Pretreatment clinical and hematologic prognostic factors of metastatic urothelial carcinoma treated with pembrolizumab: a systematic review and meta-analysis

Takafumi Yanagisawa1,2 • Keiichiro Mori1,2 • Satoshi Katayama1,3 • Hadi Mostafaei1,4 • Fahad Quhal1,5 • Ekaterina Laukhtina1,6 • Reza Sari Motlagh1,8 • Abdulmajeed Aydh1,9 • Frederik König1,10 • Nico C. Grossmann1,11,12 • Benjamin Pradere1 • Jun Miki2 • Takahiro Kimura2 • Shin Egawa2 • Shahrokh F. Shariat1,6,13,14,15,16,17

Received: 4 August 2021 / Accepted: 20 October 2021 / Published online: 10 November 2021
© The Author(s) 2021

Abstract
Pembrolizumab is the standard for the first and second lines in treating metastatic urothelial carcinoma (UC). This systematic review and meta-analysis aimed to assess the value of pretreatment clinical characteristics and hematologic biomarkers for prognosticating response to pembrolizumab in patients with metastatic UC. PUBMED®, Web of Science™, and Scopus® databases were searched for articles published before May 2021 according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. Studies were deemed eligible if they evaluated overall survival (OS) in patients with metastatic urothelial carcinoma treated with pembrolizumab and pretreatment clinical characteristics or laboratory examination. Overall, 13 studies comprising 1311 patients were eligible for the meta-analysis. Several pretreatment patients’ demographics and hematologic biomarkers were significantly associated with worse OS as follows: Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≥ 2 (Pooled hazard ratio [HR]: 3.24, 95% confidence interval [CI] 2.57–4.09), presence of visceral metastasis (Pooled HR: 1.84, 95% CI 1.42–2.38), presence of liver metastasis (Pooled HR: 4.23, 95% CI 2.18–8.20), higher neutrophil–lymphocyte ratio (NLR) (Pooled HR: 1.29, 95% CI 1.07–1.55) and, higher c-reactive protein (CRP) (Pooled HR: 2.49, 95% CI 1.52–4.07). Metastatic UC patients with poor PS, liver metastasis, higher pretreatment NLR and/or CRP have a worse survival despite pembrolizumab treatment. These findings might help to guide the prognostic tools for clinical decision-making; however, they should be interpreted carefully, owing to limitations regarding the retrospective nature of primary data.

Keywords Metastatic urothelial carcinoma • Pembrolizumab • Prognostic factor

Abbreviations
- CI: Confidence Intervals
- ECOG-PS: Eastern Cooperative Oncology Group Performance Status
- Hb: Hemoglobin
- HR: Hazard Ratio
- ICI: Immune Checkpoint Inhibitors
- IQR: Interquartile Range
- LDH: Lactate Dehydrogenase
- NA: Not Applicable
- NLR: Neutrophil Lymphocyte Ratio
- OS: Overall Survival
- ORR: Objective Response Rate
- PD-1: Programmed cell Death protein 1
- PD-L1: Programmed Death-Ligand 1
- PS: Performance Status
- RCTs: Randomized Control Trials
- UC: Urothelial Carcinoma
- UTUC: Upper urinary Tract Urothelial Carcinoma

Introduction
Urothelial carcinomas (UCs) located in the lower (bladder and urethra) or the upper (renal pelvicalyceal system and ureter) urinary tract are the 6th most common tumors in developed countries [1]. In recent years, immune
checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) have been used in patients with locally advanced or metastatic urothelial carcinomas (mUCs) [2]. Pembrolizumab and nivolumab as PD-1 inhibitors, atezolizumab, avelumab, and durvalumab as PD-L1 inhibitors have been approved by the U.S. Food and Drug Administration. However, only pembrolizumab demonstrated significant overall survival benefit in a phase III Randomized Control Trial (RCT) [3]. Therefore, in the EAU guidelines, pembrolizumab is recommended to offer patients in the second-line mUC setting (i.e., post-platinum) [4].

Despite the advances offered by ICIs, the objective response rate (ORR) of pembrolizumab is around 20% in first- and second-line mUC [3, 5]. The development of predictive biomarkers is indispensable for patient selection, specifically with the avenue of multiple novel therapeutic options such as combination therapies and targeted therapies [6–9]. For intra-tumoral biomarkers, expression of PD-1 ligand PD-L1 has been found to exhibit more or less some predictive value for anti-PD-1-directed therapy in various cancers [10–13]. However, the utility of PD-L1 expression status in patients with metastatic UCs remains controversial and unclear [14–21]. Other biomarkers helping to predict the likelihood of response to anti-PD-1-directed therapy, including immunohistochemical biomarkers, molecular subtyping, immune gene expression analysis by RNA sequencing, mutations in DNA damage repair genes, and tumor mutational burden, have been tested [14, 22–24]. However, these biomarkers remain suboptimal for clinical application due to technical issues and suffer from the complexity underlying each tumor and temporal as well as spatial heterogeneity.

Therefore, clinical prognostic factors, which are easy to use based on reliable, widely available parameters, are crucial for assessing the result of clinical trials and guiding clinical decision-making. In patients treated with first-line chemotherapy for metastatic UCs, poor performance status (PS), visceral metastases, number of visceral metastases, leukocyte count, and low hemoglobin have been demonstrated as independent prognostic factors [25–30]. For patients treated with salvage chemotherapy-refractory after platinum-based combination chemotherapy, prognostic factors were consistent with the previous report [31]. However, these prognostic factors have not been validated in the context of novel agents, including ICIs.

