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Are blood parameters assessed before taking frozen sections useful in gynecological oncology?

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Ethics Committee Approval
Ethics Committee approval was taken from the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee, 2011-KAEK-25 2022/08-21.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Inflammatory processes are often implicated in oncology, and inflammatory markers and indices have been much studied in this context. In gynecological surgery, frozen sections have proven valuable in decision-making. Here we aim to identify laboratory parameters that correlate with frozen section results and thus develop new indices in neoplastic decision-making.
Methods: In this retrospective cross-sectional study at Bursa Yüksek İhtisas Training and Research Hospital, we evaluated 139 patients diagnosed with adnexal mass and endometrial intraepithelial neoplasia. We divided the patients whose frozen sections were reported as malignant, borderline, or benign into three groups and compared the pre-operative complete blood parameters.
Results: The mean age of our patients was 57.3 (11.5) years, and frozen section reports were benign in 33 (23.7%), borderline in 43 (30.9%), and malignant in 63 (45.3%) patients. The mean corpuscular volume and mean platelet volume values were different, and this difference was significant between borderline and malignant groups in post-hoc analyses (P = 0.04 and P = 0.03, respectively). While the percentage of lymphocytes was lower in malignant groups, the percentage of neutrophils was higher (P = 0.01 and P = 0.03, respectively). According to post-hoc analysis, the percentage of neutrophils differs between benign and malignant groups (P = 0.05). The difference in lymphocyte percentage was significant between benign-borderline and benign-malignant groups (P = 0.02, P = 0.05; respectively). The blood neutrophil/lymphocyte ratio was higher in the malignant groups compared to the other two groups (P = 0.02). We used the Multi Linear Regression Analysis method to analyze the factors that play a role in predicting the frozen outcome as malignant. Accordingly, the model with the best performance used lymphocyte percentage, neutrophil/lymphocyte ratio, and Ca-125 parameters (P = 0.03).
Conclusion: This study indicates that inflammatory markers may give a clue about the character of the neoplastic mass before oncology surgery. Thus, we can make new contributions to the surgical and clinical approach in the literature by developing new malignancy indices.

Keywords: Frozen section, Gynecological oncology, Complete blood count, Lymphocyte, Neutrophil

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Introduction

Intraoperative pathological examination is an important part of surgical oncology for many reasons and is supportive in terms of gross evaluation. It can protect the patient from a possible second procedure by ensuring that appropriate surgical procedures are performed. The frozen section approach has been reported to have sensitivity and specificity values of up to 90–100% [1, 2].

The frozen section ensures sampling of the correct material to determine the tumor and degree of spread to plan surgery and assess clearance margins at the surgery [3]. In gynecologic cancers, the frozen section choices and findings can vary depending on the cancer genital tract subsite. Although frozen section histology may be done on the sentinel lymph node for cervical cancer, complete lymphadenectomy remains a universal standard. On the other hand, tumor size, grade, and depth of invasion are all findings from frozen section histology of endometrial cancer that can be utilized to determine the extent of staging procedure necessary. For ovarian cancer, frozen section histology is critical for women who are being taken for cytoreductive or staging surgery without a pre-operative cancer diagnosis [1, 4–6].

In routine histological examination, tissues are usually preserved by fixation in formaldehyde or another solution during the day and must go through many stages for evaluation. In the frozen section approach, these steps for intraoperative diagnosis are modified to shorten the process. Frozen sections are intensive welding procedures and require the skill and experience of the pathologist and good communication with the broader team [3, 7].

There is an essential variation in the use of frozen sections for diagnosing pelvic masses, and frozen is not universally used for diagnosis [3, 8]. The surgeon can use protective options or continue surgery when a borderline tumor is diagnosed. In any case, the frozen section results are compared with the diagnosis in the paraffin section. Other methods, like malignity indexes, serum markers, and imaging studies, can diagnose malignancy preoperatively [6, 9–11].

A frozen section is also recommended during hysterectomy in endometrial neoplasms or hyperplasia, especially in atypia subgroups [12, 13].

Frozen sections dramatically impact the care of gynecological oncology patients. Frozen sections allow for intraoperative evaluation to distinguish benign from malignant tumors during surgery. Frozen section diagnosis in gynecological oncology is sufficiently sensitive and specific for clinical use. Generally, the false-negative and false-positive rates are low [14]. In this study, we aimed to evaluate the predictive effect of the patient's laboratory parameters in frozen results in surgery candidates for freezing.

