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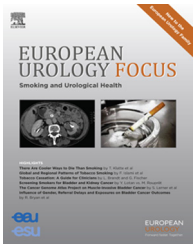

Priority Focus – Urothelial Cancer

Editorial by Brant Inman and Kae Jack Tay on pp. 64–65 of this issue

Impact of Combined Use of Blood-based Inflammatory Markers on Patients with Upper Tract Urothelial Carcinoma Following Radical Nephroureterectomy: Proposal of a Cumulative Marker Score as a Novel Predictive Tool for Prognosis

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Article info

Article history:
Accepted February 4, 2015

Associate Editor:
Gianluca Giannarini

Keywords:
Urothelial carcinoma
Upper urinary tract
C-reactive protein
Neutrophil-to-lymphocyte ratio
Fibrinogen
Outcome
Prognosis
Marker score

Abstract

Background: Previous studies showed the prognostic impact of preoperative levels of neutrophil-to-lymphocyte ratio (NLR), plasma fibrinogen, and serum C-reactive protein (CRP) in surgically treated upper tract urothelial carcinoma; however, few papers have discussed the proper use of these indices.
Objective: To investigate whether combinations of these three markers, as a cumulative marker score (CMS), improve the accuracy of prognostic models following radical nephroureterectomy (RNU).
Design, setting, and participants: A total of 394 patients from multiple institutions were included. Median follow-up was 30 mo.
Intervention: All patients underwent RNU without neoadjuvant chemotherapy.
Outcome measurements and statistical analysis: Associated outcomes were assessed using multivariate analysis. The CMS was defined as the number of elevated levels of preoperative NLR, plasma fibrinogen, and serum CRP.
Results and limitations: Multivariate analyses revealed that an increasing CMS was independently associated with high rates of disease recurrence, cancer-specific mortality, and all-cause mortality following RNU. Addition of the CMS to a model that included standard clinicopathologic predictors significantly improved predictive accuracy by 2.7% for disease recurrence, 3.9% for cancer-specific mortality, and 4.0% for all-cause mortality, which were the highest among other prognostic models using each marker alone or combinations of two. The study is limited by its retrospective nature.
Conclusions: Although the use of each inflammatory marker alone may be as predictive as clinicopathologic indices for prognosis, combinations like CMS can provide more accurate prognostic models following RNU.
Patient summary: Elevation of blood-based inflammatory markers may be useful for predicting prognosis because of their low cost and accessibility. Among blood-based indices, we examined the efficacy of preoperative neutrophil-to-lymphocyte ratio, plasma fibrinogen, and serum C-reactive protein levels. Although use of each marker alone provides additional prognostic information, the combination of all three markers would be more predictive than any single marker or combinations of two.

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http://dx.doi.org/10.1016/j.euf.2015.02.001

1. Introduction

The prognosis of upper tract urothelial carcinoma (UTUC) remains poor due to a high rate of disease relapse after resection [1–4]. Radical nephroureterectomy (RNU) is the gold standard for the treatment of nonmetastatic UTUCs; however, the 5-yr disease-specific survival rate is <50% for pT2–3 tumors and <10% for pT4 tumors [1]. To predict UTUC outcomes, many researchers have attempted to identify potent biomarkers using human tissue and blood samples [1,5,6], although the vast majority of markers have not yet been applied in clinical practice. In this regard, a growing body of evidence suggests the efficacy of systemic inflammatory markers from blood samples for predicting patient prognosis and pathologic profiles in UTUC [7–12], and these biomarkers may become useful because of their low cost and easy accessibility.

The associations between the involvement of systemic inflammation and cancer development are now evident. Tumor recruits endothelial cells, fibroblasts, and inflammatory cells into the tumor bed and then shapes its unique stroma, suggesting that the elevation of systemic inflammatory markers may reflect the development of an inflammation-associated microenvironment in tumors [13–16]. In UTUC, we and others reported the prognostic value of typical preoperative inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), plasma fibrinogen, and serum level of C-reactive protein (CRP) in patients following RNU [7–12].

In the present study, we hypothesize that combinations of these markers would provide more accurate prognostic models than a single marker. The aim of this study was to determine the associations of preoperative NLR, plasma fibrinogen, and CRP with clinicopathologic features and to develop multivariate models for prognosis based on each inflammatory marker alone or in combination.

