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

David D’Andrea a, Beat Foerster a,b, Surena F. Matin c, Ja H. Ku d, Tim Mulwijk e, Leonardo L. Monteiro f, Ross Liao g, Firas G. Petros h, Philippe E. Spiess i, Trinity J. Bivalacqua g, Kees Hendricksen j, Bas W.G. van Rhijn j, Ahmad Shabsigh k, Alberto Briganti l, Steven Joniau e, Wassim Kassouf f, Phillip M. Pierorazio g, Vitaly Margulis m, Andrea Necchi n, Shahrokh F. Shariat a,m,o,p,q,r,s,* for the UTUC collaboration

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 ≤ypT1N0. The distribution of pCR and pPR between the sexes was evaluated using χ² 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
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

### 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 |
| Yes                                      | 167 (60.1) | 114 (60) | 53 (60.2) |       |
| Not available                            | 97 (34.9) | 67 (35.3) | 30 (34.1) |       |
| 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) |       |
| ypT5                                     | 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.
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 NAC 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.

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Study concept and design: Shariat.

Acquisition of data: Foerster, Matin, Ku, Muiilwijk, Monteiro, Liao, Petros, Spiess, Bivalacqua, Hendricksen, van Rhijn, Shabsigh, Briganti, Joniau, Kassouf, Pierorazio, Margulis, Necchi.

Analysis and interpretation of data: D’Andrea, Shariat.

Drafting of the manuscript: D’Andrea.

Critical revision of the manuscript for important intellectual content: Foerster, Matin, Ku, Muiilwijk, Monteiro, Liao, Petros, Spiess, Bivalacqua, Hendricksen, van Rhijn, Shabsigh, Briganti, Joniau, Kassouf, Pierorazio, Margulis, Necchi, Shariat.

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aDepartment of Urology, Medical University of Vienna, Vienna, Austria
bDepartment of Urology, Kantonsspital Winterthur, Winterthur, Switzerland
cDepartment of Urology, MD Anderson Cancer Center, Houston, TX, USA
dDepartment of Urology, Seoul National University Hospital, Seoul, South Korea
eDepartment of Urology, University Hospitals Leuven, Leuven, Belgium
fDepartment of Surgery (Division of Urology), McGill University Health Center, Montreal, Canada
gDepartment of Urology, The James Buchanan Brady Urological Institute, The Johns Hopkins School of Medicine, Baltimore, MD, USA
hDepartment of Urology and Kidney Transplant, The University of Toledo Medical Center and Eleanor N. Dana Cancer Center, Toledo, OH, USA
iDepartment of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA
jDepartment of Urology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
kDepartment of Urology, Ohio State University, Columbus, OH, USA
lDepartment of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy
mDepartment of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA
nDepartment of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
oInstitute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia
pDepartment of Urology, Weill Cornell Medical College, New York, NY, USA
qKarl Landsteiner Institute of Urology and Andrology, Vienna, Austria
rDepartment of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic
sDepartment of Urology, University of Jordan, Amman, Jordan

corresponding author. Department of Urology, Medical University of Vienna, Währinger Gürtel 18–20, A–1090 Vienna, Austria.
Tel.: +43 1 404002615; Fax: +43 1 404002332.
E-mail address: sfshariat@gmail.com (S.F. Shariat).