Therefore, this systematic review and meta-analysis were conducted to evaluate and assess the pretreatment prognostic factors and oncologic outcomes following pembrolizumab for metastatic UCs as 2nd line therapy after platinum-based combination chemotherapy.

Methods

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42021258811).

Search strategy

This meta-analysis was carried out based on the guidelines of the Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology Statement (Supplementary Fig. 1) [32]. In May 2021, a literature search on PUBMED®, Web of Science™, and Scopus® databases was performed to identify reports that investigated the prognostic value of clinical and hematologic factors in patients with metastatic UC treated with pembrolizumab. The keywords used in our search strategy were as follows: (bladder cancer) OR (bladder carcinoma) OR (urothelial cancer) OR (urothelial carcinoma) AND (advanced OR metastatic) AND (pembrolizumab). The primary outcome of interest was overall survival (OS). Initial screening was performed independently by two investigators based on the titles and abstracts to identify ineligible reports. Potentially relevant reports were subjected to a full-text review. Additionally, reference lists of the retrieved articles were analyzed to identify further studies. Disagreements were resolved by consensus with the additional investigators.

Inclusion and exclusion criteria

Studies were included if they investigated 2nd line metastatic UC patients with pretreatment clinical or hematological abnormal factors (Patients) who were treated with pembrolizumab (Interventions) compared to those without pretreatment clinical or hematological abnormal factors (Comparisons) to assess the independent predictive value of clinical and hematological factors on OS (Outcome) utilizing multivariate Cox regression analysis (Study design) in non-randomized observational, randomized, or cohort studies.

Studies lacking original patient data, reviews, letters, editorial comments, meeting abstracts, replies from authors, case reports, and non-English articles were excluded. Studies in the neoadjuvant/adjuvant setting, 1st line metastatic UC setting, and combination with chemotherapy were also excluded. In cases of duplicate publications, the higher quality or the most recent publication was selected.
Data extraction

Data were extracted independently by two authors. First author’s name, publication year, recruitment country and institution, patient recruitment period, number of patients, age, sex, study design, follow-up duration, primary site, metastatic site, objective response rate (ORR), clinical characteristics, and hematologic biomarker were retrieved. Subsequently, the hazard ratios (HR) and 95% confidence intervals (CI) of pretreatment prognostic factors associated with OS were retrieved. The HRs were extracted from the multivariate analyses.

Risk of bias assessment

As all included studies were non-randomized observational studies, assessment of study quality and risk of bias was performed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool following the Cochrane Handbook for Systematic Reviews of Interventions. Each bias domain and overall risk of bias was judged as ‘Low’, ‘Moderate’, ‘Serious’ or ‘Critical’ risk of bias. The main confounders were identified as the critical prognostic factors of OS. The presence of confounders was determined by consensus and review of the literature. The ROBINS-I assessment of each study was performed independently by two authors. (Supplementary Table 1).

Statistical analyses

Forest plots were used to assess the multivariate HRs, to summarize them and, to describe the relationships between pretreatment clinical characteristics or hematologic biomarkers and OS. Studies were not considered in the meta-analysis if they used univariate Cox proportional hazard regression or general logistic regression analyses. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane’s Q test and the I² statistic. When significant heterogeneity (P value of <0.05 in the Cochrane Q test and a ratio >50% in I² statistics) was observed, a random-effects model was applied [33, 34]. Fixed-effects models for the calculation of pooled HRs for non-heterogeneous results were applied [1]. Funnel plots was used for assessment of publication bias (Supplementary Fig. 2). All analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and the statistical significance level was set at \( P < 0.05 \).

Results

Study selection and characteristics

Our initial search identified 1279 records. After removing duplicates, 887 records remained (Fig. 1). After screening the titles and abstracts, a full-text review was performed for 42 articles. Finally, we identified 13 studies comprising 1311 patients treated with pembrolizumab for cisplatin-refractory metastatic UCs according to our inclusion criteria [35–47]. The characteristics of included patients and the outcomes are shown in Table 1. All included studies were retrospective studies from Japan published between 2020 and 2021. The median age and follow-up range were from 70 to 74 years and 5.5 to 17.7 months, respectively. Of 1311 patients, 907 were male and 404 were female. The pooled rate of UTUC patients was 45.7% (range 35–69%), the pooled rate of liver metastasis was 21.2% (12–32%), and the pooled ORR was 25.6% (range 14.4–37%).

Meta-analysis

Association of ECOG-PS with OS in mUC treated with pembrolizumab

Ten studies provided data on the association of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) with OS in 2nd line metastatic UCs treated with pembrolizumab. Eight studies defined the patients’ cut-off as PS ≥ 2. 940 patients were analyzed. The forest plot (Fig. 2a) revealed that ECOG-PS ≥ 2 was significantly associated with worse OS (pooled HR: 3.24, 95% CI 2.57–4.09; \( z = 9.88 \)). The Cochrane’s Q test (Chi² = 9.42; \( P = 0.22 \)) and I² test (\( I^2 = 80.5\% \)) revealed no significant heterogeneity. The funnel plot seemed symmetry and did not identify any studies over the pseudo-95% CI (Supplementary Fig. 2A).

Association of metastatic site with OS in mUC treated with pembrolizumab

Four studies, including 731 patients, provided data on the association of visceral metastasis with OS in 2nd line metastatic UCs treated with pembrolizumab. The forest plot (Fig. 2b) revealed that visceral metastasis was significantly associated with worse OS (pooled HR: 1.84, 95% CI 1.42–2.38; \( z = 4.64 \)). The Cochrane’s Q test (Chi² = 2.81; \( P = 0.42 \)) and I² test (\( I^2 = 0\% \)) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Supplementary Fig. 2B).

