










Predictive role of neutrophil-to-lymphocyte ratio on upstaging of organ- confined invasive urothelial bladder cancer to non-organ- confined disease

Nötrofil lenfosit oranının organ sınırlı invaziv ürotelyal mesane kanserinin organ sınırlı olmayan hastalığa evre yükselmesini öngörmedeki rolü

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ABSTRACT

Objective: The aim of this study is to examine the usefulness of preoperative neutrophile-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratios to predict pathological upstaging of invasive bladder cancer who underwent radical cystectomy.

Material and methods: A total of 126 patients who underwent radical cystectomy at our clinic between January 2006 and March 2015 were retrospectively analysed. One hundred and twelve patients with organ-confined invasive bladder tumors (T2) detected at histopathological examination of transurethral resection material were included in the study. Upstaging was seen at histopathological examination of radical cystectomy specimens of 42 patients. We compared preoperative neutrophile-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio between upstaged and not-upstaged groups.

Results: There were no statistically significant correlation between age, time to radical cystectomy, gender, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio ratios and carcinoma in situ in upstaged and non-upstaged groups. Statistical analyses showed that preoperative neutrophile-to-lymphocyte ratio was higher in upstaged patients ($p=0.009$). In multivariate analysis preoperative neutrophile-to-lymphocyte ratio and positive surgical margin were significantly higher in upstaged group.

Conclusion: In organ-confined muscle invasive bladder cancer neutrophile-to-lymphocyte ratio seems to be an acceptable parameter to predict locally advanced disease.

Keywords: Bladder cancer; neutrophil-to-lymphocyte-ratio; upstaging.

ÖZ

Amaç: İnvaziv mesane kanseri nedeniyle radikal sistektomi yapılan hastalarda preoperatif nötrofil-lenfosit, platelet-lenfosit ve lenfosit-monosit oranlarının patolojik evre yükselmesini öngörmedeki kullanılabilirliğini araştırmak.

Gereç ve yöntemler: Ocak 2006-Mart 2015 tarihleri arasında kliniğimizde radikal sistektomi operasyonu yapılan 126 hasta retrospektif olarak incelendi. TUR patolojisi organ sınırlı invaziv mesane kanseri olarak bulunan 112 hasta çalışmaya dahil edildi. Kırk iki hastanın radikal sistektomi materyalinde evre yükselmesi görüldü. Evre yükselmesi olan ve olmayan gruplar arasında preoperatif nötrofil-lenfosit, platelet-lenfosit ve lenfosit-monosit oranları açısından karşılaştırma yapıldı.

Bulgular: Gruplar arasında yaş, radikal sistektomiye kadar geçen süre, cinsiyet lenfosit-monosit oranı, platelet lenfosit oranı ve karsinoma insitu varlığı açısından istatistiksel anlamlı fark izlenmedi. İstatistiksel analizlerde evre yükselmesi olan grupta nötrofil lenfosit oranının anlamlı olarak daha yüksek olduğu bulundu ($p=0,009$). Multivariete analizde evre yükselmesi olan grupta preoperatif nötrofil lenfosit oranı ve pozitif cerrahi sınırın daha yüksek olduğu bulundu.

Sonuç Nötrofil-lenfosit oranı organ sınırlı kas invaziv mesane kanserinde, lokal ileri hastalığı öngörmede kullanılabilir bir parametre gibi görünmektedir.

Anahtar Kelimeler: Mesane kanseri; nötrofil lenfosit oranı; evre yükselmesi.

