Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Is preoperative neutrophil-lymphocyte ratio important in patients who undergo radical nephroureterectomy for upper urinary tract urothelial cancer?

Bahri Gok[a,*]

[a]*Ankara Yildirim Beyazit University, School of Medicine Affiliated with Ankara City Hospital, Department of Urology, Ankara, Turkey*

ARTICLE INFO

Keywords:
Urothelial cancer
Upper urinary tract
Radical nephroureterectomy
Recurrence
Neutrophil-lymphocyte ratio

Received: Aug 17, 2021
Accepted: Nov 02, 2021
Available Online: May XX, 2022

DOI:
10.5455/annalsmedres.2021.08.527

Abstract

Aim: To evaluate the effect of preoperative blood count parameters and pathological features on recurrence in patients who underwent Radical Nephroureterectomy (RNU) and Bladder Cuff Resection for Upper Urinary Tract Urothelial Cancer (UTUC).

Material and Methods: The data of patients who underwent RNU for UTUC were reviewed retrospectively. According to the follow-up data, the patients were divided into 2 groups as recurrence and non-recurrence. It was examined whether there was a difference between the groups in terms of preoperative blood count parameters (neutrophil, lymphocyte, eosinophil, monocytes, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio) and final pathological features. A $p < 0.05$ was considered statistically significant.

Results: A total of 64 patients were included in the study. Recurrence developed in 24 patients during follow-up. Age (p=0.039), neutrophil-lymphocyte ratio (p=0.026), history of bladder cancer (p=0.004), pathological stage (p=0.03), multifocality (p=0.007), positive bladder cuff (p=0.006) and surgical margin positivity (p=0.029) was found to be significantly different in the recurrence group compared to the non-recurrence group.

Conclusion: In addition to pathological features, preoperative Neutrophil-Lymphocyte ratio may be associated with recurrence in patients undergoing UTUC and RNU. It should be supported by studies with a larger number of patients.

Introduction

Upper Urinary Tract Urothelial Carcinoma (UTUC) is a rare disease constituting 5% of all urothelial cancers [1]. Although it is rare, it proceeds with high rates in terms of local and distant recurrences at the time of diagnosis and in later follow-ups. The standard treatment for UTUC is radical nephroureterectomy and bladder cuff resection [2-4].

Pathological variables such as the stage, grade, lymph node status, accompanying in situ carcinoma (CIS), etc. are known to be effective in predicting recurrence. However, the majority of these variables are pathological parameters, which can be identified after the operation [5–7].

It can be argued that predicting the recurrence by using preoperative clinical parameters may provide us with many benefits in treatment strategies and follow-ups of patients undergoing UTUC and surgery [8]. There have been many studies in the literature until our present time conducted to examine the relations between cancer development, progression, and systemic inflammatory response. Among these, the Neutrophil-Lymphocyte Ratio (NLR) is the most widely known [9, 10].

In this study, the purpose was to investigate the relations between recurrence and pathological variables known to be associated with recurrence by adding blood count parameters to them.

Material and Methods

The data of a total of 64 patients who underwent radical nephroureterectomy and bladder cuff resection for UTUC between March 2007 and February 2018 were reviewed, retrospectively. This study was approved by Ankara Yildirim Beyazit University, School of Medicine, Ethics Committee. Abdominal and thorax computerized tomography were performed for each patient for preoperative clinical staging. The age, gender, tumor side, smoking status, presence of comorbidities (i.e. diabetes and hypertension), previous and concomitant bladder CA history, tumor localization, postoperative transfusion requirement, multifocality, tumor pattern, tumor size, neu-

*Corresponding author:
Email address: drbahrigok@gmail.com (Bahri Gok)

Table 1. Clinicopathological features of patients

Variables	
Age	68.1±10.8 (34-89)
Gender (F/M)	5/59
Diabetes mellitus	11 (17.1 %)
Hypertension	25 (39 %)
Smoking	41 (64 %)
Site (Right/Left)	35/29
Preoperative neutrophil count (x109/L)	5.6 (2.1-23)
Preoperative lymphocyte count (x109/L)	2 (0.4-4.1)
Preoperative eosinophil count (x109/L)	1.2 (0.1-0.8)
Preoperative monocytes count (x109/L)	0.64 (0.15-1.31)
Preoperative NLR ratio (%)	3.8 (1.1-59)
Preoperative PLR ratio (%)	154.5 (65-406)
Previous bladder cancer history (%)	18 (28%)
Hydronephrosis (%)	50 (78%)
Pathologic stage> pT2≤pT2	21 (32.8%)43 (67%)
Pathologic gradeHighLowNo tumor	40 (62.5%)22 (34.3%)2 (3%)
Lymphovascular invasion	13 (20.3%)
Concominant bladder cancer	19 (29.6%)
Tumor localizationUreterPelvicUreter+pelvic	15 (23.4%) 30 (46.8%) 17 (26.5%)
Transfusion requirements	19 (29.6%)
Positive bladder cuff	12 (18.7%)
Concominant carcinoma insitu	2 (3%)
Multifocality	21 (32.8%)
Pathologic Lymph node	3 (4.6%)
Surgical margin positivity	14 (21.8%)
Tumor size (mm)	42.3±21.3 (10-100)
Adjuvant chemotherapy	16 (25%)
Follow-up time (month)	36.5±32.2 (3-120)

