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Research

Can Factors Predicting Malignancy in Intratesticular Masses with Negative Tumor Markers Prevent Overtreatment?

Tümör Belirteçleri Negatif Olan İntratestiküler Kitlelerde Maligniteyi Öngörebilecek Faktörler Aşırı Tedaviyi Önleyebilir mi?

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ABSTRACT

Objective: There is a need for additional predictive factors for the malignant/benign differentiation to prevent overtreatment in intratesticular mass lesions with negative tumor markers. In this study, we evaluated the usability of systemic inflammatory markers, neutrophil-to-lymphocyte ratio (NLR), and tumor in the preoperative differentiation of benign and malignant intratesticular mass lesions.

Methods: The records of patients who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor between August 2007 and September 2020 were retrospectively reviewed. Patients with a malignant specimen histopathology result after radical orchiectomy were classified as group 1, and those with a benign pathology result were classified as group 2. The demographic data, tumor diameters, preoperative systemic inflammatory markers, and NLRs were statistically compared between the two groups. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Results: The study included a total of 78 patients, of whom 47 (60.3%) were in group 1 and 31 (39.7%) were in group 2. The mean tumor sizes of groups 1 and 2 were 3.74±2.24 cm and 1.87±1.30 cm, respectively, being significantly higher in group 1 ($p<0.001$). For groups 1 and 2, the mean white blood cell (WBC) counts were determined as 8.60±2.23 and 7.54±2.02 μ/L, respectively; the mean neutrophil counts as 5.30±1.77 and 4.34±1.40 μ/L, respectively; the mean neutrophil ratios as 63.0±8.22 and 56.9±7.28%, respectively; the mean lymphocyte ratios as 26.2±6.69 and 31.9±6.05%, respectively; and the mean NLR values as 2.72±1.44 and 1.87±0.54, respectively. The mean WBC count, neutrophil count, neutrophil ratio, and NLR were significantly higher in group 1 ($p=0.037$, $p=0.014$, $p<0.001$, and $p=0.002$, respectively), and the mean lymphocyte ratio was significantly higher in group 2 ($p<0.001$). The analysis of the pathological results showed that malignancy correlated positively with tumor size, WBC count, neutrophil count, neutrophil ratio, and NLR, and a negative correlation with the lymphocyte ratio.

Conclusion: Tumor diameter, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR can be used as predictive factors in the differentiation of benign-malignant intratesticular masses with negative testicular cancer markers before radical orchiectomy to prevent overtreatment. While the increased values of tumor diameter, WCB count, neutrophil count, neutrophil ratio, and NLR correlate with the possibility of malignancy, a decreased lymphocyte ratio can be evaluated in favor of malignancy.

Keywords: Testicular tumor, radical orchiectomy, tumor marker, systemic inflammatory markers

ÖZ

Amaç: Tümör belirteçleri negatif olan intratestiküler kitlesel lezyonlarda aşırı tedaviyi önlemek için malign/benign ayrımında ek ön görücü faktörlere ihtiyaç duyulmaktadır. Biz de bu çalışmamızda sistemik enflamatuvar belirteçlerin, nötrofil lenfosit oranının (NLO) ve lezyon boyutlarının intratestiküler kitlesel lezyonların preoperatif benign malign ayrımında kullanılabilirliğini değerlendirdik.

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ÖZ

Gereç ve Yöntem: Ağustos 2007 ile Eylül 2020 tarihleri arasında testis tümörü ön tanısı ile radikal inguinal orşiektomi yapılan hastaların kayıtları retrospektif olarak incelendi. Radikal orşiektomi sonrası örnek patolojisi histolojik olarak malign gelen hastalar grup 1, benign gelenler ise grup 2 olarak sınıflandırıldı. Her iki grubun demografik verileri, tümör çapları, preoperatif sistemik enflamatuvar belirteçleri ve NLO'ları istatistiksel olarak analiz edildi. NLO nötrofil sayısının lenfosit sayısına bölünmesi ile tanımlandı.