Five studies, including 695 patients, provided data on the association of liver metastasis with OS in 2nd line metastatic
UCs treated with pembrolizumab. The forest plot (Fig. 2c) revealed that liver metastasis was significantly associated with worse OS (pooled HR: 4.23, 95% CI 2.18–8.20; \( z = 4.27 \)). The Cochrane’s \( Q \) test (Chi\(^2\) = 12.45; \( P = 0.01 \)) and \( I^2 \) test \( (I^2 = 68\%) \) revealed significant heterogeneity. The funnel plot identified one study over the pseudo-95% CI (Supplementary Fig. 2C).

**Association of NLR with OS in mUC treated with pembrolizumab**

Five studies, including 777 patients, provided data on the association of neutrophil–lymphocyte ratio (NLR) with OS in metastatic UCs treated with pembrolizumab. The forest plot (Fig. 2d) revealed that pretreatment high NLR was significantly associated with worse OS (pooled HR: 1.29, 95% CI 1.07–1.55; \( z = 2.62 \)). The Cochrane’s \( Q \) test (Chi\(^2\) = 9.36; \( P = 0.05 \)) and \( I^2 \) test \( (I^2 = 57\%) \) revealed significant heterogeneity. The funnel plot identified one study over the pseudo-95% CI (Supplementary Fig. 2D).

**Association of Hb with OS in mUC treated with pembrolizumab**

Three studies, including 627 patients, provided data on hemoglobin (Hb) association with OS in 2nd line metastatic UCs treated with pembrolizumab. The forest plot (Fig. 2e) revealed that a low pretreatment Hb level was not associated with OS (pooled HR: 1.17, 95% CI 0.72–1.92; \( z = 0.63 \)). The Cochrane’s \( Q \) test (Chi\(^2\) = 15.00; \( P = 0.0006 \)) and \( I^2 \) test
| Study     | Year | N  | Nation | Period | Sex  | Median age | Primary | Metastatic site | ORR  | Follow-up (month) | Design | Significant clinical factor for OS (cut off) | Significant blood marker for OS (cut off) |
|-----------|------|----|--------|--------|------|------------|---------|----------------|------|------------------|--------|---------------------------------------------|---------------------------------------------|
| Etani     | 2020 | 52 | Japan  | 2018–2019 | M:43 F:9 | 71 | UTUC: 26 (50%) BC: 26 (50%) | LN: 21 (40%) Lung: 16 (31%) Liver: 10 (19%) | 21% | 12.2 | R | ECOG-PS (2) | Visceral mets. GNRI (92) |
| Kijima    | 2020 | 97 | Japan  | 2018–2019 | M: 76 F: 21 | 70 | UTUC: 40 (41%) BC: 57 (59%) | LN: 75 (77%) Lung: 38 (39%) Liver: 20 (21%) Bone: 13 (13%) | 26.8% | 5.5 | R | ECOG-PS (2) | Liver mets. CRP (Non-responder) |
| Funubayashi | 2020 | 34 | Japan  | 2018–2019 | M:28 F:6 | 71 | UTUC: 12 (35%) BC: 13 (38%) Both: 9 (27%) | Visceral: 27 (79%) Liver: 11 (32%) | 20.6% | 7.7 | R | Liver mets. | Time from previous chemotherapy (≥ 3 mo.) |
| Kobayashi | 2020 | 755 | Japan (Discovery cohort: n=463) | 2015–2019 | M:357 F:106 | 71 | UTUC: 179 (39%) BC: 230 (50%) Both: 27 (6%) | LN only: 156 (34%) Liver: 101 (22%) Other: 206 (44%) | ≥ Low-risk: 48.3% | 17.7 | R | ECOG-PS (2) | Visceral mets. Liver mets. Smoking history |
| Ogihara   | 2020 | 78 | Japan  | 2017–2019 | M: 44 F: 24 | 72.2 (mean) | UTUC: 35 (45%) BC: 43 (55%) | LN: 39 (50%) Lung: 28 (36%) Liver: 10 (13%) Bone: 16 (21%) | 30% | 7.4 | R | N.A. | NLR (CSS) (3.5) |
| Shimizu   | 2020 | 27 | Japan  | 2017–2019 | M: 23 F: 4 | 73 | UTUC: 12 (44%) BC: 15 (56%) | LN: 23 (85%) Lung: 15 (56%) Liver: 6 (22%) Bone: 2 (7%) | 37% | 7 | R | Sarcopenia | NLR (PFS) (4) |
| Tamura    | 2020 | 41 | Japan  | 2018–2019 | M: 29 F: 12 | 70 | UTUC: 22 (54%) BC: 19 (46%) | LN: 26 (63%) Lung: 15 (37%) Liver: 8 (20%) Bone: 7 (17%) | 14.6% | 6.2 | R | ECOG-PS (2) | Number of metastatic organs (2) |
| Inoue     | 2020 | 73 | Japan  | 2017–2019 | M: 56 F: 17 | 72 | UTUC: 41 (56%) BC: 27 (37%) Both: 5 (7%) | Lung: 34 (47%) Liver: 22 (30%) Bone: 11 (15%) | 17.8% | 5.5 | R | irAE | N.A. |
| Kadono    | 2021 | 91 | Japan  | 2018–2019 | M: 65 F: 26 | N.A. | N.A. | N.A. | N.A. | 7.9 | R | N.A. | NLR (2.9) |
| Fukuokaya | 2021 | 95 | Japan  | 2018–2020 | M: 65 F: 30 | 72 | UTUC: 51 (54%) BC: 44 (46%) | LN only: 40 (42%) Visceral: 55 (58%) | 34.7% | 8.2 | R | Smoking exposure (≥ 25 pack-years) | N.A. |
Association of CRP with OS in mUC treated with pembrolizumab