trophil, lymphocyte, monocytes, eosinophil, neutrophil-lymphocyte ratio, and platelet lymphocyte ratio (PLR) of the patients were recorded. The pathological stage, grade, lymphovascular invasion, presence of accompanying CIS, bladder cuff and surgical margin positivity, presence of pathological lymph node, and adjuvant chemotherapy were also recorded. The patients were divided into two groups as those with and without recurrence in their follow-ups. Whether there were differences between the two groups in terms of these parameters was also investigated.

Statistical analysis

The IBM Statistical Package for Social Sciences 23.0 Package Program (IBM SPSS Corp.; Armonk, NY, USA) was used for data analysis. The Kruskal-Wallis Test was used to check the conformity of the data to normal distribution. The Mann-Whitney U Test was used for the data that did not fit the normal distribution between the groups, and the Student's-t Test was used for the data that did fit the normal distribution. The Chi-Square Test was used for categorical variables.

Results

A total of 64 patients were included in the study. The mean age of the patients was 68.1±10.8 (34-89). The mean patient follow-up duration was 36.5 months. The demographic and clinical characteristics of the patients are summarized in Table 1.

Recurrence was detected in 24 patients, and recurrence was not detected in 40 patients in the follow-up of the patients. Sixteen patients received adjuvant chemotherapy. Some patients could not receive adjuvant chemotherapy due to elevated GFR after nephroureterectomy. When patients with and without recurrence were divided into two groups, no differences were detected between the groups in terms of preoperative neutrophil, lymphocyte, monocyte, eosinophil, and PLR ratios. It was also found that the NLR was statistically significantly higher in the group with recurrence than those without (6.3±4.6, 5.3±2.1, respectively p=0.065).

Also, no differences were detected in terms of tumor size, hydronephrosis grade, gender, smoking, concomitant bladder cancer (BCA), tumor localization, transfusion requirement, grade, lymphovascular invasion, and presence of pathological accompanying CIS in nephroureterectomy spesimens (Table 2). The mean patient age, previous history of BCA, positive bladder cuff, multifocal tumor, pathological T stage, positive surgical margin, and adjuvant chemotherapy were statistically more significant in the group with recurrence compared to the group without (Table 2).

Discussion

In this retrospective single-center study, whether preoperative blood count parameters had an effect on recurrence was evaluated, as well as pathological features known to be effective in this respect. Among the pathological parameters, previous BCA history, positive bladder cuff, multifocality, pathological T stage, and surgical margin positivity were found to be significant; and among the preoperative blood count parameters, only NLR was associated with recurrence.

Tumor-induced inflammation is important in the development of malignancy, and is also effective in every stage of tumorigenesis. The immune response of the host to malignancy may cause changes in cellular element levels such as lymphocytes, neutrophils, platelets, and monocytes. It is known that inflammation markers such as NLR and PLR have prognostic roles in some malignancies. There are also articles that investigate the role of these prognostic markers in UTUC [11-14].

Various studies conducted on inflammatory markers have been reported in the literature until our present time. Most reports are related to the NLR ratios among these. De Larco et al. showed that tumor-associated neutrophils might have important roles in the tumor microenvironment and local angiogenesis [15]. Tumor angiogenesis also triggers the progression and migration of tumor cells. Also, weak immunity in lymphopenia against the tumor results in the triggering of the aggressiveness of the tumor. Although this relation seems important, it was insufficient in predicting poor pathological characteristics in the final pathology [16]. In a study conducted by Luo et al. with 234 patients, it was stated that the pathological stage and preoperative NLR had independent predictive