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Introduction

Bladder cancer is a heterogeneous disease with a variable natural history.^[1] When considering the aggressive nature of the disease, the prevention the progression of Ta high-grade, T1, and CIS to higher stages demands intense care and requires timely treatment such as radical cystectomy (RC).^[2] RC is the treatment of choice in patients with muscle-invasive bladder cancer (MIBC). While nearly half of the cases is understaged, 32% to 43% of the patients with clinically organ-confined (OC) (\leq T2) bladder tumors are upstaged to nonorgan-confined pathological stage (NOC) (\geq T3) at the time of RC.^[3-5] Upstaging at the time of RC is associated with poor prognostic factors such as short disease-specific survival and higher risk for disease recurrence.^[5,6] Beyond that patients with stage T2 bladder tumors who are subsequently upstaged at the time of cystectomy can potentially benefit mostly from neoadjuvant chemotherapy.^[7] But the inability to identify such patients at the outset weakens its potential advantage, as documented by a modest 5% absolute 5-year overall survival benefit.^[8] The correlations between T2 staging, hydronephrosis, carcinoma in situ (CIS), high-grade disease, lymphovascular invasion and female gender with pathological upstaging were considered in some studies.^[9,10] But precystectomy parameters which are used for extravesical upstaging at the time of RC are not very reliable and sufficient to guide clinical decision making process.^[11,12] For this reason, other reliable pretreatment prognostic factors are urgently needed.^[12]

Cancer-related inflammation is the seventh hallmark of cancer, with inflammatory cells and mediators being an essential component of the tumor micro-environment.^[13] Changes in host inflammatory responses and tumor relations have been increasingly recognized in various tumor types and inflammatory cells around the tumor cells play a significant role in the progress and prognosis of tumors.^[14] The systemic inflammatory response is usually measured by surrogate biochemical parameters, such as C-reactive protein or circulating inflammatory blood cells. This inflammatory response is detectable in the peripheral blood, evidenced by neutrophilia and/or lymphopenia.^[15] Neutrophil-to-lymphocyte-ratio (NLR) is a well-known inexpensive and effective representative marker of inflammatory condition.^[16] Platelets are key elements linking the processes of hemostasis, inflammation, and tissue repair.^[17] The presence of both neutrophilia and thrombocytosis tends to represent a nonspecific response to cancer-related inflammation.^[18] The predictive role of platelet-to-lymphocyte ratio (PLR) was investigated with preoperative lymphocyte-to-monocyte ratio (LMR) so as to predict overall survival in patients with bladder cancer undergoing RC.^[19] The preoperative LMR is another inflammatory marker which has been shown to be a potential prognostic marker in patients with non-metastatic clear cell renal carcinoma.^[20]

The aim of this study was to investigate the predictive role of preoperative NLR, PLR and LMR for upstaging of stage T2 organ- confined invasive urothelial bladder cancer to non-organ- confined disease at RC.

Material and methods

Study design

We retrospectively reviewed the data of patients with urinary bladder cancer who underwent RC at our clinic between January 2006 and March 2015. No patients received neo-adjuvant therapy. Patients who had organ- confined invasive urothelial urinary bladder cancer (T2) included. Finally 112 patients met the study criteria. We divided the patients into two groups; patients with (Group 1) and without (Group 2) upstaging from organ- confined invasive bladder cancer to non-organ-confined disease. Staging was made according to tumor-node-metastasis (TNM) classification system. We investigated preoperative NLR, PLR, LMR, age, gender, time to RC, CIS and postoperative pathological findings such as number of lymph node (LN) excised, LN metastasis, percentage of positive LNs, presence of positive surgical margin. We calculated NLR, LMR and PLR from a preoperative blood samples obtained within three days. Upstaging to non-organ- confined disease was defined as \geq T3 disease. Our research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”. Written informed consent was obtained from all patients who participated in this study.

Statistical analysis

Statistical analyses were performed with Statistical Package of Social Sciences version 21 (IBM Corp.; Armonk, NY, USA). Categorical variables were presented as numbers and percentages and compared with *chi-square* and Fischer’s exact test. Continuous variables were presented as means and standard deviations and compared with independent sample-t test. Multivariate logistic regression analysis was performed to assess the potential association between tumor upstaging and NLR, number and percentage of positive LNs, LN metastasis and positive surgical margins. Receiver operating characteristic (ROC) curve was generated to assess the predictive role of NLR for upstaging. A cut-off value for NLR was calculated using Youden index method.