Two studies, including 195 patients, provided data on c-reactive protein (CRP) association with OS in 2nd line metastatic UCs treated with pembrolizumab. The forest plot (Fig. 2f) revealed that pretreatment CRP was significantly associated with worse OS (Pooled HR: 2.49, 95% CI 1.52–4.07; $z = 2.62$). The Cochrane’s $Q$ test (Chi2 = 0.01; $P = 0.94$) and $I^2$ test ($I^2 = 0\%$) revealed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo-95% CI (Supplementary Fig. 2F).

Other factors associated with OS

As for hematological biomarkers, high pretreatment level of LDH was significantly associated with worse OS [36]. In addition to high pretreatment level of NLR and CRP, percentage changes in these levels after initiation of pembrolizumab treatment were also significantly associated with OS in one study each [42, 46]. UTUC [40] and smoking history/exposure [37, 43] as pretreatment patients’ characteristics were significantly associated with OS. As for systemic nutritional condition, Geriatric Nutritional Risk Index [35]: a nutritional assessment tool defined by serum albumin levels and the ratio of actual to ideal body weight, Prognostic Nutritional Index [40]: a prognostic model comprising serum lymphocyte counts and albumin, and sarcopenia [45] were all significantly associated with OS.

Discussion

Despite large progress effected by pembrolizumab in patients with metastatic UCs, the rate and length of ORR and OS benefits are still not satisfactory [3, 5]. Identification of predictive biomarkers and prognostic factors is indispensable for precise and patient-centered clinical decision-making. This systematic review and meta-analysis suggests that poor performance status (PS), visceral (particularly liver) metastasis, high pretreatment level of NLR and CRP are all associated with OS.

ECOG-PS has been used as a tool to guide clinicians regarding fitness for systemic therapy [48]. It has been shown to be an independent prognostic factor for OS in patients with advanced melanoma treated with ICIs [49] and advanced/metastatic UC treated with chemotherapy [26, 31]. In a recent retrospective cohort study focused on association with ECOG-PS and survival in advanced UCs patients
treated with ICIs, OS was shorter in patients with ECOG-PS ≥ 2, particularly in the 1st line setting [50]. Our analysis suggests that ECOG-PS ≥ 2 was significantly associated with OS in platinum-refractory metastatic UC patients treated with pembrolizumab. Parikh et al. reported that although mortality seemed to be favorable after approval of ICIs, the use of ICIs at the end of life in patients with metastatic UC has been rising dramatically [51]. The establishment of guidelines and policy implications for treating poor PS patients with ICIs is mandatory.

Regarding the site of metastasis, visceral metastasis and especially liver metastasis, are associated with worse OS. The presence of liver metastases has been previously reported to be a poor prognostic factor for the patients treated with chemotherapy [3, 31]. In the subgroup analysis of the phase 3 trial, KEYNOTE-045, liver metastasis was associated with worse OS in patients treated with pembrolizumab or chemotherapy [3]. In agreement with this study, our analysis confirmed liver metastasis to confer a significantly higher risk of ICI therapy failure.

Recently, pretreatment hematologic inflammation biomarkers such as NLR have been shown to prognosticate ICI response in various cancers alone or in combination with other predictors for these patients [52–57]. Moreover, hematologic markers, such as NLR, have been suggested as biomarkers for progression after radical cystectomy [58]. However, it remains controversial whether pretreatment NLR provides prognostic information for identifying clinical
responses to pembrolizumab in platinum-refractory metastatic UC patients. Previous studies have shown that a high neutrophil count was correlated with a decreased number of CD8-positive T cells [59], and the increased infiltration of lymphocytes in the tumor region was associated with a better response to ICIs [60]. Furthermore, it is credible that alterations of circulating lymphocytes could be associated with the efficacy of ICIs [61], because they could enhance antitumor immunity by blocking negative regulators of T-cell function [62].

The elevation of CRP levels is a representative acute phase reactant that is widely used to evaluate systemic inflammation. The correlation between inflammation and malignant potential is widely known [63]. The elevation of CRP levels has been reported as a poor predictor of advanced UCs [64] and metastatic melanoma treated with ICIs [49, 65, 66]. In the present study, CRP and NLR, which might be affected in the tumor microenvironment by immune cells, were associated with worse OS. Pretreatment CRP may also help, along with other markers in a model, to guide clinical decision-making for ICIs, as it is likely to reflect the biology of the tumor and/or its microenvironment[67].

In the chemotherapy era, Sonpavde et al. demonstrated that serum albumin was externally validated as a prognostic factor for OS in addition to Hb, ECOG-PS, and liver metastasis in advanced UC patients with ten prospective phase II trials of salvage systemic agent therapy following platinum-based chemotherapy [31, 68]. Our findings are consistent with previous studies and could confirm the utility of these prognostic factors in the ICI treatment era; furthermore, we added the importance of inflammatory markers such as NLR and CRP as promising biomarkers for mUC patients treated with ICIs.

Finally, the most recent study using patient-level data from phase I/II trials to build a prognostic model for metastatic UCs treated with atezolizumab, demonstrated that

![Fig. 2](continued)
ECOG-PS, liver metastasis, platelet count, NLR, and LDH are factors for prognosticating OS [69]. Together with our findings, we conclude that ECOG-PS, liver metastasis, and NLR are essential prognostic factors in patients of metastatic UCs treated with PD-1/PD-L1 inhibitors.