Materials and methods

We conducted this retrospective cross-sectional study at Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences, Department of Obstetrics and Gynecology, Bursa, Turkey. Our study groups consisted of patients with endometrial or ovarian masses, for whom we applied frozen section between 2017 and 2020 and whose malignant-benign distinction was not made before surgery. We divided the patients whose frozen section results were reported as malignant, borderline, or benign into three groups and compared the pre-operative whole blood parameters. Ethics approval was obtained by the committee of Bursa Yüksek İhtisas Training and Research Hospital with the number 2011-KAEK-25 2022/08-21.

Patients with incomplete pre-operative complete blood count data, a previous history of other cancer, a history of splenectomy, a history of chemotherapy and radiotherapy, a history of steroid use, a history of chronic systemic disease, and patients with documented vitamin B12 or folate deficiencies were excluded from the study.

We analyzed 139 patients diagnosed with adnexal mass and endometrial intraepithelial neoplasia. Hemoglobin values, white blood cell, platelet, neutrophil, lymphocyte, mean erythrocyte volume, mean platelet volume, and erythrocyte distribution volume were evaluated in the last month before surgery. In addition, NLR, which is the number of neutrophils divided by the number of lymphocytes, and PLR, which is the number of platelets divided by the number of lymphocytes, were assessed. We investigated the relationship between frozen and advanced pathology results using statistical methods.

Statistical analysis

Windows-based SPSS 22.0 statistical analysis program (SPSS Inc., USA) was used for appropriate statistical analysis. Variables were examined visually (histograms, probability charts), and analytical methods (Shapiro-Wilk test) were used to determine whether the data showed normal distribution. In descriptive analyzes, variables were defined as mean (standard deviation) (X [SD]), the mean difference between groups, 95% confidence interval (95% CI), median (minimum-maximum [min-max]), U value, frequency (n), and percentage (%). The student t-test and Mann-Whitney U tests compared normally distributed and non-normally distributed variables in the two-group analysis. ANOVA and Kruskal-Wallis tests analyzed variables involving more than two groups. Tukey tests were used in cases where variances were homogeneously distributed from post hoc tests, and Games-Howell tests were used in cases where they were not homogeneously distributed for the double group analysis of the results that were significant in multiple analyses. Homogeneity of variances was evaluated by the Levene test. *P*-value < 0.05 was considered significant.

Results

Demographic and laboratory characteristics and descriptive analysis of the patients are given in Table 1. One-hundred-thirty-nine patients were included in the study. The mean age of our patients was 57.3 (11.5) years. Mean hemoglobin values were 12.4 (1.6) g/dl, and the median red blood cell distribution width was 13.7. The median neutrophil percentage was 63.5%, while the median lymphocyte percentage was 26.9%. Frozen results of our patients were reported as benign in 33 (23.7%), borderline in 43 (30.9%), and malignant in 63 (45.3%). Postoperative final pathology results were generally correlated with frozen results, and 34 patients were reported as benign, 33 as borderline, and 72 as malignant. The gross pathology of one patient whose frozen result was found to be

borderline was benign, and nine patients were reported as malignant (Table 1).

Table 1: Descriptive analysis table of patient characteristics and laboratory data

Characteristics and Laboratory data	Frozen section (n=139)
	Mean (SD) / Median (min-max)
Age*	57.3 (11.5)
Hemoglobin (g/dl)*	12.4 (1.6)
Mean corpuscular volume (fl)	85.1 (60.5-98)
Mean platelet volume (fl)	9 (6.9-12.6)
Red cell distribution width (%)	13.7 (11.6-19.7)
Neutrophil percentage (%)*	63.5 (38.5-95.9)
Lymphocyte percentage (%)*	26.9 (2.4-47.2)
White blood cell (mcl)	7.550 (3.920-25.980)
Platelets (mcl)	277.000 (148.000-672.000)
Creatinine (mg/dl)	0.79 (0-3.6)
Alanine Transaminase (ALT) (u/l)	14 (0-157)
Aspartate Transaminase (AST) (u/l)	19 (0-89)
Plasma glucose level (mg/dl)	106 (76-503)
Fibrinogen (milligram)	385 (246-741)
Ca 125 (u/ml)	50.6 (0.8-512.9)
Ca 19-9 (u/ml)	24.9 (0.0-336)
Neutrophil/Lymphocyte Ratio	2.4 (0.8-23.3)
Frozen Result (n;%)	Benign (33; 23.7)
	Borderline (43; 30.9)
	Malign (63; 45.3)
Gross Pathology Result (n;%)	Benign (34;24.5)
	Borderline (33; 23.7)
	Malign (72; 51.8)

g/dl: gram/deciliter, fl: femtolitre, ml: milliliter, u:unit, mcl: microliter,%: percent, cm: centimeter, SD: standard deviation, min: minimum, max: maximum. Descriptive analyses were performed using mean and standard deviation, marked as *, for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data.