Bulgular: Toplam 78 hasta çalışmaya dahil edildi. Bu hastaların 47'si (%60,3) grup 1'de, 31'i (%39,7) grup 2'deydi. Gruplar için ortalama lezyon boyutları sırasıyla 3,74±2,24 cm ve 1,87±1,30 cm olmak üzere grup 1'de anlamlı olarak fazla bulunmuştur (p≤0,001). Sırasıyla grup 1 ve grup 2 için ortalama beyaz kan hücresi (WBC) sayıları 8,60±2,23 µ/L ve 7,54±2,02 µ/L, ortalama nötrofil sayıları 5,30±1,77 µ/L ve 4,34±1,40 µ/L, ortalama nötrofil oranları %63,0±8,22 ve %56,9±7,28, ortalama lenfosit oranları %26,2±6,69 ve %31,9±6,05, ortalama NLO ise 2,72±1,44 ve 1,87±0,54 idi. Ortalama WBC sayıları, nötrofil sayıları, nötrofil oranları ve NLO değerleri grup 1'de anlamlı yüksek bulundu (p=0,037, p=0,014, p<0,001, p=0,002). Ortalama lenfosit oranları ise grup 2'de anlamlı olarak yüksek bulundu (p<0,001). Patolojik değerlendirme sonucunun malign saptanması tümör boyutu, WBC sayısı, nötrofil sayısı, nötrofil oranları ve NLO ile pozitif korelasyon, lenfosit oranları ile negatif korelasyon gösterdi.

Sonuç: Testis kanseri belirteçleri negatif olan intratestiküler kitlelerin radikal orşiektomi öncesi benign-malign ayrımında aşırı tedaviden kaçınmak için tümör çapı, WBC sayısı, nötrofil sayısı, nötrofil oranları, lenfosit oranları ve NLO ön görücü faktör olarak kullanılabilir. Tümör çapı, WBC sayısı, nötrofil sayısı, nötrofil oranları ve NLO artışı malignite olma ihtimali ile korelasyon gösterirken, lenfosit oranlarının azalması ise yine malignite lehine değerlendirilebilir.

Anahtar Kelimeler: Testis tümörü, radikal orşiektomi, tümör belirteci, sistemik enflamatuvar belirteçler

INTRODUCTION

Although testicular cancer accounts for less than 1% of all tumors in men, it is the most common solid tumor in those aged 20 to 34 years, with a steadily increasing global incidence over the last few decades (1). The standard initial treatment of testicular tumors is radical orchiectomy. However, it is considered that fertility may be affected after orchiectomy in these patients, and thus, sperm banking is recommended before the operation (2). Another factor to considered is the negative psychological effects of orchiectomy on the patient. Therefore, many studies emphasize that patients should receive counseling on testicular prosthesis insertion before and after orchiectomy (3). For all these reasons, a correct diagnosis of testicular cancer is critical. For this purpose, scrotal ultrasonography (USG) and serum tumor markers [human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH)] are used (4). However, although 90% of testicular cancers are histologically germ cell tumors (5), these markers are expressed in <60% of cases (6). Which may result in unnecessary radical orchiectomy due to misdiagnosis. Therefore, particularly in intratesticular mass lesions with negative tumor markers, there is a need for additional predictive factors to predict malignant-benign differentiation to prevent overtreatment. Some studies have evaluated the relationship of testicular tumors with systemic inflammatory markers examined in routine peripheral blood count analysis, particularly the neutrophil-to-lymphocyte ratio (NLR) (7-9). However, none of these studies evaluated whether systemic inflammatory markers and NLR could be used in the prediction of the benign/malignant differentiation before orchiectomy in intratesticular masses with negative tumor markers. In the current study, we evaluated the usability of systemic inflammatory markers, NLR, and lesion size in the preoperative differentiation of benign and malignant intratesticular mass lesions.

METHODS

After obtaining approval from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2022-03-06, date: 07.02.2022) and written consent from the patients, we retrospectively reviewed the records of all patients who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor between August 2007 and September 2020. The diagnosis of the patients and lesion size determination was undertaken using preoperative scrotal color Doppler USG and additionally by the magnetic resonance imaging of the scrotum in some cases. Patients with elevated testicular tumor markers, paratesticular lesions, metastases in relevant screening, single testis, another active infective focus, chronic inflammatory disease, known hematological pathologies, and incomplete pre-orchiectomy data related to tumor markers and hematological parameters were excluded from the study. Patients with histologically malignant pathologies after radical orchiectomy were classified as group 1, and those with benign lesions were classified as group 2. The patients' demographic data (age, gender, etc.), preoperative biochemical results, and histopathological results of orchiectomy material were obtained from the hospital database. Biochemical tests included tumor markers (HCG, AFP, and LDH) and complete blood count (CBC) parameters.