Results

One hundred and twelve out of 126 consecutive patients undergoing RC met the study criteria. There were two groups; patients with (Group 1) and without (Group 2) upstaging from organ-confined invasive bladder cancer to non-organ- confined disease. Eight patients were female. The mean age of Groups 1 and 2

was 63.5±8.7 and 63.7±9.9 years, respectively. Table 1 shows the characteristics of Groups 1 and 2. Of the patients with cT2 tumors 58 (51.7%) had pT2 tumors, 12 (10%) were down staged, 20 (17.8%) were upstaged to locally invasive cancer (pT3) and 22 (19.6%) were upstaged to metastatic (pT4) disease. 60% of the patients with pT3 disease had no LN metastasis.

In univariate analysis there were no statistically significant correlation between upstaging and age, time to RC, gender, LMR, PLR, and CIS in the groups. Preoperatively, increased NLR was significantly correlated with upstaging (p=0.009). We also analyzed postoperative findings such as number of positive LNs, percentage of positive LNs, and positive surgical margin. Number of patients with positive LNs, percentage of positive LNs, positive surgical margins and LN metastasis was higher in Group 1 (p=0.004, p=0.001, p=0.001 and p=0.003, respectively). In multivariate analysis NLR and positive surgical margin had significant association with upstaging (p=0.002) (Table 2). For 112 patients with organ- confined cancer as histopathologically detected in TURBT specimens, preoperative NLR of 4.05 calculated by ROC curve showed the best sensitivity and specificity rates. Area under curve of (AUC) NLR was 0.661 (p=0.004 and 95% confidence interval (CI), 0.555-0.767) (Figure 1).

Table 1. Comparison of the patients with (Group 1) and without (Group 2) upstaging regarding preoperative and postoperative characteristics

	Group 1 (n=42)	Group 2 (n=70)	p
	mean±SD (min-max)		
Age (years)	63.5±8.7 (37-79)	63.7±9.9 (39-83)	0.921*
Time to RC (days)	38.3±14.9 (19-109)	36.4±9.1 (17-63)	0.459*
NLR	3.7±1.3 (1.6-7.7)	3.0±1.4 (0.7-9.7)	0.009*
LMR	4.0±2.0 (1.4-11.9)	3.9±1.8 (0.9-12)	0.892*
PLR	143.9±64.7 (30.7-315.7)	155.1±66.2 (57.1-383.7)	0.383*
Number of LN excised	8.7±5.4 (0-24)	8.1±5.1 (0-33)	0.577*
Number of positive LN	1.1±0.4 (0-12)	0.2±0.1 (0-4)	0.004*
Positive LN (%)	12.9±4.1 (0-100)	2.4±0.8 (0-33.3)	0.001*
Gender (male/female)	41/1	63/7	0.255†
CIS, n (%)	12 (29)	14 (20)	0.206‡
LN metastasis, n (%)	14 (33)	9 (13)	0.003‡
Positive surgical margin, n (%)	11 (26)	2 (3)	<0.001†
Preoperative grade (Gr1 or Gr2/Gr3)	1/41	3/67	0.176‡

*Independent sample t test, †Fischer's exact test, ‡Chi-square test. SD: standard deviation; RC: radical cystectomy; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LN: lymph node; CIS: carcinoma in situ

Discussion

Clinical staging is a fundamental step, both in the treatment planning and when counseling patients with bladder cancer.^[9] Despite modern techniques, discordance in clinical and pathological staging which is based on histopathological examination of the excised specimens after RC, is a common finding.^[9] Pathological staging has the strongest predictive value for patient outcome. Survival is high in patients with non-muscle invasive bladder cancer after RC; and survival is favourable in patients treated with early RC compared to those having radical surgery after recurrence of tumors.^[21] It is very important to