Although we found a strong association between several clinical/hematologic characteristics and mortality in 2nd line metastatic UC patients treated with pembrolizumab, our study suffers from several limitations that need to be taken into account. First, statistical analysis for assessing funnel plots was not performed due to a small number of included studies, but reporting bias could have led to the non-publication of negative results. All the studies included were retrospective in design, thus increasing the risk of selection bias. Second, unknown pretreatment factors (e.g., nutritional deficiencies, comorbidities, medications, and lifestyle factors) may have affected the hematologic biomarkers, thus producing systematic bias. Third, there was no established definition of cut-off values for hematologic biomarkers among the studies evaluated. Most investigators chose the cut-off value based on statistical methods, the lower or higher limit of standard or pre-defined biomarker cut-off values in the literature. Fourth, all the studies included were from Asia, Japan; thus, the interpretation of this study might not be reflective for patient of the whole world. Finally, heterogeneity was detected in the OS analysis; thus, the value of these results is limited. Although the random effect model was used to address heterogeneity among the studies evaluated, the conclusions should be carefully interpreted.

Conclusions

In 2nd line metastatic UC patients treated with pembrolizumab after platinum-based systemic chemotherapy, patient characteristics with poor PS and visceral metastasis, particularly liver metastasis, were associated with worse OS. Furthermore, pretreatment high NLR and CRP were blood-based prognosticators of OS. Our findings might help to guide the prognostic tools for clinical decision-making; however, they should be interpreted carefully, owing to limitations regarding the retrospective nature of primary data. Further investigation is mandatory to explore these and other biomarkers to build a reliable, generalizable, accurate, and easy-to-use predictive tool.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-021-02061-0.

Acknowledgements Nico C. Grossmann is supported by the Zurich Cancer League.

Author contributions TY contributed to protocol/project development, data collection and management, data analysis, and manuscript writing/editing. KM contributed to data analysis and manuscript writing/editing. SK, HM, FQ, EL, PR, RSM, AA, FK, NCG, and BP contributed to manuscript writing/editing. JM, TK, and SE contributed to manuscript editing. SFS contributed to protocol/project development/management and manuscript editing.

Funding Open access funding provided by Medical University of Vienna. Not applicable (no external funding provided).

Availability of data and materials All data generated or analyzed during this study are included in this published article.

Code availability Not applicable.

Declarations

Conflict of interest Shin Egawa is a paid consultant/advisor of Takeda, Astellas, AstraZeneca, Sanofi, Janssen, and Pfizer. Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen and Sanofi. Shahrokh F. Shariat is a paid consultant/advisor of Astellas, AstraZeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. Consulting or Advisory Role: Astellas, AstraZeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. Speakers Bureau: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen, Movember Foundation. The other authors declare no conflicts of interest associated with this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Siegel RL, Miller KD, Fuchs HE et al (2021) Cancer Statistics, 2021. CA Cancer J Clin 71(1):7–33. https://doi.org/10.3322/caac.21654 (Epub 2021/01/13, PubMed PMID: 33439946)

2. Flagg TW, Spiess PE, Agarwal N et al (2020) Bladder cancer, version 3. 2020, NCCN clinical practice guidelines in oncology.
4. Witjes JA, Bruins HM, Cathomas R et al (2021) European association of urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol 79(1):82–104. https://doi.org/10.1016/j.eururo.2020.10.006

5. Lundgren KT, Farina MS, Bellmunt J (2017) Pembrolizumab versus chemotherapy for metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 391(10122):748–757. https://doi.org/10.1016/S0140-6736(17)33297-X

6. Bronimann S, Lemberger U, Bruchbacher A (2020) Poly(ADP-ribose) polymerase inhibitors in prostate and urothelial cancer. Curr Opin Urol 30(4):557–565. https://doi.org/10.1097/MOU.00000000000010872 (Epub 2020/05/27 PubMed PMID: 32452999)

7. Ertl IE, Shariat SF, Mostafaei H (2020) Fibroblast growth factor receptor: a systematic review and meta-analysis of prognostic value and therapeutic options in patients with urothelial bladder carcinoma. Urol Oncol. https://doi.org/10.1016/j.uroonc.2021.01.025 (Epub 2021/03/02, PubMed PMID: 33642228)

8. Schmidinger M, Resch I, Fajkovic H (2021) Dual immune checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: a systematic review and meta-analysis. Eur J Cancer 151:35–48. https://doi.org/10.1016/j.ejca.2021.03.049 (Epub 2021/05/08 PubMed PMID: 33962359)

9. Herbst RS, Soria JC, Kowanetz M et al (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515(7528):563–567. https://doi.org/10.1038/nature14011 (Epub 2014/11/28 PubMed PMID: 25428504; PubMed Central PMCID: PMCPMC4836193)

10. Maurer MS, Soria JC, obviously MC et al (2017) Pembrolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 391(10122):748–757. https://doi.org/10.1016/S0140-6736(17)33297-X

11. Moris K, Pradere B, Moschini M et al (2021) First-line immune checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: a systematic review and meta-analysis. Eur J Cancer 151:35–48. https://doi.org/10.1016/j.ejca.2021.03.049 (Epub 2021/05/08 PubMed PMID: 33962359)

12. Herbst RS, Soria JC, Kowanetz M et al (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515(7528):563–567. https://doi.org/10.1038/nature14011 (Epub 2014/11/28 PubMed PMID: 25428504; PubMed Central PMCID: PMCPMC4836193)