Table 2. Comparison of clinicopathological features between groups

Variables	Recurrence+	Recurrence-	p value
Age	70.7±8.2	66.6±11.9	0.039
Gender (M/F)	21/3	38/2	0.355
Smoking	15 (62.5%)	26 (65%)	0.84
Diabetes mellitus	4 (16.6%)	7 (17.5%)	p > 0.05
Hypertension	5 (20.8%)	20 (50%)	0.033
Preoperative neutrophil count (x109/L)	6.3±4.6	5.3±2.1	0.065
Preoperative lymphocyte count (x109/L)	1.9±0.6	2±0.6	0.834
Preoperative eosinophil count (x109/L)	0.16±0.15	0.19±0.15	0.747
Preoperative monocytes count (x109/L)	0.59±0.25	0.66±0.23	0.850
Preoperative NLR ratio	5.46±11.7	2.9±1.9	0.026
Preoperative PLR ratio	161.9±75.7	150±73.2	0.722
Previous bladder cancer history	12 (50%)	6 (15%)	0.004
Hydronephrosis	20 (83.3%)	30 (75%)	0.541
Pathologic stage> pT2	12 (50%)	9 (22.5 %)	0.03
≤pT2	12 (50%)	31 (77.5 %)	
Pathologic gradeHighLowNo tumor	19 (79.1%)5 (20.8%)	21 (52.5%)17 (42.5%)2 (5%)	0.084
Lymphovascular invasion	6 (25%)	7 (17.5%)	0.53
Concominant bladder cancer	8 (33.3%)	11 (27.5%)	0.778
Transfusion requirements	9 (37.5%)	10 (25%)	0.398
Positive bladder cuff	9 (37.5%)	3 (7.5%)	0.006
Concominant carcinoma insitu	2 (8.3%)	0	0.137
Multifocality	13 (54.1%)	8 (2%)	0.007
Pathologic Lymph node	2 (8.3%)	1 (2.5%)	0.551
Surgical margin positivity	9 (37.5%)	5 (12.5%)	0.029
Tumor size (mm)	36.2	30.2	0.21

roles for cancer-related death and recurrence after RNU [13]. Dalpiaz et al. found that high preoperative NLR and PLR were associated with cancer-related mortality in 202 patients that underwent UTUC and RNU [17]. In a multicenter study that included 665 patients, Tanaka et al. found that high preoperative NLR was closely associated with disease recurrence and mortality, as well as poor characteristics in the final pathology [12]. Vartolomei et al. reported in their multicenter study with 2.477 patients that preoperative NLR rate was associated with tumor aggressiveness [11].

In their multicenter study conducted with 10,339 patients, Shao et al. found that the preoperative NLR and PLR rates were associated with low survival and poor prognosis [9]. In their study conducted with 424 patients, Jan et al. developed a Systemic Inflammation Index Model, and reported that NLR and PLR rates were associated with progression and survival [18]. Zheng et al. [19], Son et al. [20], Altan et al. [8], Huang et al. [21], and Song et al. [22] found that preoperative PLR [200B?][200B?]was associated with poor prognosis following UTUC and radical nephroureterectomy.

We examined the results of UTUC and radical nephroureterectomy in our series based on the studies in the literature. In our series, recurrence developed in 24 patients. We compared the preoperative NLR, PLR, neutrophil, lymphocyte, eosinophil, and monocyte counts of patients with and without recurrence. According to our results, it was found that the NLR was associated with recurrence between the groups with and without recurrence. It was also found that the mean age, previous history of BCA, positive bladder cuff, multifocal tumor, pathological T stage, and positive surgical margin of the patient were the factors associated with recurrence. In our results, smoking was not found to be associated with tumor grade, lymphovascular invasion, accompanying BCA, and accompanying CIS recurrence, which seems to be inconsistent with the literature data. However, we believe that this is related to the low number of our patients.

To the best of our knowledge, there are no other studies in which radical nephroureterectomy was performed for UTUC and the effect of all blood count parameters was examined in terms of recurrence in the literature. The low number of patients and the retrospective nature of our study are among its most important limitations.

Conclusion

Preoperative Neutrophil-to Lymphocyte Ratio is associated with recurrence after radical nephroureterectomy and bladder cuff resection in upper urinary tract urothelial cancers. However, this must be supported by multicenter studies with a higher number of patients.

References

1. Soria F, Shariat SF, Lerner SP, Fritsche H-M, Rink M, Kassouf W, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol. 2017 Mar;35(3):379–87.
2. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018 Jan;73(1):111–22.