Table 2. Multivariate analysis of perioperative characteristics of the patients in relation to upstaging

	B coefficient	Upstaging		
		Odds ratio	95% CI	p
NLR	0.674	1.96	1.29-2.99	0.002
Number of positive LN	0.035	1.04	0.41-2.61	0.940
Percentage of positive LN	0.063	1.07	0.93-1.22	0.361
LN metastasis	-0.239	0.79	0.08-8.14	0.841
Positive surgical margin	2.61	13.60	2.63-70.20	0.002

NLR: neutrophil-to-lymphocyte ratio; LN: lymph node

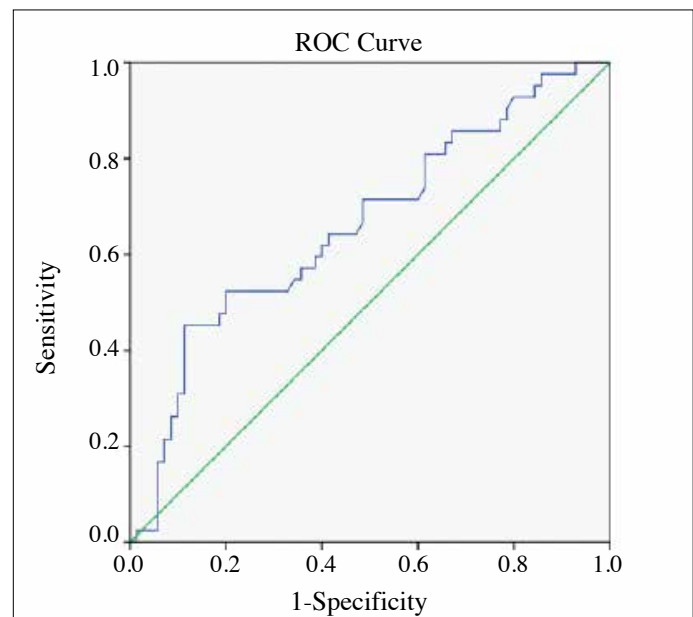


Figure 1. Receiver operating characteristic (ROC) curves for NLR in predicting tumor upstaging

ROC analysis revealed area under curve (AUC) of 0.661 (p=0.004 and 95% CI, 0.555-0.767). A cut-off value of 4.05 (sensitivity, 45% and specificity, 88%) was calculated for preoperative NLR

predict the true stage for planning neo-adjuvant chemotherapy to improve survival rates in patients with possible non-organ-confined disease. Some novel inflammatory indicators can be established by combining peripheral blood cell counts, such as NLR, PLR, and LMR, which have been investigated for their predictive prognostic values in malignant tumors.^[12] Based on the numbers of circulating inflammatory cells, some indexes have been calculated and used as valuable prognostic predictors.^[12] In this study, our purpose is to determine the predictive value of preoperative inflammatory markers for upstaging of bladder cancer in patients who underwent RC.

Increasing evidence supports the involvement of systemic inflammation in cancer development and progression.^[15] For various types of cancer, the degree of systemic inflammation reflects the tumor burden.^[22] Evidence of systemic inflammation, as marked by leukocytosis or elevated C-reactive protein, is a known poor prognostic factor in cancers and such markers portend worse prognosis and response to therapy.^[11] The preoperative NLR may be a prognostic biomarker for patients undergoing RC for urothelial bladder carcinoma.^[23,24] Kawahara et al.^[25] showed that the NLR was an independent prognostic factor in bladder cancer patients who underwent RC. Potretzke et al.^[11] demonstrated that patients with preoperative NLR elevation could be upstaged at the time of RC and might benefit from neo-adjuvant chemotherapy. In the current study, NLR was the only parameter significantly correlated with upstaging in both univariate and multivariate analysis ($p=0.009$, and $p=0.002$ respectively). The other inflammatory parameters, PLR and LMR, were not statistically significant for upstaging of bladder cancer. There were higher number of positive LNs and higher percentage of positive LNs in patients with upstaged bladder cancer ($p=0.004$, and $p=0.001$ respectively). Also this group of patients had more positive surgical margins and LN metastasis than the other group ($p=0.001$ and $p=0.003$ respectively).