13. Maurer MS, Soria JC, obviously MC et al (2017) Pembrolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 391(10122):748–757. https://doi.org/10.1016/S0140-6736(17)33297-X

14. Bellmunt J, de Wit R, Vaughn DJ et al (2017) Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 376(11):1015–1026. https://doi.org/10.1056/NEJMoa1613683 (Epub 2017/02/18, PubMed PMID: 28212060; PubMed Central PMCID: PMCPMC5635424)

15. Massari F, Di Nuncio V (2018) Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma. Lancet 391(10122):716–718. https://doi.org/10.1016/S0140-6736(17)33298-1 (Epub 2017/12/23 PubMed PMID: 29268949)

16. Powles T, Duran I, van der Heijden MS et al (2018) Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 391(10122):748–757. https://doi.org/10.1016/S0140-6736(17)33297-X

17. Reck M, Rodriguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375(19):1823–1833. https://doi.org/10.1056/NEJMoa1606774 (Epub 2016/10/11 PubMed PMID: 27718847)

18. Xiang X, Yu PC, Long D et al (2018) Prognostic value of PD-L1 expression in patients with primary solid tumors. Oncotarget 9(4):5058–5072. https://doi.org/10.18632/oncotarget.23580 (Epub 2018/02/13, PubMed PMID: 29435162; PubMed Central PMCID: PMCPMC5979033)

19. Zhao T, Li C, Wu Y (2017) Prognostic value of PD-L1 expression in tumor infiltrating immune cells in cancers: a meta-analysis. PLoS ONE 12(4):e0176822. https://doi.org/10.1371/journal.pone.0176822 (Epub 2017/04/30, PubMed PMID: 28453554; PubMed Central PMCID: PMCPMC4901885)

20. Fan Z, Liang Y, Yang X et al (2019) A meta-analysis of the efficacy and safety of PD-1/PD-L1 immune checkpoint inhibitors as treatments for metastatic bladder cancer. Onco Targets Ther 12:1791–1801. https://doi.org/10.2147/OTT.S186271 (Epub 2019/03/19, PubMed PMID: 30881032; PubMed Central PMCID: PMCPMC6404681)

21. Buder-Bakhaya K, Hassel JC (2018) Biomarkers for clinical benefit of immune checkpoint inhibitor treatment-a review from the melanoma perspective and beyond. Front Immunol 9:1474. https://doi.org/10.3389/fimmu.2018.01474 (Epub 2017/08/02, PubMed PMID: 30002656; PubMed Central PMCID: PMCPMC6031714)

22. Mariathanas S, Turley SJ, Nickles D et al (2018) TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature 554(7693):544–548. https://doi.org/10.1038/nature25501 (Epub 2018/02/15, PubMed PMID: 29443960; PubMed Central PMCID: PMCPMC6028240)

23. Xylina E, Robinson BD, Kluth LA et al (2014) Association of T-cell co-regulatory protein expression with clinical outcomes following radical cystectomy for urothelial carcinoma of the bladder. Eur J Surg Oncol 40(1):121–127. https://doi.org/10.1016/j.ejso.2013.08.023 (Epub 2013/10/22 PubMed PMID: 24140000)

24. Apolo AB, Ostrovnaia Y, Halabi S et al (2013) Prognostic model for predicting survival of patients with metastatic urothelial cancer treated with cisplatin-based chemotherapy. J Natl Cancer Inst 105(7):499–503. https://doi.org/10.1093/jnci/djt015 (Epub 2013/02/16, PubMed PMID: 23411591; PubMed Central PMCID: PMCPMC3691944)

25. Bajorin DF, Dodd PM, Mazumdar M et al (1999) Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 17(10):3173–3181. https://doi.org/10.1200/JCO.1999.17.10.3175 (Epub 1999/10/03 PubMed PMID: 10506615)

26. Bellmunt J, Albanel J, Paz-Ares L et al (2002) Pretreatment prognostic factors for survival in patients with advanced urothelial tumours treated in a phase II/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 95(4):751–757. https://doi.org/10.1002/cncr.10762 (Epub 2002/09/05 PubMed PMID: 12209718)
28. De Santis M, Bellmunt J, Mead G et al (2012) Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 30(2):191–199. https://doi.org/10.1200/JCO.2011.37.3571 (Epub 2011/12/14. PubMed PMID: 22162575; PubMed Central PMCID: PMCPMC3255563)

29. Galsky MD, Mosher I, Krege S et al (2013) Nomogram for predicting survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy. Cancer 119(16):3012–3019. https://doi.org/10.1002/cncr.28146 (Epub 2013/05/31 PubMed PMID: 23720216)

30. Sengelov L, Kamby C, von der Maase H (2001) Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. Eur Urol 39(6):634–642. https://doi.org/10.1159/000052520 (Epub 2001/07/21 PubMed PMID: 11464051)

31. Bellmunt J, Choueiri TK, Fouty L et al (2010) Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 28(11):1850–1855. https://doi.org/10.1200/JCO.2009.25.4599 (Epub 2012-03-17 PubMed PMID: 20231682)

32. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6(7):e1000100. https://doi.org/10.1371/journal.pmed.1000100 (Epub 2009/07/22. PubMed PMID: 19621070; PubMed Central PMCID: PMCPMC2707010)

33. DerSimonian R, Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 28(2):105–114. https://doi.org/10.1016/j.cct.2006.04.004 (Epub 2006/06/30 PubMed PMID: 16807131)

34. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188. https://doi.org/10.1016/0197-2456(86)90046-2 (Epub 1986/09/01 PubMed PMID: 3802833)

