the product between sensitivity and specificity. The ROC curve analysis showed that only the lymphocyte/monocyte was able to predict the tumor grade, with an area of 0.68 (95% CI: 0.56–0.82) (Table 3). The optimal cutoff value for lymphocyte/monocyte analysis was 2.5. The other relations did not present satisfactory values in relation to the ROC curve (platelets and N/L: 0.58 (95% CI: 0.43–0.74); N/L and lymphocytes: 0.60 (95% CI: 0, 44–0.76); platelets and lymphocytes: 0.62 (95% CI: 0.49–0.76).

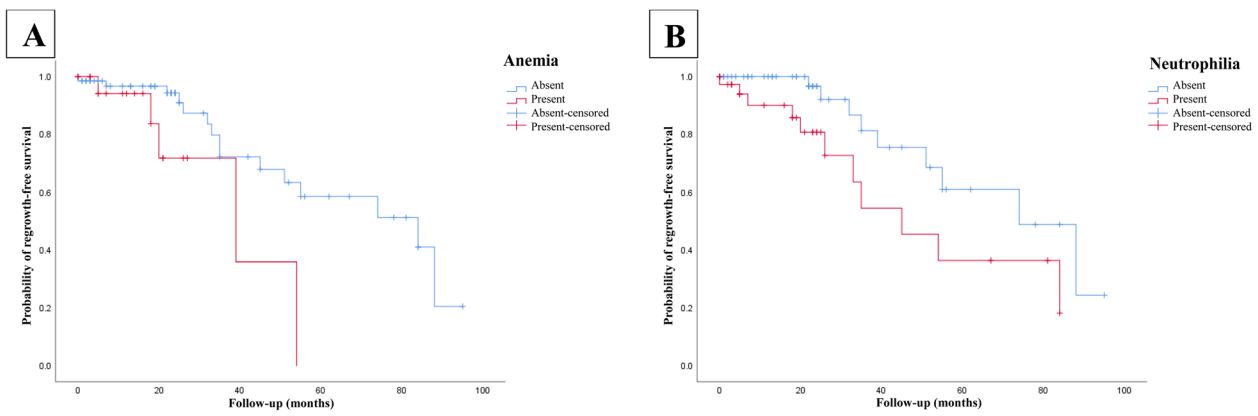

Fig. 2 Kaplan-Meier curve demonstrating recurrence-regrowth free survival in patients with (**A**) anemia and (**B**) neutrophilia

Table 3 Median and interquartile range in relation to tumor grade

Ratio	Grade I	Grade II	P-valor
Neutrophil / Lymphocyte	3,9 (IQ: 2,0-8,7)	6,5 (IQ: 2,4-15,4)	0,191
Platelets / N/L ratio	573,4 (IQ: 245,4-1182,7)	558,9 (IQ: 157,9-983,6)	0,265
Platelets / Lymphocyte	168,7 (IQ: 108,2-216,0)	189,39 (IQ: 141,5-251,6)	0,117
Lymphocyte / Monocyte	3,3 (IQ: 1,9-4,9)	2,1 (IQ: 0,9-3,4)	0,018*

* $p < 0.05$, *IQ* Interquartile Range

The Kaplan-Meier curve demonstrated that the RFS in patients with anemia and N/L > 4.1 was 35 months (95% CI: 16–54) and in patients with only one parameter or neither anemia nor N/L > 4.1 was 65 months (95% CI: 55–75) .

Discussion

This study aimed to identify parameters capable of evaluating the recurrence-regrowth profile of meningiomas prior to surgery. We evaluated a series of 89 cases with mean age, female predominance, tumor grade I and subtypes according to previous studies (Perry 2017; Zouaoui et al. 2018).

The intracranial locations of meningiomas were collected from medical records, but we did not find any relationship with hematological parameters. In order to optimize the statistical analysis, we dichotomize the locations into central or peripheral according to Splavski et al. 2017. The peripheral region was more prevalent, in agreement with other studies (Karsy et al. 2016; Splavski et al. 2017). According to Apra and collegues (2018), central location is associated with worse prognosis due to proximity to important structures. Partial surgical extension, as well as tumor size > 3 cm, have been shown to be a risk factor for recurrence-regrowth (Champeaux and Dunn 2016; Winther and Torp 2017).

Preoperative evaluation of hematological markers may be useful for the prognosis of patients with different tumor types (Xia et al. 2017; Zhao et al. 2018), however, its role in meningiomas has been poorly studied.

The clinical outcome evaluated in our study was RFS, considered the most appropriate method for tumor growth assessment (Machado et al. 2010; Rose et al. 2015; Azar et al. 2017). Our RFS mean time was 62 months, similar to that found in other series, from 47 to 57 months (Mansouri et al. 2008; Nowak et al. 2015; Hua et al. 2018). Regarding recurrence, the rate observed was 22.4%, as described by other groups, from 10.2 to 32.2% (Mansouri et al. 2008; Nowak et al. 2015; Hua et al. 2018).

In the present study, the hematological parameters significantly associated with shorter RFS were anemia, neutrophilia, and N/L > 4.1 and to tumor grade L/M > 2.5.

Anemia, as well as alteration in iron metabolism and erythropoiesis, is considered an unfavorable prognostic factor in patients with various tumors, including brain (Ludwig et al. 2004; Vaupel and Mayer 2005). Anemia and hypoxia are associated with genetic instability, increased angiogenesis, decreased response to apoptosis and free radicals and radiation resistance (Gaspar et al. 2015). The occurrence of anemia in patients with meningiomas is still controverse (Subeikshanan et al. 2016; Lin et al. 2019).