Neutrophil-to-lymphocyte-ratio reflects the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses.^[26] A high NLR value reflects an augmented inflammatory reaction, which in turn, correlates with decreased tumor-specific immunity.^[27] But a clear definition of cut-off values remains to be determined. In a recent review, Marchioni et al.^[26] reported that NLR was considered as a prognostic marker in 87.5%, 80%, and 60% of the studies on upper urothelial cancer, urothelial bladder cancer, and metastatic and advanced disease, respectively. They suggested a clear definition of NLR cut-off value, and asserted that ≥ 2 value can be appropriate to define a high NLR.^[26] Morizawa et al.^[28] showed that the pretreatment NLR (≥ 2.6) and an infiltrative growth pattern at the tumor invasion front were significantly associated with recurrence-free survival, cancer-specific survival and overall survival. Gondo et al.^[29] observed that NLR was an independent prognostic factor

with a NLR cut-off value of 2.5. With a similar cut-off value, Krane et al.^[30] reported that the patients with elevated NLR before RC have worse overall survival than patients without markers of systemic inflammation. In another study, Kang et al.^[31] revealed that postoperative NLR during the early recovery period demonstrated prognostic significance for bladder cancer patients undergoing RC with pelvic lymph node dissection with a NLR cut-off value of 2. They also stated that NLR is associated with extravesical disease.^[31] In our study, a preoperative cut-off value of NLR was found as 4.05 with a 45% sensitivity, 88% specificity in patients with organ-confined cancer as detected histopathologically in TURBT specimens. Our results showed higher number of positive LNs and a higher rate of positive LNs in this group of patients. Also there were greater number of patients with positive surgical margins and LN metastases in this group. Although this threshold of NLR value was higher than that found in similar studies, our analysis showed that this cut-off value gave us significant knowledge about the possibility of extravesical spread of the disease. This is an important finding for encouraging an extended lymphadenectomy for most urologists who are desiring to perform a successful curative surgery.

Another important subject matter in the treatment of bladder cancer is the median delay from diagnosis to RC which mostly results with upstaging of the cancer. European Association of Urology (EAU) recommends to perform RC within 3 months after diagnosis of muscle-invasive bladder cancer is made.^[3] In the current approaches, reliable predictors of extravesical upstaging at the time of RC do not exist.^[11] T2 staging, high grade disease, female gender and hydronephrosis are some of these expected predictors for a possible progressive tumor and poorer overall survival. In the present study, we did not find any correlation between upstaging and age, time to RC, and gender. We have found that preoperative NLR is useful to predict upstaging of organ-confined invasive bladder cancer to non-organ-confined disease. If those patients likely to have non-organ confined disease could be accurately identified before RC, they could be offered neo-adjuvant therapy which provides a survival advantage.^[11] Preoperative NLR is a simple measurement that can be used to identify high-risk patients who may be upstaged at the time of RC.^[11]

There are some limitations of this study. First, the study design is retrospective. Secondly, study group consists of a small sample size. Thirdly, the restaging TURMT is operator-dependent and pathological evaluation is pathologists-dependent. Finally, there is still no accepted NLR cut-off value which is different in various studies.

In conclusion, NLR is a useful and an acceptable parameter to predict locally advanced disease in organ-confined muscle

invasive bladder cancer. NLR should be a part of accurate clinical staging before RC to prevent upstaging and to provide optimal treatment approach which identifies high risk extravesical disease for neo-adjuvant chemotherapy before undergoing RC.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”, (amended in October 2013).

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