Additionally, NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Statistical Analysis

Categorical variables were given as numbers and percentages, and continuous variables as mean and standard deviation. The normality of the distribution of continuous variables was evaluated with the Shapiro-Wilk test. The mean values of two normally distributed independent groups were compared with Student's t-test, and those of two non-normally distributed groups were compared using the Mann-Whitney U test. The percentage of categorical variables was compared with the Pearson chi-square test, and the cut-off values for malignancy were determined using the receiver operating characteristics (ROC) curve analysis. The correlation between malignancy and tumor size and hematological parameters was tested using the sperm correlation analysis. The results were considered statistically significant at $p<0.05$.

RESULTS

The study included a total of 78 patients with testicular tumor markers (HCG, AFP, and LDH) within normal limits who underwent radical inguinal orchiectomy with a preliminary diagnosis of testicular tumor. The demographic data and laboratory characteristics of the patients are shown in Table 1. According to postoperative mass specimen histopathology, 47 (60.3%) patients were in the malignant group (group 1) and 31 (39.7%) were in the benign group (group 2). The mean age of the patients significantly differed between the groups, being determined as 35±9.8 years for group 1 and 44.4±18.5 years for group 2 (p=0.046). There was no significant difference between the two groups in relation to the laterality and preoperative diagnostic imaging methods used (Table 2). The mean lesion size was 3.74±2.24 cm in group 1 and 1.87±1.30 cm in group 2, indicating a significantly higher value for the former (p<0.001). Of the patients with malignant histopathology, 37 (79%) had seminoma, five (11%) had Leydig cell tumors, two (4%) had mixed germ cell tumors, two (4%) had embryonal carcinomas, and one (2%) had a yolk sac tumor. Of the patients with benign histopathology, twelve (39%) had fibrotic granulation, three (10%) had adenomatoid tumors, three (10%) had nodular Leydig cell hyperplasia, one (3%) had angyomixoma, one (3%) had hemorrhagic infarct, two (6%) had interstitial congestion, two (6%) had interstitial hyalinization, four (13%) had seminiferous tubular atrophy, two (6%) had intraparenchymal hemorrhage, one (3%) had leiomyoma. There was no significant difference between the groups in terms of testicular tumor markers. For groups 1 and 2, the mean white blood cell (WBC) counts were determined as 8.60±2.23 and 7.54±2.02 µ/L, respectively; the mean neutrophil counts as 5.30±1.77 and 4.34±1.40 µ/L, respectively, the mean neutrophil ratios as 63.0±8.22 and 56.9±7.28%, respectively; the mean lymphocyte ratios as 26.2±6.69 and 31.9±6.05%, respectively; and the mean NLR values as 2.72±1.44 and 1.87±0.54, respectively. The mean WBC count, neutrophil count, neutrophil ratio, and NLR were significantly higher in group 1 (p=0.037, p=0.014, p<0.001, and p=0.002, respectively), whereas the mean lymphocyte ratio was significantly higher in group 2 (p<0.001). There was no significant difference between the groups in terms of the remaining hematological parameters (Table 2).

The ROC curve analysis was performed to calculate the cut-off and area under the curve (AUC) values of the parameters predicting malignancy. The cut-off and AUC values were determined as 1.95 cm and 0.802, respectively for tumor size; 7.72 µ/L and 0.638, respectively for WBC; 5.32 µ/L and 0.649, respectively for neutrophil count; 64.2% and 0.686, respectively for neutrophil ratio; 29.7% and 0.267, respectively, for lymphocyte ratio; and 2.72 and 0.707, respectively for NLR (Table 3 and Figure 1). The correlation analysis performed between a malignant pathological result and tumor size, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR revealed that malignancy development correlated negative with the lymphocyte ratio and a positive correlation with the remaining parameters (Table 4).

DISCUSSION

The standard initial treatment of testicular tumors is radical orchiectomy (2). However, an unpredictable diagnosis may result in patients being more exposed to harmful effects on endogenous testosterone, fertility, and body image due to overtreatment (10). Therefore, many researchers have conducted studies on partial orchiectomy in testicular tumors (10,11). Studies on all testis-sparing procedures recently show the importance of an accurate diagnosis preoperatively (10,11). Negative tumor markers, which are used to support the diagnosis process, may make it difficult to differentiate between benign and malignant intratesticular mass lesions. Thus, there is a need for additional predictive factors that can predict the benign-malignant differentiation in this patient group.