In our study, the prevalence of anemia was 23% and was associated with a significant increase in the risk of recurrence-regrowth, similar to data from Karimi's group in a study with meningiomas (21%) (Karimi et al. 2017). The Kaplan-Meier curve showed a reduction in survival time in patients with and without anemia (38 versus 66 months). Karimi found no association between anemia and shorter survival time (Karimi et al. 2017).

Neutrophils are traditionally described as important defense cells and regulators of chronic inflammation (Chen et al. 2017; Albini et al. 2018). Nevertheless, neutrophils may also play a significant role in tumor development, presenting a pro-tumorigenic phenotype (Seignez and Phillipson 2017). High neutrophil count has been reported in several tumors and considered as a clinically relevant prognostic marker (Schernberg et al. 2018; Wang et al. 2019).

In our study, the prevalence of neutrophilia was 41.5%, higher than the study by Karimi et al. (2017) (23%). Neutrophilia was related to grade II and III (Liang et al. 2019; Lin et al. 2019) and observed with more frequency in meningiomas when compared to other brain tumors (Kayhan et al. 2018; Zheng et al. 2018). Regarding the tumor grade, the ratio L/M > 2.5 was capable to distinguish the WHO grades.

Our study demonstrated that patients with neutrophilia had more risk of recurrence-regrowth and shorter time of RFS (50 versus 69 months), according to Karimi et al. (2017). Other authors did not perform analyses of survival for comparisons (Kayhan et al. 2018; Zheng et al. 2018; Liang et al. 2019; Lin et al. 2019).

We also found a positive correlation between neutrophils and leukocytes. Meningiomas are tumors with frequent presence of inflammatory infiltrate, being more aggressive in the presence of mast cells (Polyzoidis et al. 2015). Corroborating the literature, we found small peritumoral inflammatory foci, however, due to the small

number of cells found, it was not possible to quantify or statistically analyze them. We emphasize that the presence of mast cells was not observed.

A significant association between lymphopenia and anemia along with neutrophilia was observed. Lymphopenia is an important marker related to poor prognosis and survival rates in several diseases, and also common in immunodeficient patients (Ménétrier-Caux et al. 2019).

Lymphopenia and anemia were related to unfavorable prognosis in patients with colorectal tumors and lymphoma (Caro et al. 2001; Fridman et al. 2012). Patients with anemia and lymphopenia have shorter survival due to resistance to radio and chemotherapy (Jiang et al. 2016). To date, there is no description in the literature of the association between lymphopenia and anemia in meningiomas.

The N/L ratio represents the balance between protumor inflammatory response (neutrophils) and antitumor immune response (lymphocytes), already cited as a systemic inflammatory marker (Wang et al. 2018; Cho et al. 2017). Mei and colleages, in a recent systematic review, described an increase in N/L ratio in advanced tumors and shorter overall survival rates (Mei et al. 2017). The N/L ratio cutoff point used in our study (> 4.1) was similar to the data of a meta-analysis with the cutoff point of 5.0, range 2.0 to 7.7 (10). Our results showed an increased risk of recurrence-regrowth and shorter RFS (48 versus 70 months), according to Subeikshanan et al. (2016) and Kayhan et al. (2018) in a series of meningiomas and in disagreement with Karimi et al. (2017), that not associated N/L ratio to poor prognosis.

We observed a positive correlation between neutrophils and N/L > 4.1 and a negative correlation between lymphocytes and N/L > 4.1, as described in other tumors (Mei et al. 2017; Chowdhary et al. 2018) and previously described in meningiomas (Subeikshanan et al. 2016; Lin et al. 2019).

The multivariate analysis showed a significant interaction between anemia and N/L > 4.1, associating it with increased risk of recurrence-regrowth and shorter RFS (35 versus 65 months). In the study by Gorphe similar interaction was found in laryngeal carcinoma in multivariate analysis (Gorphe et al. 2019). In a small cell lung tumor series, normal hemoglobin and N/L < 5 were associated with higher survival rates confirming the possible role of these markers with tumor progression (Cata et al. 2016). There are no reports in the literature about this interaction in meningiomas.

The authors describe possible limitations in this study, such as retrospective data collection. Our study presents a small number of cases and absence of tumors grade III, although, we obtained statistically significant results with clinical repercussion. Therefore, we suggest a prospective and multicenter study to expand the number of cases, increasing the strength of the results obtained.

In conclusion, the preoperative presence of anemia, neutrophilia, N/L > 4.1 and L/M > 2.5 were related to an increased risk of tumor recurrence-regrowth and shorter RFS. These hematological inflammatory parameters could be promising as prognostic factors, considering the easy evaluation of hemogram exam in the preoperatory medical routine.

Abbreviations

AUCs: Areas under the curve; HE: Hematoxylin and eosin; HR: Hazards analysis; L/M: Lymphocyte/monocyte; NLR: Neutrophil/lymphocyt ratio; RFS: Recurrence-regrowth free survival; ROC: Receiver operating characteristic; WHO: World Health Organization

Supplementary Information

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Additional file 1 Table 1. Pathological features. Table 2. Tumor location.

Acknowledgements

Not applicable.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Camila Batista de Oliveira Silva, Bruna Araújo, Bárbara Roberta Ongaratti, Tainá Mafalda dos Santos, Lígia Barbosa Coutinho and Carolina Leães Rech. The first draft of the manuscript was written by Nelson Pires Ferreira, Miriam da Costa Oliveira and Júlia Fernanda Semmelmann Pereira-Lima, and all authors reviewed and complemented the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available in the main text and by request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee (Report n° 1.446.130.
and 1.509.852) and conducted in accordance the Helsinki Declaration.

Consent for publication

The participants have consented to the submission of the research to the journal.

Competing interests

The authors declare that they have no conflict of interest.

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