In Table 2, we compared the pre-operative laboratory data of all three groups according to the frozen result. While hemoglobin values did not differ significantly between the groups (P = 0.58), mean corpuscular volume and mean platelet volume values were statistically different (P = 0.04 and P = 0.03, respectively). While the mean corpuscular volume differed between the borderline and malignant groups, the mean platelet volume was significantly different between the benign and borderline groups (P = 0.042 and P < 0.01, respectively). While the percentage of lymphocytes was lower in malignant groups, the percentage of neutrophils was higher and statistically significant (P = 0.01 and P = 0.03, respectively). In pairwise comparisons, the percentage of lymphocytes was significantly different between benign, borderline, and malignant groups (P = 0.02 and P = 0.05, respectively). While the blood neutrophil/lymphocyte ratio was significantly higher in the malignant groups compared to the other two groups, the median neutrophil/lymphocyte ratio was 3 in these groups (P = 0.02). One of the cancer markers, the Ca-125 value, was statistically significantly higher in malignant groups compared to the other two groups (P = 0.01). The remainder of the analysis is summarized in Table 2.

We used the Multi Linear Regression Analysis Enter method and MCV, MPV, Neutrophil, Lymphocyte, Ca-125 and NLR variables to analyze the factors that play a role in predicting the result of the frozen section. According to the results obtained, the model with the best performance (correlation with frozen section malignant findings) was: -0.115 (Lymphocyte percentage [%]) + 0.08 (Ca-125) + 0.175 (Neutrophil/Lymphocyte Ratio) (R2: 0.364, P = 0.03) (Table 3).

Table 2: Comparison analysis table in terms of laboratory data of all three groups

	Benign (n=33) Mean (SD) Median (min-max)	Border (n=43) Mean (SD) Median (min-max)	Malign (n=63) Mean (SD) Median (min-max)	*P*-value Comparison of Three groups Benign vs Border Benign vs Malign Border vs Malign
Age*	55.9 (12.8)	58.3 (12.2)	56.6 (10.5)	0.65
Hemoglobin (g/dl)*	12.5 (1.3)	12.5 (1.3)	12.2 (1.8)	0.58
Mean corpuscular volume (fl)	86.4 (60.5-96.5)	86.5 (60.5-98)	83.9 (66.3-90.2)	0.04 0.98 0.22 0.042
Mean platelet volume (fl)	9.5 (7.2-12.6)	8.3 (6.9-11.8)	9.2 (7.1-11.6)	0.03 <0.01 0.18 0.09
Red cell distribution width (%)	13.3 (11.6-19.7)	14 (12.5-19.7)	13.8 (11.6-17.6)	0.54
Neutrophil percentage (%)	58.8 (40.4-90.3)	62.3 (38.5-96)	66.7 (40.4-89.9)	0.03 0.22 0.05 0.96
Lymphocyte percentage (%)	31.2 (7-47.2)	26.7 (2.4-40.2)	24 (9.2-47.2)	0.01 0.02 0.05 0.80
White blood cell (mcl)	6.8 (3.9-25.9)	8 (4-20)	7.7 (3.9-15.4)	0.31
Platelets (mcl)	277 (181-672)	272 (148-558)	283 (155-452)	0.59
Creatinine (mg/dl)	0.82 (0.6-1.1)	0.79 (0.1-3.6)	0.8 (0.1-1.4)	0.75
Alanine Transaminase (ALT) (u/l)	14 (5-157)	13 (1-114)	17 (1-64)	0.09
Aspartate Transaminase (AST) (u/l)	19 (1-88)	17 (1-46)	19 (1-39)	0.77
Plasma glucose level (mg/dl)	105 (76-503)	106 (83-229)	103 (77-258)	0.81
Fibrinogen (milligram)	346 (176-654)	344 (189-712)	355 (167-491)	0.46
Ca-125	36.6 (7-291)	27.4 (5.4-124)	75.3 (7.7-512.9)	0.01 0.31 0.03 0.07
Ca-19-9	19.6 (0.7-136)	36.7 (0.1-196.7)	75.7 (35.7-336)	0.05 0.80 0.96 0.57
Neutrophil/Lymphocyte Ratio	1.8 (0.8-12.9)	2.1 (0.8-20.1)	3 (1.3-23.3)	0.02 0.31 0.04 0.96

Descriptive analyses were performed using mean and standard deviation, marked as *, for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data. *P*-value < 0.05 was considered significant (*: One Way ANOVA, Others: Kruskal Wallis).