Technological developments recently have improved the resolution of USG devices and increased the diagnosis of incidental testicular masses. Carmignani et al. (12) reported that non-palpable testicular lesions with a size of less than 2.5 cm on USG could be diagnosed incidentally, and 80%

Table 1. Demographic data and laboratory characteristics

Number of patients	78
Mean age ± SD, year	38.7±14.5
Laterality, n (%)	
Right (0)	48 (61.5)
Left (1)	30 (38.5)
Imaging method, n (%)	
1	31 (39.7)
2	47 (60.3)
Mean tumor diameter ± SD, cm	3.00±2.12
Mean WBC count ± SD, µ/L	8.18±2.20
Mean RBC count ± SD, 10^6 µ/L	5.17±0.71
Mean HGB count ± SD, g/dL	14.7±1.77
Mean HTC count ± SD, %	43.5±4.77
Mean PLT count ± SD, 10^3 µ/L	273±85.8
Mean MCV count ± SD, fL	84.9±5.58
Mean MCH count ± SD, pg	28.2±4.05
Mean MCHC count ± SD, g/dL	33.6±1.96
Mean RDW-CV count ± SD, %	13.1±1.49
Mean neutrophil count ± SD, µ/L	4.92±1.69
Mean lymphocyte count ± SD, µ/L	2.25±0.70
Mean eosinophil count ± SD, µ/L	0.16±0.14
Mean monocyte count ± SD, µ/L	0.61±0.20
Mean basophil count ± SD, µ/L	0.40±1.54
Mean neutrophil ratio ± SD, %	60.6±8.35
Mean lymphocyte ratio ± SD, %	28.5±6.99
Mean eosinophil ratio ± SD, %	2.37±1.70
Mean monocyte ratio ± SD, %	7.80±2.02
Mean basophil ratio ± SD, %	0.64±0.32
Mean MPV count ± SD, fL	9.62±1.26
Mean PCT ratio ± SD, %	0.26±0.09
Mean PDW-CV count ± SD, %	14.3±3.49
Mean NLR ± SD	2.38±1.23
Mean PLR ± SD	134±66.5
Mean LMR ± SD	3.88±1.38
Mean preop AFP ± SD, ng/mL	2.91±1.56
Mean preop bHCG ± SD, mIU/mL	0.66±0.84
Mean preop LDH ± SD, U/L	197±30.6

SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, AFP: Alfa-fetoprotein, bHCG: Human chorionic gonadotropin, LHD: Lactate dehydrogenase

of these lesions had a benign histology result. In another study by Guner and Tonyalı (13), it should be considered that the lesions may be highly benign, especially in patients aged between 15-34 years, who are small, non-palpable, do not cause elevation in serum tumor markers, and where testicular tumors are common, and if necessary, testicular sparing surgery should be planned. In the current study, we evaluated whether tumor size could be a predictive parameter in the differentiation of benign and malignant lesions. We determined that the mean tumor size was 3.74±2.24 cm in the malignant group and 1.87±1.30 cm in the benign group, being significantly higher in the former ($p<0.001$). Similarly, the increase in tumor size showed a significant correlation with malignancy, with the cut-off value being calculated as 1.95 cm. Thus, our results contribute to the current literature by demonstrating that tumor size can be a predictive parameter in the differentiation of benign and malignant lesions.

Studies conducted in the past decade suggest that immune and inflammatory cells contribute to angiogenesis to facilitate the survival and even proliferation of cancer cells during tumor development stages, and they produce various cytokines and chemokines for this purpose (14). In particular, the excessive release of interleukin (IL)-8 from tumor cells has a chemoattractant effect on neutrophils. It is known that IL-8 not only contributes to angiogenesis but also facilitates the growth and migration of tumoral cells with the enzymes secreted by neutrophils (15). Lymphocytes, on the other hand, are known as a surrogate for host cell-mediated immunity, playing a role in host defense against malignancy. In a patient with cancer, the lymphocyte count can be reduced by lymphocytic cytokines secreted by the tumor. This has been proven by the *in vivo* demonstration of ligands such as FasL and tumor necrosis factor β produced for cancer-induced lymphocyte apoptosis in cancer cases (16). All this evidence suggests that systemic inflammatory markers that can be determined in a simple CBC analysis can support the preliminary diagnosis of many malignancies and provide preliminary information about their prognosis.