2. Patients and methods

After institutional review board approval, a total of seven Japanese institutions—Keio University Hospital and six affiliated institutions—provided data on 457 patients who underwent open or laparoscopic RNU for localized UTUC between 1995 and 2011. We excluded patients with a history of muscle-invasive urothelial carcinoma (UC) of the urinary bladder and those who received neoadjuvant chemotherapies. After excluding patients without a full set of blood data and those with active infection accompanied by fever (>38 °C), the presence of hematological

Table 1 – Association of baseline clinicopathologic characteristics and elevation of preoperative neutrophil-to-lymphocyte ratio, plasma fibrinogen, and serum C-reactive protein in 394 patients treated with radical nephroureterectomy

Characteristic	All patients (*n* = 394), *n* (%)	Elevation of preoperative marker levels								
		NLR, *n* (%)			Plasma fibrinogen, *n* (%)			Serum CRP, *n* (%)		
		Elevated (*n* = 108)	Nonelevated (*n* = 286)	*p* value	Elevated (*n* = 117)	Nonelevated (*n* = 277)	*p* value	Elevated (*n* = 93)	Nonelevated (*n* = 301)	*p* value
Age at RNU										
≤70 yr	205 (52.0)	46 (42.6)	159 (55.6)		57 (48.7)	148 (53.4)		46 (49.5)	159 (52.8)	
>70 yr	189 (48.0)	62 (57.4)	127 (44.4)	0.021	60 (51.3)	129 (46.6)	0.392	47 (50.5)	142 (47.2)	0.571
Sex										
Male	289 (73.4)	77 (71.3)	212 (74.1)		84 (71.8)	205 (74.0)		68 (73.1)	221 (73.4)	
Female	105 (26.6)	31 (28.7)	74 (25.9)	0.571	33 (28.2)	72 (26.0)	0.650	25 (26.9)	80 (26.6)	0.954
Tumor location										
Renal pelvis	232 (58.9)	64 (59.3)	168 (58.7)		70 (59.8)	162 (58.5)		53 (57.0)	179 (59.5)	
Ureter	162 (41.1)	44 (40.7)	118 (41.3)	0.926	47 (40.2)	115 (41.5)	0.804	40 (43.0)	122 (40.5)	0.671
Tumor grade										
G1/2	128 (32.5)	27 (25.0)	101 (35.3)		31 (26.5)	97 (35.0)		24 (25.8)	104 (34.6)	
G3	266 (67.5)	81 (75.0)	185 (64.7)	0.051	86 (73.5)	180 (65.0)	0.099	69 (74.2)	197 (65.4)	0.116
Pathologic T stage										
pTa-1	125 (31.7)	24 (22.2)	101 (35.3)		30 (25.6)	95 (34.3)		24 (25.8)	101 (33.6)	
pT2	57 (14.5)	16 (14.8)	41 (14.3)		11 (9.4)	46 (16.6)		12 (12.9)	45 (15.0)	
pT3	201 (51.0)	63 (58.3)	138 (48.3)		69 (59.0)	132 (47.7)		51 (54.8)	150 (49.8)	
pT4	11 (2.8)	5 (4.6)	6 (2.1)	0.055	7 (6.0)	4 (1.4)	0.005	6 (6.5)	5 (1.7)	0.052
Lymphovascular invasion										
Negative	224 (56.9)	59 (54.6)	165 (57.7)		57 (48.7)	167 (60.3)		40 (43.0)	184 (61.1)	
Positive	170 (43.1)	49 (45.4)	121 (42.3)	0.584	60 (51.3)	110 (39.7)	0.034	53 (57.0)	117 (38.9)	0.002
Concomitant carcinoma in situ										
Negative	320 (81.2)	95 (88.0)	225 (78.7)		93 (79.5)	227 (81.9)		74 (79.6)	246 (81.7)	
Positive	74 (18.8)	13 (12.0)	61 (21.3)	0.035	24 (20.5)	50 (18.1)	0.567	19 (20.4)	55 (18.3)	0.641
Lymph node involvement										
pNx	357 (90.6)	96 (88.9)	261 (91.3)		103 (88.0)	254 (91.7)		80 (86.0)	277 (92.0)	
pN0	8 (2.0)	2 (1.9)	6 (2.1)		4 (3.4)	4 (1.4)		4 (4.3)	4 (1.3)	
pN+	29 (7.4)	10 (9.3)	19 (6.6)	0.670	10 (8.5)	19 (6.9)	0.364	9 (9.7)	20 (6.6)	0.119
Adjuvant chemotherapy										
No	306 (77.7)	84 (77.8)	222 (77.6)		80 (68.4)	226 (81.6)		67 (72.0)	239 (79.4)	
Yes	88 (22.3)	24 (22.2)	64 (22.4)	0.974	37 (31.6)	51 (18.4)	0.004	26 (28.0)	62 (20.6)	0.136

CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio; RNU = radical nephroureterectomy.