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Brief Correspondence

Impact of Sex on Response to Neoadjuvant Chemotherapy in Patients with Upper-tract Urothelial Cancer

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The standard therapy for high-risk upper-tract urothelial cancer (UTUC) is radical nephroureterectomy (RNU) with bladder-cuff excision [1]. Although the use of neoadjuvant chemotherapy (NAC) is not supported by high-quality data, it is associated with better oncologic outcomes and survival [2–5]. Accurate patient selection is of paramount importance for clinical counseling and to avoid overtreatment and undertreatment. In bladder urothelial cancers, sex-based differences in response to NAC and in survival have been observed [6,7]. However, to the best of our knowledge, the impact of sex on response and survival after NAC has not been investigated among patients with UTUC.

To fill this gap in knowledge, we analyzed an international multicenter database of patients treated with NAC followed by RNU for UTUC.

Pathologic complete response (pCR) was defined as ypT0N0. Pathologic partial response (pPR) was defined as \leq ypT1N0. The distribution of pCR and pPR between the sexes was evaluated using χ^2 tests. Logistic regression analysis was used to investigate the association of sex with pCR and pPR. The association of sex with recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) was evaluated using Cox regression analyses.

A total of 287 patients were identified from a multicenter collaborative data set. Nine patients with metastatic disease were excluded, leaving 278 patients (190 males and 88 females) for final analyses. Two patients

were lost to follow-up and were not included in the survival analyses. Chemotherapy regimens included were gemcitabine-cisplatin; methotrexate, vinblastine, doxorubicin, and cisplatin; and non-cisplatin-based regimens (other). Clinicopathologic features are shown in Table 1. After NAC administration, the proportions of males experiencing pCR and/or pPR were not significantly different to the proportions of females (Fig. 1). On logistic regression analyses, sex was not associated with either pCR (odds ratio [OR] for females 1.43, 95% confidence interval [CI] 0.57–3.41; $p = 0.42$) or pPR (OR for females 1.21, 95% CI 0.67–2.14; $p = 0.52$).

Over median follow-up of 26.5 mo (interquartile range 11–57), 93 patients (33.7%) experienced disease recurrence, 61 (22.1%) died of UTUC, and 26 (31.5%) died of other causes (Fig. 2). On univariable Cox regression analyses, sex was not associated with RFS (hazard ratio [HR] for females 1.03, 95% CI 0.67–1.58; $p = 0.89$), CSS (HR for females 1.38, 95% CI 0.83–2.28; $p = 0.21$), or OS (HR for females 1.24, 95% CI 0.83–1.85; $p = 0.30$).

In the current study, we found no significant difference in the distribution of males and females for pCR and pPR after NAC. Moreover, we did not observe any association of sex with survival outcomes.

The literature is scarce regarding the association of sex with UTUC incidence, pathologic stage, and survival [8–10]. In a multicenter retrospective analysis of 1362 patients treated with RNU without preoperative chemotherapy, the

Table 1 – Clinicopathologic features of 278 patients treated with NAC and radical nephroureterectomy for upper-tract urothelial cancer

Parameter	Overall	Male	Female	p value
Patients (n)	278	190	88	
Median age, yr (IQR)	68 (62–74)	67 (61–74)	71 (65–74)	0.04
Variant histology, n (%)	9 (3.2)	6 (3.2)	3 (3.4)	1.00
Clinical T3/T4 stage, n (%)				0.94
No	167 (60.1)	114 (60)	53 (60.2)	
Yes	97 (34.9)	67 (35.3)	30 (34.1)	
Not available	14 (5.0)	9 (4.7)	5 (5.7)	
Clinical grade, n (%)				0.02
Low grade	38 (13.7)	29 (15.3)	9 (10.2)	
High grade	146 (52.5)	89 (46.8)	57 (64.8)	
Not available	94 (33.8)	72 (37.9)	22 (25)	
Clinical N stage, n (%)				0.22
cN0	88 (31.7)	66 (34.7)	22 (25)	
cN positive	72 (25.9)	49 (25.8)	23 (26.1)	
cNx	118 (42.4)	75 (39.5)	43 (48.9)	
NAC regimen, n (%)				0.30
Gemcitabine-cisplatin	125 (45.0)	85 (44.7)	40 (45.5)	
MVAC	87 (31.3)	64 (33.7)	23 (26.1)	
Other	59 (21.2)	38 (20.0)	21 (23.9)	
Not available	7 (2.5)	3 (1.6)	4 (4.5)	
Number of NAC cycles, n (%)				0.21
1	5 (1.8)	2 (1.1)	3 (3.4)	
2–4	233 (83.8)	162 (85.3)	71 (80.7)	
5–8	31 (11.2)	22 (11.6)	9 (10.2)	
Not available	9 (3.2)	4 (2.1)	5 (5.7)	
ypT stage, n (%)				0.67
ypT0	32 (11.5)	19 (10)	13 (14.8)	
ypTa/Tis/T1	102 (36.7)	69 (36.3)	33 (37.5)	
ypT2	30 (10.8)	20 (10.5)	10 (11.4)	
ypT3/T4	112 (40.3)	81 (42.6)	31 (35.2)	
ypTx	2 (0.7)	1 (0.5)	1 (1.1)	
Pathologic grade, n (%)				0.39
G0	32 (11.5)	19 (10)	13 (14.8)	
Low grade	14 (5.0)	11 (5.8)	3 (3.4)	
High grade	232 (83.5)	160 (84.2)	72 (81.8)	
ypN stage, n (%)				0.70
ypN0	175 (62.9)	119 (62.6)	56 (63.6)	
ypN positive	64 (23.0)	46 (24.2)	18 (20.5)	
ypNx	39 (14.0)	25 (13.2)	14 (15.9)	
Median nodes removed, n (IQR)	12 (5–20)	11 (5–19)	14 (6–20)	0.16
Median positive nodes, n (IQR)	1 (1–3)	1 (1–3)	1 (1–3)	0.96
Soft-tissue surgical margin, n (%)				0.95
Negative	248 (89.2)	169 (88.9)	79 (89.8)	
Positive	21 (7.6)	15 (7.9)	6 (6.8)	
Not evaluable	9 (3.2)	6 (3.2)	3 (3.4)	
Adjuvant chemotherapy, n (%)	24 (8.6)	13 (6.8)	11 (12.5)	0.18