Some studies have stated that systemic inflammatory markers and NLR may be important markers in predicting the prognosis of urological malignancies (17). Recently, many researchers have presented an association between testicular cancer and systemic inflammatory markers and NLR (7-9). Gokcen et al. (7) compared peripheral blood count and NLR between 39 patients that underwent radical orchiectomy for testicular cancer and 82 patients that underwent varicocelectomy and reported that the WBC count of the testicular cancer group was significantly higher

Table 2. Comparison of patient characteristic according to the pathology results

Variables	Malignant	Benign	p-value
Number of patients	47	31	
Mean age ± SD, year	35.0±9.82	44.4±18.5	0.046**
Laterality, n (%)			
Right (0)	30 (63.8)	18 (58.1)	0.609#
Left (1)	17 (36.2)	13 (41.9)	
Imaging method, n (%)			
1	18 (38.3)	13 (41.9)	0.748#
2	29 (61.7)	18 (58.1)	
Mean tumor diameter ± SD, (cm)	3.74±2.24	1.87±1.30	<0.001**
Mean WBC count ± SD, µ/L	8.60±2.23	7.54±2.02	0.037*
Mean RBC count ± SD, 10^6 µ/L	5.09±0.63	5.30±0.82	0.195*
Mean HGB count ± SD, g/dL	14.6±1.94	14.8±1.49	0.594*
Mean HTC count ± SD, %	43.3±5.31	43.8±3.69	0.648*
Mean PLT count ± SD, 10^3 µ/L	277±93.5	266±73.4	0.575*
Mean MCV count ± SD, fL	85.2±5.53	84.4±5.71	0.526*
Mean MCH count ± SD, pg	28.1±4.89	28.5±2.34	0.684*
Mean MCHC count ± SD, g/dL	33.7±1.54	33.4±2.49	0.573*
Mean RDW-CV count ± SD, %	13.2±1.59	12.8±1.29	0.155*
Mean neutrophil count ± SD, µ/L	5.30±1.77	4.34±1.40	0.014*
Mean lymphocyte count ± SD, µ/L	2.17±0.76	2.36±0.60	0.240*
Mean eosinophil count ± SD, µ/L	0.17±0.15	0.15±0.11	0.462*
Mean monocyte count ± SD, µ/L	0.61±0.22	0.62±0.19	0.977*
Mean basophil count ± SD, µ/L	0.49±1.71	0.26±1.25	0.521*
Mean neutrophil ratio ± SD, %	63.0±8.22	56.9±7.28	<0.001*
Mean lymphocyte ratio ± SD, %	26.2±6.69	31.9±6.05	<0.001*
Mean eosinophil ratio ± SD, %	2.50±1.91	2.18±1.32	0.410*
Mean monocyte ratio ± SD, %	7.52±2.20	8.21±1.68	0.135**
Mean basophil ratio ± SD, %	0.65±0.36	0.63±0.26	0.800*
Mean MPV count ± SD, fL	9.76±1.24	9.41±1.27	0.237*
Mean PCT ratio ± SD, %	0.27±0.10	0.25±0.08	0.277*
Mean PDW-CV count ± SD, %	13.8±3.35	15.0±3.63	0.146*
Mean NLR ± SD	2.72±1.44	1.87±0.54	0.002**
Mean PLR ± SD	145±78.9	116±36.1	0.143**
Mean LMR ± SD	3.80±1.58	4.01±1.00	0.524*
Mean preop AFP ± SD, ng/mL	2.91±1.65	2.91±1.45	0.988*
Mean preop bHCG ± SD, mIU/mL	0.74±0.99	0.52±0.55	0.267*
Mean preop LDH ± SD, U/L	198±31.1	197±30.2	0.921*

SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, AFP: Alfa-fetoprotein, bHCG: Human chorionic gonadotropin, LHD: Lactate dehydrogenase
*Independent-samples t-test
**Mann-Whitney U test
#Pearson chi-square test