3. Xylinas E, Rink M, Cha EK, Clozel T, Lee RK, Fajkovic H, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2014 Jan;65(1):210–7.
4. Soria F, Giordano A, D'Andrea D, Moschini M, Rouprêt M, Margulis V, et al. Prognostic value of the systemic inflammation modified Glasgow prognostic score in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy: Results from a large multicenter international collaboration. Urol Oncol. 2020 Jun;38(6):602.e11-602.e19.
5. Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche H-M, Bastian PJ, et al. Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. Eur Urol. 2010 Jun;57(6):1064–71.
6. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009 Mar 15;115(6):1224–33.
7. Kohada Y, Hayashi T, Goto K, Kobatake K, Abdi H, Honda Y, et al. Preoperative risk classification using neutrophil-lymphocyte ratio and hydronephrosis for upper tract urothelial carcinoma. Jpn J Clin Oncol. 2018 Sep 1;48(9):841–50.
8. Altan M, Haberal HB, Akdoğan B, Özen H. A critical prognostic analysis of neutrophil-lymphocyte ratio for patients undergoing nephroureterectomy due to upper urinary tract urothelial carcinoma. Int J Clin Oncol. 2017 Oct;22(5):964–71.
9. Shao Y, Li W, Wang D, Wu B. Prognostic value of preoperative lymphocyte-related systemic inflammatory biomarkers in upper tract urothelial carcinoma patients treated with radical nephroureterectomy: a systematic review and meta-analysis. World J Surg Oncol. 2020 Oct 23;18(1):273.
10. Cimen HI, Halis F, Saglam HS, Gokce A. Can neutrophil to lymphocyte ratio predict lamina propria invasion in patients with non muscle invasive bladder cancer? Int Braz J Urol Off J Braz Soc Urol. 2017 Feb;43(1):67–72.
11. Vartolomei MD, Mathieu R, Margulis V, Karam JA, Rouprêt M, Lucca I, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol. 2017 Jan;35(1):121–30.
12. Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Shirotake S, Miyazaki Y, et al. A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. Ann Surg Oncol. 2014 Nov;21(12):4041–8.
13. Luo H-L, Chen Y-T, Chuang Y-C, Cheng Y-T, Lee W-C, Kang C-H, et al. Subclassification of upper urinary tract urothelial carcinoma by the neutrophil-to-lymphocyte ratio (NLR) improves prediction of oncological outcome. BJU Int. 2014 May;113(5b):E144-149.
14. Zhao, Z., Xie, S., Feng, B., Zhang, S., Sun, Y., Guo, H., & Yang, R. (2020). Preoperative Risk Classification Using Neutrophil-to-Lymphocyte Ratio and Albumin for Upper Tract Urothelial Carcinoma Treated with Radical Nephroureterectomy. Cancer management and research, 12, 9023–9032. https://doi.org/10.2147/CMAR.S274332
15. De Larco JE, Wuertz BRK, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res Off J Am Assoc Cancer Res. 2004 Aug 1;10(15):4895–900.
16. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology. 2007 May;121(1):1–14.
17. Dalpiaz O, Ehrlich GC, Mannweiler S, Hernández JMM, Gerger A, Stojakovic T, et al. Validation of pretreatment neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. BJU Int. 2014 Sep;114(3):334–9.
18. Jan H-C, Yang W-H, Ou C-H. Combination of the Preoperative Systemic Immune-Inflammation Index and Monocyte-Lymphocyte Ratio as a Novel Prognostic Factor in Patients with Upper-Tract Urothelial Carcinoma. Ann Surg Oncol. 2019 Feb;26(2):669–84.
19. Zheng Y, Chen Y, Chen J, Chen W, Pan Y, Bao L, et al. Combination of Systemic Inflammation Response Index and Platelet-to-Lymphocyte Ratio as a Novel Prognostic Marker of Upper Tract Urothelial Carcinoma After Radical Nephroureterectomy. Front Oncol. 2019;9:914.
20. Son S, Hwang E-C, Jung S-I, Kwon D-D, Choi S-H, Kwon T-G, et al. Prognostic value of preoperative systemic inflammation markers in localized upper tract urothelial cell carcinoma: a large, multicenter cohort analysis. Minerva Urol E Nefrol Ital J Urol Nephrol. 2018 Jun;70(3):300–9.
21. Huang J, Yuan Y, Wang Y, Zhang J, Kong W, Chen H, et al. Prognostic value of preoperative plasma fibrinogen level and platelet-to-lymphocyte ratio (F-PLR) in patients with localized upper tract urothelial carcinoma. Oncotarget. 2017 May 30;8(22):36761–71.
22. Song X, Zhang G-M, Ma X-C, Luo L, Li B, Chai D-Y, et al. Comparison of preoperative neutrophil-lymphocyte, lymphocyte-monocyte, and platelet-lymphocyte ratios in patients with upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy. OncoTargets Ther. 2016;9:1399–407.