35. Inoue S, Sassa N, Kato T et al (2020) Presence of constipation between pretreatment neutrophil-to-lymphocyte ratio and outcome markers during therapy. Oncotarget 7(47):77404–77415. https://doi.org/10.18632/oncotarget.16139-9 (Epub 2020/09/20 PubMed PMID: 32949825)

36. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5(6):649–655 (Epub 1982/12/01 PubMed PMID: 7165009)

37. Kadono Y, Kawaguchi S, Nohara T et al (2021) Blood cell count biomarkers predicting efficacy of pembrolizumab as second-line therapy for advanced urothelial carcinoma. Anticancer Res 41(3):1607–1614. https://doi.org/10.21873/anticancerres.14922 (PubMed PMID: WOS:000632018100011)

38. Furubayashi N, Kuroiwa K, Tokuda N et al (2020) Treating advanced urothelial carcinoma resistant to platinum-based chemotherapy. Anticancer Res 41(3):1599–1606. https://doi.org/10.21873/anticancerres.14921 (Epub 2021/04/01 PubMed PMID: 33788755)

39. Inoue S, Sassa N, Kato T et al (2021) Risk stratification for the prognosis of patients with chemoresistant urothelial cancer treated with pembrolizumab. Cancer Sci 112(2):760–773. https://doi.org/10.1111/cas.14762 (Epub 2020/12/08. PubMed PMID: 33283385; PubMed Central PMCID: PMCPMC7893997)

40. Etani T, Naiki T, Sugiyama Y et al (2020) The pretreatment neutrophil-to-lymphocyte ratio is a novel biomarker for predicting clinical responses to pembrolizumab in platinum-resistant metastatic urothelial carcinoma patients. Urol Oncol 38(6):602.e1. https://doi.org/10.1016/j.urolonc.2020.02.005 (Epub 2020/03/07. PubMed PMID: 32139290)

41. Kijima T, Yamamoto H, Saito K et al (2021) Early C-reactive protein kinetics predict survival of patients with advanced urothelial cancer treated with pembrolizumab. Cancer Immunol Immunother 70(3):657–665. https://doi.org/10.1007/s00262-020-02709-2 (Epub 2020/09/03 PubMed PMID: 32876736)

42. Sengelov L, Kamby C, von der Maase H (2001) Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. Eur Urol 39(6):634–642. https://doi.org/10.1159/000052520 (Epub 2001/07/21 PubMed PMID: 11464051)

43. De Santis M, Bellmunt J, Mead G et al (2012) Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 30(2):191–199. https://doi.org/10.1200/JCO.2011.37.3571 (Epub 2011/12/14. PubMed PMID: 22162575; PubMed Central PMCID: PMCPMC3255563)

44. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188. https://doi.org/10.1016/0197-2456(86)90046-2 (Epub 1986/09/01 PubMed PMID: 3802833)

45. Inoue S, Sassa N, Kato T et al (2020) Presence of constipation between pretreatment neutrophil-to-lymphocyte ratio and outcome markers during therapy. Oncotarget 7(47):77404–77415. https://doi.org/10.18632/oncotarget.16139-9 (Epub 2020/09/20 PubMed PMID: 32949825)

46. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5(6):649–655 (Epub 1982/12/01 PubMed PMID: 7165009)

47. Nakamura Y, Kitano S, Takahashi A et al (2016) Nivolumab for advanced melanoma: pretreatment prognostic factors and early outcome markers during therapy. Oncotarget 7(47):77404–77415. https://doi.org/10.18632/oncotarget.12677 (Epub 2016/10/21. PubMed PMID: 27764805; PubMed Central PMCID: PMCPMC5363594)

48. Khaki AR, Li A, Diamantopoulos LN et al (2020) Impact of performance status on treatment outcomes: a real-world study of advanced urothelial cancer treated with checkpoint inhibitors. Cancer 126(6):1208–1216. https://doi.org/10.1002/cncr.32645 (PubMed PMID: WOS:000502160300001)

49. Parikh RB, Galsky MD, Gyawali B et al (2019) Trends in checkpoint inhibitor therapy for advanced urothelial cell carcinoma at the end of life: insights from real-world practice. Oncologist 24(6):e397–e399. https://doi.org/10.1634/theoncologist.2019-0039 (Epub 2019/04/05. PubMed PMID: 30944183; PubMed Central PMCID: PMCPMC6656487 article)
with nivolumab. Clin Genitourin Cancer 16(3):e563–e575. https://doi.org/10.1016/j.clgc.2017.12.015 (Epub 2018/02/07. PubMed PMID: 29402706; PubMed Central PMCID: PMCPMC5970007)

53. Chasseuil E, Saint-Jean M, Chasseuil H et al (2018) Blood predictive biomarkers for nivolumab in advanced melanoma. Acta Derm Venereol 98(4):406–410. https://doi.org/10.2340/00015555-2872 (Epub 2018/01/13 PubMed PMID: 29327065)

54. Ferrucci PF, Asciento PA, Piggozzo J et al (2016) Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. Ann Oncol 27(4):732–738. https://doi.org/10.1093/annonc/mdw016 (Epub 2016/01/24 PubMed PMID: 26802161)

55. Jeyakumar G, Kim S, Bumma N et al (2017) Neutrophil lymphocyte ratio and duration of prior anti-angiogenic therapy as biomarkers in metastatic RCC receiving immune checkpoint inhibitor therapy. J Immunother Cancer 5(1):82. https://doi.org/10.1186/s40425-017-0287-5 (Epub 2017/10/19. PubMed PMID: 29041991; PubMed Central PMCID: PMCPMC646127)