(8.4±2.2 vs. 7.1±1.5). Similarly, in our study, WBC count was significantly higher in the malignant group, and its cut-off value was determined as 7.72 in the ROC analysis. In another study comparing the preoperative peripheral blood values between 36 patients with testicular cancer and 36 patients that underwent varicocelectomy, the authors reported that the neutrophil count and neutrophil ratio were significantly higher and the lymphocyte ratio was significantly lower in the testicular cancer group (8). Similarly, we observed that neutrophil count and neutrophil ratio were significantly higher in the malignant group, whereas lymphocyte ratio was significantly lower. We calculated the cut-off values of neutrophil count, neutrophil ratio, and lymphocyte ratio as 5.32, 64.2, and 29.7, respectively. In the literature, the mean NLR value in testicular cancer ranges from 2.37 to 3.18, and NLR is reported to be significantly higher in patients with localized testicular cancer compared to controls (8,9,18). Ilktac et al. (18) determined the mean NLR value of patients with localized testicular cancer as 2.78±1.84 before radical orchiectomy and 1.57±0.58 postoperatively, noting a significantly higher mean value in the preoperative period. In our study, the mean NLR value was 2.72±1.44, and it was significantly higher in the malignant group. A common goal of these studies was to determine the optimal cut-off value of NLR in testicular cancer (7,8). Gokcen et al. (7) determined the cut-off value of NLR for testicular cancer as 2.25, while another study determined the NLR cut-off value as 2.06 for testicular cancer (8). In our study, the NLR cut-off value was 2.72. Almost all the studies discussed in this paper evaluated the relationship of testicular cancer with systemic inflammatory markers and NLR, selecting controls from patients that underwent varicocelectomy due to another pathophysiology. In contrast, in our control group, we included patients that underwent orchiectomy with a preliminary diagnosis of testicular cancer but were found to have benign specimen pathology results. Thus, unlike the literature, all the patients included in our sample had negative testicular tumor markers. Therefore, we consider that the systemic inflammatory markers and NLR data

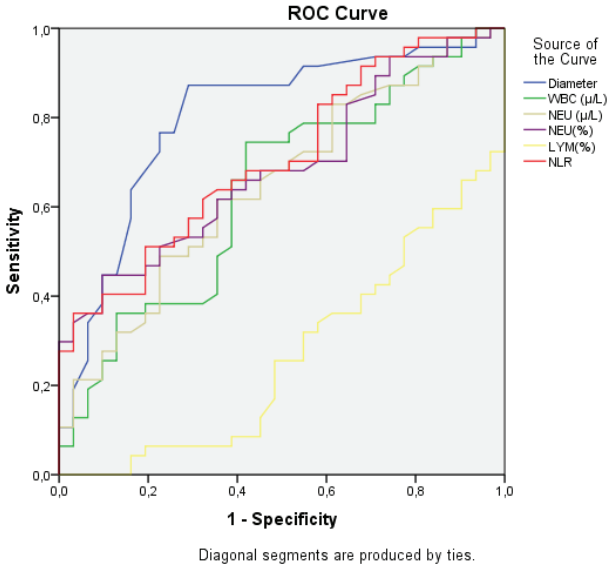

Figure 1. Receiver operating characteristic (ROC) analysis of the investigated parameters with their optimal cut-off values
ROC: Receiver operating characteristic, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio

Table 3. ROC curve analysis results of the parameters predicting malignancy

	Cut-off value	Sensitivity-specificity	AUC	95% CI	p-value
Variables					
Tumor diameter	1.95	(87.2-71.0%)	0.802	0.698-0.906	<0.001
WBC count (µ/L)	7.72	(61.3-66.0%)	0.638	0.512-0.764	0.040
Neutrophil count (µ/L)	5.32	(48.9-77.4%)	0.649	0.526-0.772	0.026
Neutrophil ratio (%)	64.2	(44.7-90.3%)	0.686	0.570-0.802	0.006
Lymphocyte ratio (%)	29.7	(63.8-67.7%)	0.267	0.156-0.378	0.001
NLR	2.72	(36.2-96.8%)	0.707	0.593-0.821	0.002

WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, AUC: Area under the curve, CI: Confidence interval

Table 4. Correlation of malignancy with tumor diameter and hematological parameters

Spearman's rho		Diameter	WBC (µ/L)	Neu (µ/L)	Neu (%)	Lym (%)	NLR
Malignancy	CC	0.432	0.237	0.278	0.355	-0.401	0.337
	Sig. (2-tailed)	<0.001	0.037	0.014	0.001	<0.001	0.003

WBC: White blood cell, Neu: Neutrophil, Lym: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio

obtained from our study can provide a new perspective for the literature in terms of the differentiation of benign/malignant testicular masses with negative tumor markers before orchiectomy.