NAC = neoadjuvant chemotherapy; IQR = interquartile range; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin.

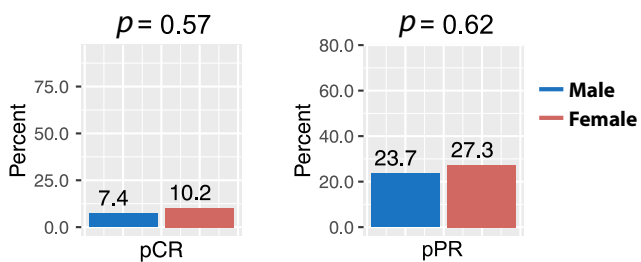


Fig. 1 – Proportion of patients with pathologic complete response (pCR) and pathologic partial response (pPR) among 278 patients treated with neoadjuvant chemotherapy and nephroureterectomy for upper-tract urothelial cancer.

incidence of UTUC was twice as frequent among males but females were significantly older (68 vs 72 yr). No other differences in clinicopathologic features, RFS (HR 1.01; $p = 0.45$), or CSS (HR 1.07; $p = 0.55$) were observed [10]. An analysis of 4850 patients from the Surveillance, Epidemiology and End Results registry showed that females had a higher proportion of pT3 disease (43.1% vs 39%; $p = 0.02$). However, multivariable competing-risks regression analysis revealed no significant association between sex and CSS (HR 1.07; $p = 0.4$) [9]. A more recent multicenter retrospective analysis of 754 patients revealed a higher proportion of males (68.4%) treated with RNU and confirmed that females

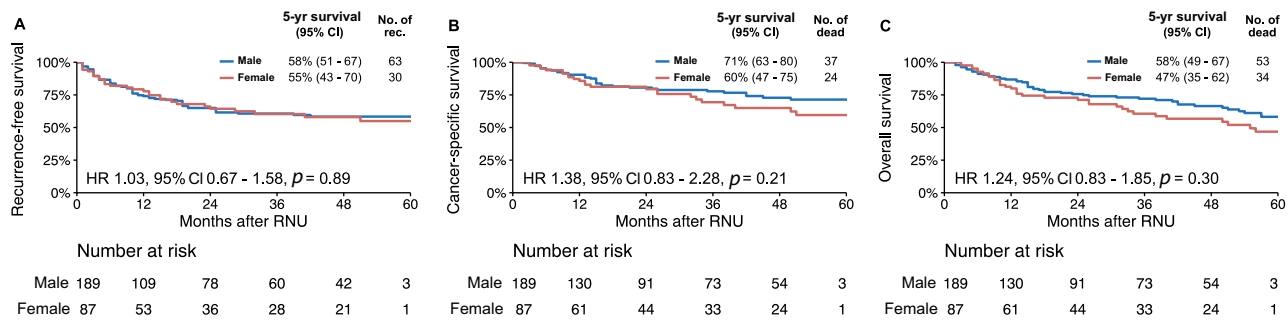


Fig. 2 – Kaplan-Meier curves for (A) recurrence-free survival, (B) cancer-specific survival, and (C) overall survival among 276 patients treated with neoadjuvant chemotherapy and radical nephroureterectomy (RNU) for upper-tract urothelial cancer. CI = confidence interval; HR = hazard ratio.

were older at the time of RNU (69 vs 66 yr; $p = 0.0003$). However, the authors could not find significant differences in other clinicopathologic features or survival between males and females [8]. These studies did not include patients treated with preoperative chemotherapy.

We expanded on previous reports showing no difference between the sexes among patients treated with RNU alone. For the current cohort of patients treated with NAC and RNU, we provide data on the association of sex with NAC and survival and show no difference between the groups. While there seem to be differences in the response to systemic chemotherapy and outcomes between the sexes in bladder urothelial carcinoma, there are no such differences between sexes in UTUC.

We acknowledge the limitations of our study, which are mainly inherent to its retrospective design. Surgical quality, lymphadenectomy template, patient selection, preoperative staging, and NAC protocols were not standardized. Despite all these limitations, to the best of our knowledge, this is the first report on the effect of NAC on pathologic response and survival among patients with UTUC. These results could help in clinical decision-making and planning of future trials.

Author contributions: David D'Andrea had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shariat.

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