Table 3: Multiple linear regression to predict malignancy after frozen section in gynecology

	B	*P*-value	OR
Lymphocyte percentage (%)	-0.115	0.04	0.89
Ca-125	0.08	0.03	1.008
Neutrophil/Lymphocyte Ratio	0.175	0.036	0.839

B: Standardized regression coefficient. OR: odds ratio. *P*-value < 0.05 was considered significant.

Discussion

In oncological surgeries, the frozen section is a valuable method that is globally accepted and directs surgery today. It is a surgical method recommended and frequently used in gynecology, especially in the approach to adnexal masses and hyperplasia surgeries with endometrial atypia. The perioperative malignant-benign distinction is valuable for in-patient management, avoiding unnecessary surgical burdens or preventing a second surgery later.

In this study, we examined whether whole blood parameters, which are easy to analyze before surgery, could be associated with a possible frozen result in gynecological surgeries. We decided to use a frozen section. Mean corpuscular volume, mean platelet volume, neutrophil percentage, lymphocyte percentage, and neutrophil/lymphocyte ratios in whole blood were significantly correlated with frozen results. As there are many examples in the literature [15–19], these parameters, which play a role in the inflammatory process, had data that could provide clues in the differentiation of benign-borderline-malignant during surgery. We found that blood lymphocyte ratio, Ca-125, and neutrophil/lymphocyte ratio values have the most significant findings regarding the parameters that are the most predictive feature of the malignancy

indicator. The findings in this study will be valuable to those planning future studies on this topic.

Many studies show that the progression of patients with endometrial cancer may be related to cancer-related risk factors and laboratory parameters. Ekici et al. [20] showed that preoperatively elevated white blood cells may be associated with advanced endometrial cancer. Matsuo et al. [21] showed that increased monocyte levels might be associated with poor prognosis in endometrial cancer. Metindir et al. [22] also showed that low hemoglobin levels might be associated with poor endometrial cancer prognoses. Heng et al. [23] stated that there might be a relationship between thrombocytosis and endometrial cancer in terms of poor prognosis. Haruma et al. [24] and Cummings et al. [25] also stated that an increased neutrophil/lymphocyte ratio might be associated with advanced endometrial cancer. An article published in 2021 reported that lymphocyte values are associated with endometrial cancer prognostic factors [26].

Zhao et al. [27], in a meta-analysis of 3467 patients, concluded that the neutrophil/lymphocyte ratio might be a prognostic factor of ovarian cancer. In addition, Sanna et al. [28] stated that the neutrophil/lymphocyte ratio might be a predictive marker of the response to neoadjuvant chemotherapy in advanced serous ovarian cancers. Williams et al. [29] published an article in 2014 and mentioned the neutrophilic marker in ovarian cancer. Accordingly, increased neutrophil/lymphocyte ratio was identified as a risk factor for aggressive ovarian cancer. Neutrophils reflected the immediate release of neutrophilic growth factor and CA-125 from the tumor and correlated with CA-125 values.

It is now known that inflammation and inflammatory cells play an essential role in malignant neoplasms, poor prognosis, and response to treatment [30–32]. Since the relationship between cancer and inflammation was first reported, many studies have been conducted on this subject. Today, we know that many cells we evaluate with complete blood count play a role in the chronic inflammatory pathway.

We consider the evaluation of complete blood parameters and inflammatory markers, which are easy to evaluate and cost-effective before surgery, can give a clue before the neoplastic case approach. Finding new malignancy indices and new markers that can be correlated with frozen or gross pathological examination will provide insight into the clinical approach in gynecological oncology. Studies related to this issue are published frequently and typically support this situation.

In this study, we found that frozen reports in gynecologic oncologic surgery may be associated with some pre-operative inflammatory markers. Especially when lymphopenia, high CA-125, and high neutrophil/lymphocyte ratio are evaluated together, this may provide a clue about the malignancy potential of the case. We believe that these data should form a basis for more comprehensive studies. Meta-analyses are needed with a much larger number of other parameters, patients with different demographics, and a more comprehensive range of oncologic cases.

Limitations

Our study has limitations. It was a retrospective single-center analysis with a relatively small patient number. Also, a selection bias may exist, and the surveillance duration was relatively short.

Conclusion

Based on our findings, we propose that complete blood count and inflammatory parameters, taken before gynecological oncology surgery, may provide clues about the prognostic components of the disease and the type of neoplasia. Complete blood lymphopenia and a high neutrophil/lymphocyte ratio may be associated with a higher probability of gynecologic malignancy.

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