This study has certain limitations, such as the retrospective and single-center design. Therefore, our findings should be confirmed by prospective randomized studies.

CONCLUSION

Tumor diameter, WBC count, neutrophil count, neutrophil ratio, lymphocyte ratio, and NLR can be used as predictive factors in the differentiation of benign-malignant intratesticular masses with negative testicular cancer markers before radical orchiectomy to prevent overtreatment. While the increased values of tumor diameter, WBC count, neutrophil count, neutrophil ratio, and NLR correlate with the possibility of malignancy, a decreased lymphocyte ratio can be evaluated in favor of malignancy.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision no: 2022-03-06, date: 07.02.2022).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Authorship Contributions

Surgical and Medical Practices: T.K., A.B., A.İ.T., Concept: T.K., F.A., M.E., H.P., A.B., A.İ.T., Design: F.A., A.E.F., M.E., E.G., Data Collection or Processing: F.A., A.E.F., İ.E., E.G., H.P., Analysis or Interpretation: T.K., E.G., H.P., K.G., Literature Search: T.K., A.E.F., M.E., E.G., K.G., Writing: T.K., F.A., A.E.F., H.P.

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REFERENCES

1. Gilligan T, Lin DW, Aggarwal R, Chism D, Cost N, Derweesh IH, et al. Testicular Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:1529-54.
2. Shpunt I, Leibovici D, Ikher S, Kovalyonok A, Avda Y, Jaber M, et al. Spermatogenesis in Testicles with Germ Cell Tumors. Isr Med Assoc J 2018;20:642-4.
3. Clifford TG, Burg ML, Hu B, Loh-Doyle J, Hugen CM, Cai J, et al. Satisfaction With Testicular Prosthesis After Radical Orchiectomy. Urology 2018;114:128-32.
4. Smith ZL, Werntz RP, Eggener SE. Testicular Cancer: Epidemiology, Diagnosis, and Management. Med Clin North Am 2018;102:251-64.
5. Leman ES, Gonzalgo ML. Prognostic features and markers for testicular cancer management. Indian J Urol 2010;26:76-81.
6. Mir MC, Pavan N, Gonzalgo ML. Current Clinical Applications of Testicular Cancer Biomarkers. Urol Clin North Am 2016;43:119-25.
7. Gokcen K, Dundar G, Gulbahar H, Gokce G, Gultekin EY. Can routine peripheral blood counts like neutrophil-to-lymphocyte ratio be beneficial in prediagnosis of testicular cancer and its stages? J Res Med Sci 2018;23:64.
8. Yuksel OH, Verit A, Sahin A, Urkmez A, Uruc F. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker. Int Braz J Urol 2016;42:53-9.
9. Arda E, Arikan G, Akdere H, Akgul M, Yuksel I. Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer. Int Braz J Urol 2020;46:216-23.
10. Raison N, Warrington J, Alnajjar HM, Muneer A, Ahmed K. The role of partial orchidectomy in the management of small testicular tumours: Fertility and endocrine function. Andrology 2020;8:988-95.
11. Woo LL, Ross JH. Partial orchiectomy vs. radical orchiectomy for pediatric testis tumors. Transl Androl Urol 2020;9:2400-7.
12. Carmignani L, Gadda F, Gazzano G, Nerva F, Mancini M, Ferruti M, et al. High incidence of benign testicular neoplasms diagnosed by ultrasound. J Urol 2003;170:1783-6.
13. Guner E, Tonyalı S. Benign testiscular masses and their characteristics determined in patients who underwent radical orchiectomy. The New J Urol 2018;13:44-7.
14. Grivennikov SI, Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev 2010;20:65-71.
15. De Larco JE, Wuertz BR, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res 2004;10:4895-900.
16. Teck Seo S, Singh VA, Yasin NF. Preoperative lymphocyte count in relation to sarcoma prognosis. J Orthop Surg (Hong Kong) 2019;27:2309499019854957.
17. Wei Y, Jiang YZ, Qian WH. Prognostic role of NLR in urinary cancers: a meta-analysis. PLoS One 2014;9:e92079.
18. Ilktac A, Dogan B, Ersoz C, Akcay M, Akbulut H. The relationship of neutrophil to lymphocyte ratio with testicular cancer. Int Braz J Urol 2020;46:101-7.