56. Park W, Lopes G (2019) Perspectives: neutrophil-to-lymphocyte ratio as a potential biomarker in immune checkpoint inhibitor for non-small-cell lung cancer. Clin Lung Cancer 20(3):143–147. https://doi.org/10.1016/j.cllc.2018.12.003 (Epub 2019/01/27 PubMed PMID: 30683629)

57. Zaragoza J, Caille A, Beneton N et al (2016) High neutrophil to lymphocyte ratio measured before starting ipilimumab treatment is associated with reduced overall survival in patients with melanoma. Br J Dermatol 174(1):146–151. https://doi.org/10.1111/bjd.14155 (Epub 2015/09/08 PubMed PMID: 26343230)

58. Mori K, Miura N, Mostafaei H et al (2020) Prognostic value of neutrophil-to-lymphocyte ratio as a potential biomarker in immune checkpoint inhibitor therapy. J Immunother Cancer 5(1):82. https://doi.org/10.1186/s40425-017-0287-5 (Epub 2017/10/19. PubMed PMID: 29041991; PubMed Central PMCID: PMCPMC646127)

59. Karal J, Busch SE, Yang GH et al (2017) Neutrophils dominate the immune cell composition in non-small cell lung cancer. Nat Commun 8:14381. https://doi.org/10.1038/s41467-017-01690-1 (Epub 2020/05/27. PubMed PMID: 32451768; PubMed Central PMCID: PMCPMC7399293)

60. Gooden MJ, de Bock GH, Jeffers N (2011) The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer 105(1):93–103. https://doi.org/10.1038/bjc.2011.189 (Epub 2011/06/02. PubMed PMID: 21629244; PubMed Central PMCID: PMCPMC3137407)

61. Bagley SJ, Kothari S, Aggarwal C et al (2017) Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 106:1–7. https://doi.org/10.1016/j.lungcan.2017.01.013 (Epub 2017/03/14 PubMed PMID: 28285682)

62. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12(4):252–264. https://doi.org/10.1038/nrc3239 (Epub 2012/03/23. PubMed PMID: 22437870; PubMed Central PMCID: PMCPMC48856023)

63. Roxburgh CS, McMillan DC (2010) Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol 6(1):149–163. https://doi.org/10.2217/fon.09.136 (Epub 2009/12/22 PubMed PMID: 20021215)

64. Saito K, Kawakami S, Ohtsuka Y et al (2007) The impact of pre-operative serum C-reactive protein on the prognosis of patients with upper urinary tract urothelial carcinoma treated surgically. BJU Int 100(2):269–273. https://doi.org/10.1111/j.1464-410X.2007.06934.x (Epub 2007/05/10 PubMed PMID: 17488302)

65. Krajsio I, Aremberger P, Lakomy R et al (2015) Long-term survival with ipilimumab: experience from a national expanded access program for patients with melanoma. Anticancer Res 35(11):6303–6310 (Epub 2015/10/28 PubMed PMID: 26504067)

66. Simeone E, Gentilcore G, Giannarelli D et al (2014) Immunological and biological changes during ipilimumab treatment and their potential correlation with clinical response and survival in patients with advanced melanoma. Cancer Immunol Immunother 63(7):675–683. https://doi.org/10.1007/s00262-014-1545-8 (Epub 2014/04/04 PubMed PMID: 24695951)

67. Fuji J, Naing A, Rolfo C et al (2018) Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol 130:108–120. https://doi.org/10.1016/j.critrevonc.2018.07.010 (Epub 2018/09/11 PubMed PMID: 30196907)

68. Sonpavde G, Pond GR, Rosenberg JE et al (2016) Improved prognostic and biological changes during ipilimumab treatment and their potential correlation with clinical response and survival in patients with advanced melanoma. Cancer Immunol Immunother 63(7):675–683. https://doi.org/10.1007/s00262-014-1545-8 (Epub 2014/04/04 PubMed PMID: 24695951)

69. Sonpavde G, Manitz J, Gao C et al (2020) Five-factor prognostic model for survival of post-platinum patients with metastatic urothelial carcinoma receiving PD-L1 inhibitors. J Urol 195(2):277–282. https://doi.org/10.1097/JU.0000000000001190 (Epub 2020/06/20. PubMed PMID: 26292040; PubMed Central PMCID: PMCPMC5205874)

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Takafumi Yanagisawa1,2 · Keiichiro Mori1,2 · Satoshi Katayama1,3 · Hadi Mostafaei1,4 · Fahad Quhal1,5 · Ekaterina Laukhina1,6 · Pawel Rajwa1,7 · Reza Sari Motalagh1,8 · Abdulmajeed Aydh1,9 · Frederik König1,10 · Nico C. Grossmann1,11,12 · Benjamin Pradere1 · Jun Miki2 · Takahiro Kimura2 · Shin Egawa2 · Shahrokh F. Shariat1,6,13,14,15,16,17

1 Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Wahringer Guertel 43 18-20, 1090 Vienna, Austria

2 Department of Urology, The Jikei University School of Medicine, Tokyo, Japan

3 Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

4 Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
5 Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia
6 Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia
7 Department of Urology, Medical University of Silesia, Zabrze, Poland
8 Men’s Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
9 Department of Urology, King Faisal Medical City, Abha, Saudi Arabia
10 Department of Urology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
11 Department of Urology, University Hospital Zurich, Zurich, Switzerland
12 Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland
13 Division of Urology, Department of Special Surgery, Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan
14 Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA
15 Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic
16 Department of Urology, Weill Cornell Medical College, New York, NY, USA
17 Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria