

Prognosis of Patients Receiving Chemotherapy for Metastatic Upper Tract Urothelial Carcinoma Compared With Metastatic Urinary Bladder Cancer

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Abstract. *Background/Aim:* The treatment strategy for metastatic upper tract urothelial carcinoma (mUTUC) is currently based on the evidence from metastatic urinary bladder cancer (mUBC). However, some reports have shown that the outcomes of UTUC differ from those of UBC. Therefore, we retrospectively analyzed the prognosis of patients with mUBC and mUTUC treated with first-line platinum-based chemotherapy. *Patients and Methods:* Patients who underwent platinum-based chemotherapy at the Kindai University Hospital and affiliated hospitals between January 2010 and December 2021 were included in the study. There were 56 patients with mUBC and 73 with mUTUC. Kaplan–Meier curves were used to estimate progression-free (PFS) and overall (OS) survival. Multivariate analyses were performed using Cox proportional hazards model to predict prognostic factors. *Results:* The median PFS was 4.5 and 4.0 months for the mUBC and mUTUC groups, respectively

($p=0.094$). The median OS was 17.0 months for both groups ($p=0.821$). The multivariate analysis showed no prognostic factor for PFS. The multivariate analysis for OS showed that younger age at the initiation of chemotherapy and immune checkpoint inhibitor use after first-line therapy were significantly associated with better OS. *Conclusion:* Platinum-based chemotherapy had a similar effect on patients with mUTUC and mUBC.

Upper tract urothelial carcinoma (UTUC) is a rare malignant disease of the renal pelvis and ureter, accounting for approximately 5-10% of urothelial cell carcinomas, with an incidence of 1-2 per 100,000 individuals annually (1). Treatment strategies for metastatic UTUC (mUTUC) are currently based on the evidence of urinary bladder cancer (UBC). However, some reports have shown that the outcomes of UTUC differ from those of UBC (2). While UTUC shares similar histology with UBC, both have some distinct features (3). For example, UTUC arises from mesoderm-derived epithelium, whereas the UBC arises from endodermal structures (4). UTUC is more often invasive than bladder cancer at the time of surgery (1). Additionally, UTUC is associated with Lynch syndrome and can be induced by aristolochic acid. In contrast, UBC is rarely associated with Lynch syndrome or aristolochic acid exposure (5-7). Genetic analysis has also revealed that some characteristics of UTUC and UBC are different (8). Therefore, treatment of metastatic UTUC may require a different clinical management strategy from that of metastatic UBC (4). Owing to the small number of patients with UTUC, an evidence-based treatment derived from that for UBC is used in UTUC. Cisplatin-based chemotherapy is the standard first-line treatment for metastatic UBC (mUBC). Combination

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Key Words: Metastatic upper tract urothelial carcinoma, mUTUC, metastatic urinary bladder cancer, mUBC, platinum-based chemotherapy, prognostic factor, overall survival, OS.

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Table I. Patient characteristics.

Characteristic		mUBC	mUTUC	p-Value
Patients, n (%)	Total	56 (43.4)	73 (56.6)	
Age, years	Median, (range)	70.5 (54-84)	72 (45-84)	0.43
Sex, n (%)	Male	36 (64.3)	58 (79.5)	0.072
	Female	20 (35.7)	15 (20.5)	
Nephroureterectomy or cystectomy, n (%)	Yes	27 (48.2)	51 (69.9)	0.018
	No	29 (51.8)	22 (30.1)	
Histology, n (%)	UC	53 (94.6)	65 (89.0)	0.35
	Other/NA	3 (5.4)	8 (11.0)	
T-Stage, n (%)	Tis	5 (8.9)	1 (1.4)	0.041
	Ta	1 (1.8)	1 (1.4)	
	T1	9 (16.1)	3 (4.1)	
	≥T2	33 (58.9)	48 (65.8)	
	NA	8 (14.3)	20 (27.4)	
Site of metastasis, n (%)	Lymph node	38 (67.9)	45 (61.6)	0.58
	Lung	13 (23.2)	39 (53.4)	0.0006
	Liver	4 (7.1)	10 (13.7)	0.27
	Bone	12 (21.4)	8 (11.0)	0.14
eGFR, ml/min/1.73 m ²	Median (range)	54 (6-134)	46 (25-94)	0.28
1 st -Line treatment, n (%)	GCI	39 (69.6)	43 (58.9)	0.54
	GCa	16 (28.6)	27 (37.0)	
	MVAC	1 (1.8)	2 (2.7)	
	GN	0 (0)	1 (1.4)	
2 nd -Line treatment, n (%)	Pembrolizumab	13 (23.2)	28 (38.4)	0.098
	MVAC	2 (3.6)	4 (5.5)	
	GCI/GCa	2 (3.6)	1 (1.4)	
	TG	2 (3.6)	8 (11.0)	
	other	9 (16.1)	6 (8.2)	
	BSC	18 (32.1)	14 (19.2)	
ICI use after 1st-line treatment, n (%)	NA/none	10 (17.8)	12 (16.4)	0.592
	Yes	21 (37.5)	31 (42.5)	

BSC: Best supportive care; eGFR: estimated glomerular filtration rate; GCa: gemcitabine with carboplatin; GCI: gemcitabine and cisplatin chemotherapy; GN: gemcitabine with nedaplatin; ICI: immune checkpoint inhibitor; mUBC: metastatic urinary bladder cancer; mUTUC: metastatic upper tract urothelial carcinoma; MVAC: methotrexate with vinblastine, doxorubicin, and cisplatin; NA: not available; TG: paclitaxel with gemcitabine.

treatments using gemcitabine/cisplatin (GCI), or methotrexate with vinblastine, doxorubicin and cisplatin (MVAC), and dose-dense MVAC are the most commonly used regimens, leading to a median overall survival (OS) of 12-14 months in patients with mUBC (9, 10). Therefore, we retrospectively analyzed the clinical characteristics and prognosis of patients treated with first-line platinum-based chemotherapy for mUTUC compared with those treated for mUBC.

Patients and Methods

This study was approved by the Institutional Ethical Review Board (no. R02-247), and the requirement for individual consent for this retrospective analysis was waived. Patients with mUBC and mUTUC who underwent platinum-based first-line chemotherapy at the Kindai University Hospital and affiliated hospitals between January 2010 and December 2021 were included. Those with previously untreated metastatic disease, postoperative recurrence, and post-neoadjuvant or post-adjuvant chemotherapy were included. We analyzed patient age,

sex, T-stage, metastatic sites, total renal function, second-line therapy, and use of immune checkpoint inhibitors (ICIs). T-Stage was defined according to the eighth edition of the TNM Classification of Malignant Tumors (11). GCI, MVAC, and gemcitabine/carboplatin (GCa) therapies were administered as platinum-based chemotherapy. GCI therapy consisted of 1,000 mg/m² gemcitabine on days 1, 8 and 15, and 70 mg/m² cisplatin on day 2. Patients with renal dysfunction were administered a reduced dose or GCa therapy, as appropriate, at the discretion of the physician. GCa therapy comprised 1,000 mg/m² gemcitabine and carboplatin calculated by area under the concentration–time curve 4-5 (mg/ml min) on day 1 and 1,000 mg/m² gemcitabine on days 8 and 15, with the dosage reduced at the discretion of the physician, considering the patient's age and condition. MVAC therapy consisted of 30 mg/m² methotrexate on days 1, 15, and 22; 3 mg/m² vinblastine on days 2, 15, and 22; 30 mg/m² doxorubicin on day 2; and 70 mg/m² of cisplatin on day 2.

Imaging studies after chemotherapy were performed using computed tomography every 3 months. Evaluation of the therapeutic effect was performed using Response Evaluation Criteria for Solid Tumors ver. 1.1 (12).

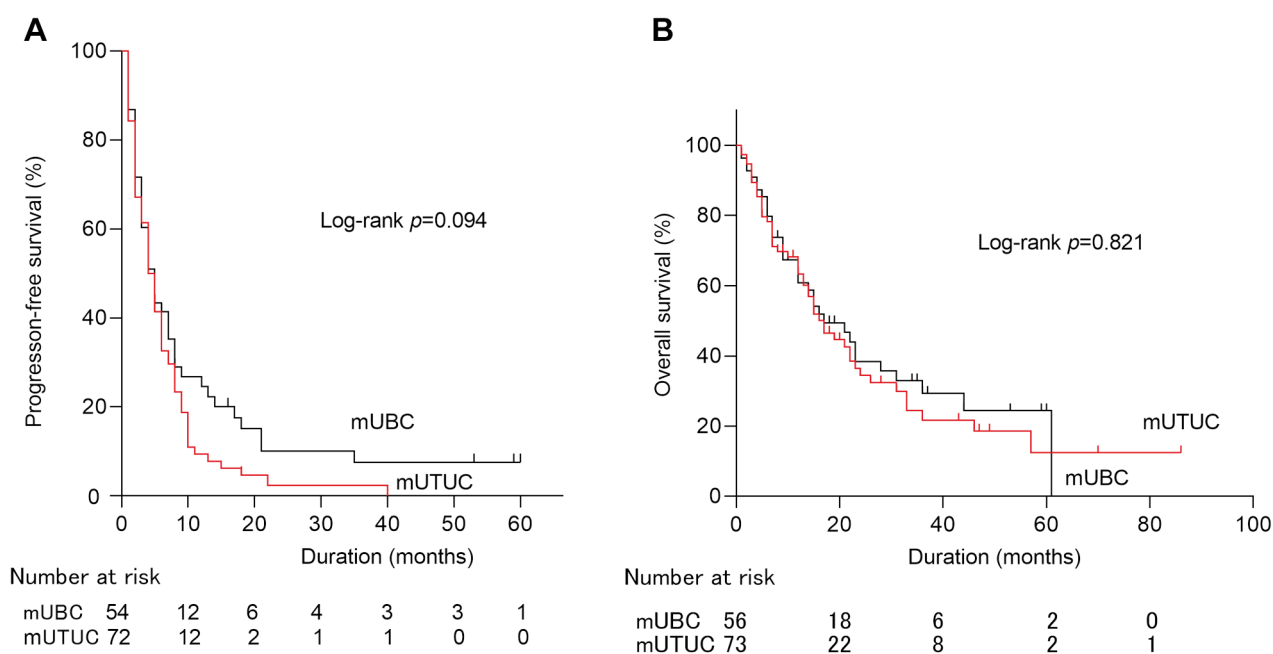


Figure 1. Progression-free (A) and overall (B) survival in patients with metastatic upper tract urothelial carcinoma (mUTUC) and metastatic urinary bladder cancer (mUBC).

Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (5). The association of the parameters between the two groups was analyzed using Fisher's exact test. Kaplan-Meier curves were used to estimate progression-free survival (PFS) and OS. PFS was defined as the duration from the initiation of chemotherapy to disease progression. OS was defined as the duration from the initiation of chemotherapy to death. Age, estimated glomerular filtration rate, liver metastasis, UTUC, and ICI use after first-line treatment were entered into multivariate analysis using a Cox proportional-hazards model to predict PFS and OS. Statistical significance was set at $p < 0.05$.

Results

There were 56 patients with mUBC and 73 with mUTUC. The median age at the initiation of chemotherapy was 70.5 years for those with mUBC and 72 years for those with mUTUC. Patients with mUTUC underwent surgery more frequently than those with mUBC (56% vs. 27%, $p=0.0179$). Lung metastases were more frequent in the mUTUC group than in the mUBC group (41% vs. 13%, $p=0.0006$). The median estimated glomerular filtration rate was not statistically different between the mUBC and mUTUC groups (46 vs. 54 ml/min/1.73 m², $p=0.284$) (Table I).

In this study, 28 patients (50%) with mUBC and 47 (64.4%) with mUTUC received second-line treatment. ICI treatment on progression after first-line chemotherapy was observed in 37.5% of patients with mUBC and 42.5% with mUTUC ($p=0.592$).

For first-line chemotherapy, complete response, partial response, stable disease, and progressive disease were found in 14.8% and 12.5% ($p=0.794$), 24.1% and 15.3% ($p=0.255$), 24.1% and 9.7% ($p=0.0469$), and 37% and 62.5% ($p=0.00672$) of patients with mUBC and, respectively. The overall response rate was 38.9% for UBC and 27.8% for UTUC ($p=0.249$).

Median follow-up duration was 13 months in both patients with mUBC (range=0-61 months) and mUTUC (range=1-86 months). In our study, 20% of all patients were censored because of lost to follow-up. Almost all of these were due to transfer to another hospital for best supportive care. The median PFS was 4.5 months in patients with mUBC and 4.0 months in those with mUTUC, showing a favorable trend in mUBC; however, there was no statistical difference (log-rank test, $p=0.094$) (Figure 1A). The median OS was 17.0 months for both groups, with no statistical difference (log-rank test, $p=0.821$) (Figure 1B). The multivariate analysis showed no significant prognostic factor for PFS (Table II). In contrast, the multivariate analysis showed that younger age and ICI use after first-line therapy were significantly associated with better OS (Table III).

Discussion

In this study, we retrospectively compared the prognoses of patients with mUBC and mUTUC who received platinum-based chemotherapy. There were no statistically significant differences in PFS and OS between the mUBC and mUTUC

Table II. Cox proportional-hazards analysis for progression-free survival.

Variable		Univariate			Multivariate		
		HR	95% CI	p-Value	HR	95% CI	p-Value
Age, years	Continuous	1.026	0.996-1.058	0.092	1.025	0.994-1.058	0.119
eGFR	<40 vs. ≥40 ml/min/1.73 m ²	1.231	0.820-1.848	0.317	1.046	0.682-1.606	0.837
Liver metastasis	Yes vs. no	1.444	0.808-2.581	0.215	1.601	0.849-3.020	0.146
Disease	mUTUC vs. mUBC	1.347	0.924-1.962	0.121	1.232	0.838-1.814	0.289

CI: Confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; mUBC: metastatic urinary bladder cancer; mUTUC: metastatic upper tract urothelial carcinoma.

Table III. Cox proportional hazards analysis for overall survival.

		Univariate			Multivariate		
		HR	95% CI	p-Value	HR	95% CI	p-Value
Age, years	Continuous	1.036	1.000-1.073	0.053	1.04	1.002-1.079	0.0384
eGFR	<40 vs. ≥40 ml/min/1.73 m ²	1.248	0.751-2.076	0.393	1.159	0.682-1.968	0.586
Liver metastasis	Yes vs. no	1.066	0.461-2.461	0.882	0.94	0.362-2.440	0.899
Disease	mUTUC vs. mUBC	1.051	0.677-1.633	0.825	1.242	0.775-1.992	0.368
ICI use after 1 st -line therapy	Yes vs. no	0.427	0.267-0.683	0.00038	0.399	0.242-0.655	0.00029

CI: Confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ICI: immune checkpoint inhibitor; mUBC: metastatic urinary bladder cancer; mUTUC: metastatic upper tract urothelial carcinoma.

groups. GCI therapy and dose-dense MVAC are recommended as the first-line chemotherapy for mUBC in the National Comprehensive Cancer Network Guidelines Version 3.2020 (13). The first-line chemotherapy for mUTUC is considered the same as that for mUBC, and GCI has been commonly used. Many patients with UTUC who undergo radical nephroureterectomy have chronic kidney disease. Tafuri *et al.* reported that 403 (70.0%) patients who underwent radical nephroureterectomy for UTUC had an estimated glomerular filtration rate <60 ml/min at 6 months (14). Patients with UTUC with obstruction of the ureter also showed loss of renal function. Renal insufficiency results in a dose reduction of platinum-based chemotherapy. Surprisingly, the renal function of the patients with mUBC was similar to that of those with mUTUC in our study. Many patients with mUBC also have chronic kidney disease, which makes them ineligible for platinum-based chemotherapy.

Some reports have shown genetic differences between UBC and UTUC. Audenet *et al.* compared the frequency of gene mutations between 195 cases of UTUC and 454 cases of UBC and reported that mutations in fibroblast growth factor receptor 3 (*FGFR3*) and HRas proto-oncogene, GTPase (*HRAS*) were found more frequently in UTUC than in UBC (15). In a subgroup analysis of metastatic cancer, the frequency of mutations in retinoblastoma 1 (*RBI*), erb-b2 receptor tyrosine

kinase (*ERBB2*), and cell cycle-related genes were significantly higher in UBC than in UTUC (*RBI*: 27% vs. 3%, *ERBB2*: 27% vs. 0%, cell cycle-related genes: 71% vs. 43%) (15). Cisplatin induces cross-links in DNA, causing DNA damage and inducing apoptosis. Mutations in DNA damage-response genes are associated with increased sensitivity to chemotherapy in patients with urothelial carcinoma (16, 17). In patients with UBC, basal tumors conferred a worse prognosis than luminal tumors (18). Inoue *et al.* reported that patients with basal-type urothelial carcinoma who received pembrolizumab after platinum-based chemotherapy had significantly shorter PFS and cancer-specific survival than those with pure urothelial carcinoma (19). Plimack *et al.* also found that among patients with invasive bladder cancer treated with cisplatin-based neoadjuvant chemotherapy, those with ataxia telangiectasia mutated (*ATM*)/*RBI*/fanconi anemia complementation group C (*FANCC*) mutations had longer PFS and OS than those without such mutations (20). These findings suggest possible differences in the response to and efficacy of platinum-based chemotherapy between UTUC and UBC.

Pembrolizumab was approved by the US Food and Drug Administration in May 2017 as a second-line treatment for advanced disease after platinum-based chemotherapy as a result of the KEYNOTE-045 trial (21). The KEYNOTE-045 trial enrolled 542 patients with advanced urothelial

carcinoma after platinum-based chemotherapy, of whom 76 (14%) had UTUC. Subgroup analysis of OS showed a hazard ratio (HR) of 0.77 [95% confidence interval (CI)=0.60-0.97] for bladder cancer and 0.53 (95% CI=0.28-1.01) for upper urothelial cancer. In contrast, a subgroup analysis of the CheckMate-274 trial for postoperative nivolumab adjuvant therapy in muscle-invasive bladder cancer reported that there may be differences in efficacy between bladder cancer and renal pelvic ureteral cancer (22). The HR for disease-free survival in UBC and UTUC were 0.62 (95% CI=0.49-0.78) and 1.23 (95% CI=0.67-2.23), respectively, possibly due to the small number of UTUC cases.

Enfortumab vedotin, an antibody–drug conjugate is composed of a fully human monoclonal antibody specific for nectin-4, and monomethyl auristatin E, an agent that disrupts microtubule formation (23). Targeted delivery of monomethyl auristatin E results in cell-cycle arrest and apoptosis (23, 24). The EV-301 trial for advanced urothelial carcinoma had an OS HR of 0.67 (95% CI=0.51-0.88) in UBC and 0.85 (95% CI=0.57-1.27) in UTUC (25).

In our study, there was no significant difference in OS between patients with mUTUC and those with mUBC. The PFS for the mUTUC group was worse than that of the mUBC group; however, the difference was not statistically significant ($p=0.094$). Platinum-based chemotherapy had similar effects on OS in the mUTUC and mUBC groups. As the number of patients treated with enfortumab vedotin increases, there may be a difference in prognosis between mUTUC and mUBC, which can be investigated in the future.

A comparison of patient backgrounds showed that patients with mUTUC had higher frequency of lung metastasis than those with mUBC. Liu *et al.* reported that the sites of metastasis in 1,035 patients with stage IV metastatic bladder cancer were lymph nodes in 25.4%, bone in 24.7%, lung in 19.4%, liver in 18.1%, and brain in 3.1% (26). Chen *et al.* reported that the sites of metastasis in 424 patients with metastatic renal pelvic carcinoma were lymph nodes in 30.0%, bone in 36.1%, lung in 45.3%, liver in 32.3%, and brain in 2.8%, respectively (27). The frequency of metastasis, such as lung and liver, were higher in patients with metastatic renal pelvic carcinoma than those with metastatic bladder cancer. These findings suggest that UTUC is more likely to undergo hematogenous metastasis than UBC; however, the mechanism is unknown.

Multivariate analysis of OS showed that older age (HR=1.04) were significantly associated with a poor prognosis and that ICI use after first-line therapy (HR=0.399) were significantly associated with a good prognosis. However, this result does not directly indicate the effects of ICI administration. Patients who did not experience rapid progression might have received ICIs after first-line therapy. Patients were also included in this study who had been treated before the approval of ICIs. Bajorin *et al.* identified liver metastasis as poor prognostic factor (28). Li *et al.* reported

that liver metastasis before ICI were associated with increased risk of death (29). However, in our study, liver metastasis was not associated with poor prognosis.

This study has several limitations. First, this was a retrospective study with a small number of patients. Second, the selection and dose of chemotherapy regimens were determined by the judgment of the institution and attending physician, and the same is true for dose reduction and discontinuation in consideration of the patient's condition and adverse events. Third, because both patients before and after ICIs approval were included, there was no treatment option for ICIs administration for pre-approval patients, and there were other confounding factors, such as tumor grade and site of metastasis, in the multivariate analysis. There was no difference in survival between patients with mUTUC and those with mUBC. This study confirmed that platinum-based chemotherapy has a similar effect on both mUTUC and mUBC. The appropriate treatment strategies for patients with mUTUC and mUBC after first-line chemotherapy may differ.

Conflicts of Interest

There are no conflicts of interest related to this study.

Authors' Contributions

S. Adomi and K. Fujita conceived the study. H. Kita, K. Kuwahara, Y. Akashi, N. Matsumura and K. Sugimoto collected patients' data. T. Minami, M. Nozawa, H. Tahara and A. Esa performed analysis and interpretation of data. S. Adomi and M. Nishimoto prepared the original article. K. Fujita, A. Hirayama and T. Nishioka revised the article. K. Yoshimura and H. Uemura supervised the article. All Authors read and agreed to the published version of the article.

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References

- 1 Siegel R, Miller K, Fuchs H, Jemal A: Cancer statistics, 2022. *CA Cancer J Clin* 72(1): 7-33, 2022. DOI: 10.3322/caac.21708
- 2 Catto J, Azzouzi A, Rehman I, Feeley K, Cross S, Amira N, Fromont G, Sibony M, Cussenot O, Meuth M, Hamdy F: Promoter hypermethylation is associated with tumor location, stage, and subsequent progression in transitional cell carcinoma. *J Clin Oncol* 23(13): 2903-2910, 2005. DOI: 10.1200/JCO.2005.03.163
- 3 Green D, Rink M, Xylinas E, Matin S, Stenzl A, Roupert M, Karakiewicz P, Scherr D, Shariat S: Urothelial carcinoma of the bladder and the upper tract: disparate twins. *J Urol* 189(4): 1214-1221, 2013. DOI: 10.1016/j.juro.2012.05.079
- 4 Leow J, Chong K, Chang S, Bellmunt J: Upper tract urothelial carcinoma: a different disease entity in terms of management. *ESMO Open* 1(6): e000126, 2017. DOI: 10.1136/esmoopen-2016-000126

- 5 Carlo M, Ravichandran V, Srinivasan P, Bandlamudi C, Kemel Y, Ceyhan-Birsoy O, Mukherjee S, Mandelker D, Chaim J, Knezevic A, Rana S, Fnu Z, Breen K, Arnold A, Khurram A, Tkachuk K, Cipolla C, Regazzi A, Hakimi A, Al-Ahmadie H, Dalbagni G, Cadoo K, Walsh M, Teo M, Funt S, Coleman J, Bochner B, Iyer G, Solit D, Stadler Z, Zhang L, Rosenberg J, Taylor B, Robson M, Berger M, Vijai J, Bajorin D, Offit K: Cancer susceptibility mutations in patients with urothelial malignancies. *J Clin Oncol* 38(5): 406-414, 2020. DOI: 10.1200/JCO.19.01395
- 6 Chen C, Dickman K, Moriya M, Zavadil J, Sidorenko V, Edwards K, Gnatenko D, Wu L, Turesky R, Wu X, Pu Y, Grollman A: Aristolochic acid-associated urothelial cancer in Taiwan. *Proc Natl Acad Sci USA* 109(21): 8241-8246, 2012. DOI: 10.1073/pnas.1119920109
- 7 Hoang M, Chen C, Sidorenko V, He J, Dickman K, Yun B, Moriya M, Niknafs N, Douville C, Karchin R, Turesky R, Pu Y, Vogelstein B, Papadopoulos N, Grollman A, Kinzler K, Rosenquist T: Mutational signature of aristolochic acid exposure as revealed by whole-exome sequencing. *Sci Transl Med* 5(197): 197ra102, 2013. DOI: 10.1126/scitranslmed.3006200
- 8 Sfakianos J, Gul Z, Shariat S, Matin S, Daneshmand S, Plimack E, Lerner S, Roupert M, Pal S: Genetic differences between bladder and upper urinary tract carcinoma: implications for therapy. *Eur Urol Oncol* 4(2): 170-179, 2021. DOI: 10.1016/j.euo.2020.12.007
- 9 Witjes J, Bruins H, Cathomas R, Comp erat E, Cowan N, Gakis G, Hern andez V, Linares Espin os E, Lorch A, Neuzillet Y, Rouanne M, Thalmann G, Veskim ae E, Ribal M, Van der Heijden A: European Association of Urology Guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol* 79(1): 82-104, 2021. DOI: 10.1016/j.eururo.2020.03.055
- 10 Bellmunt J, Petrylak D: New therapeutic challenges in advanced bladder cancer. *Semin Oncol* 39(5): 598-607, 2012. DOI: 10.1053/j.seminoncol.2012.08.007
- 11 Brierley JD, Gospodarowicz MK, Wittekind C: *TNM Classification of malignant Tumours, Eighth Edition*. Wiley-Blackwell, 2016.
- 12 Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45(2): 228-247, 2009. DOI: 10.1016/j.ejca.2008.10.026
- 13 Flaig T, Spiess P, Agarwal N, Bangs R, Boorjian S, Buyyounouski M, Chang S, Downs T, Efstathiou J, Friedlander T, Greenberg R, Guru K, Guzzo T, Herr H, Hoffman-Censits J, Hoimes C, Inman B, Jimbo M, Kader A, Lele S, Michalski J, Montgomery J, Nandagopal L, Pagliaro L, Pal S, Patterson A, Plimack E, Pohar K, Preston M, Sexton W, Siefker-Radtke A, Tward J, Wright J, Gurski L, Johnson-Chilla A: Bladder cancer, version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 18(3): 329-354, 2020. DOI: 10.6004/jnccn.2020.0011
- 14 Tafuri A, Marchioni M, Cerrato C, Mari A, Tellini R, Odorizzi K, Veccia A, Amparore D, Shakir A, Carbonara U, Panunzio A, Trovato F, Catellani M, Janello L, Bianchi L, Novara G, Dal Moro F, Schiavina R, De Lorenzis E, Parma P, Cimino S, De Cobelli O, Maiorino F, Bove P, Crocerossa F, Cantiglio F, D'Andrea D, Di Cosmo F, Porpiglia F, Dittono P, Montanari E, Soria F, Gontero P, Liguori G, Trombetta C, Mantica G, Borghesi M, Terrone C, Del Giudice F, Sciarra A, Galosi A, Moschini M, Shariat S, Di Nicola M, Minervini A, Ferro M, Cerruto M, Schips L, Pagliarulo V, Antonelli A: Changes in renal function after nephroureterectomy for upper urinary tract carcinoma: analysis of a large multicenter cohort (Radical Nephroureterectomy Outcomes (RaNeO) Research Consortium). *World J Urol* 40(11): 2771-2779, 2022. DOI: 10.1007/s00345-022-04156-3
- 15 Audenet F, Isharwal S, Cha E, Donoghue M, Drill E, Ostrovnaya I, Pietzak E, Sfakianos J, Bagrodia A, Murugan P, Dalbagni G, Donahue T, Rosenberg J, Bajorin D, Arcila M, Hechtman J, Berger M, Taylor B, Al-Ahmadie H, Iyer G, Bochner B, Coleman J, Solit D: Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. *Clin Cancer Res* 25(3): 967-976, 2019. DOI: 10.1158/1078-0432.CCR-18-2039
- 16 Teo M, Bambury R, Zabor E, Jordan E, Al-Ahmadie H, Boyd M, Bouvier N, Mullane S, Cha E, Roper N, Ostrovnaya I, Hyman D, Bochner B, Arcila M, Solit D, Berger M, Bajorin D, Bellmunt J, Iyer G, Rosenberg J: DNA damage response and repair gene alterations are associated with improved survival in patients with platinum-treated advanced urothelial carcinoma. *Clin Cancer Res* 23(14): 3610-3618, 2017. DOI: 10.1158/1078-0432.CCR-16-2520
- 17 Liu D, Plimack E, Hoffman-Censits J, Garraway L, Bellmunt J, Van Allen E, Rosenberg J: Clinical validation of chemotherapy response biomarker ERCC2 in muscle-invasive urothelial bladder carcinoma. *JAMA Oncol* 2(8): 1094, 2016. DOI: 10.1001/jamaoncol.2016.1056
- 18 Goutas D, Tzortzis A, Gakiopoulou H, Vlachodimitropoulos D, Giannopoulou I, Lazaris A: Contemporary molecular classification of urinary bladder cancer. *In Vivo* 35(1): 75-80, 2021. DOI: 10.21873/invivo.12234
- 19 Inoue S, Sassa N, Kawanishi H, Yuguchi Y, Suzuki T, Nagayama J, Matsui H, Miyata Y, Soeda Y, Tochigi K, Yamauchi Y, Maeda M, Kobayashi I, Hattori R, Matsukawa Y, Kato M: Impact of histological variants on clinical responses to pembrolizumab in patients with metastatic urothelial cancer. *Anticancer Res* 42(7): 3627-3636, 2022. DOI: 10.21873/anticancer.15851
- 20 Plimack E, Dunbrack R, Brennan T, Andrade M, Zhou Y, Serebriiskii I, Slifker M, Alpaugh K, Dulaimi E, Palma N, Hoffman-Censits J, Bilusic M, Wong Y, Kutikov A, Viterbo R, Greenberg R, Chen D, Lallas C, Trabulsi E, Yelensky R, McConkey D, Miller V, Golemis E, Ross E: Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer. *Eur Urol* 68(6): 959-967, 2015. DOI: 10.1016/j.eururo.2015.07.009
- 21 Bellmunt J, De Wit R, Vaughn D, Fradet Y, Lee J, Fong L, Vogelzang N, Climent M, Petrylak D, Choueiri T, Necchi A, Gerritsen W, Gurney H, Quinn D, Culine S, Sternberg C, Mai Y, Poehlein C, Perini R, Bajorin D: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 376(11): 1015-1026, 2017. DOI: 10.1056/NEJMoa1613683
- 22 Bajorin D, Witjes J, Gschwend J, Schenker M, Valderrama B, Tomita Y, Bamias A, Leuret T, Shariat S, Park S, Ye D, Agerbaek M, Enting D, McDermott R, Gajate P, Peer A, Milowsky M, Nosov A, Neif Antonio J, Tupikowski K, Toms L, Fischer B, Qureshi A, Collette S, Unsal-Kacmaz K, Broughton E, Zardavas D, Koon H, Galsky M: Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 384(22): 2102-2114, 2021. DOI: 10.1056/NEJMoa2034442

- 23 Rosenberg J, Sridhar S, Zhang J, Smith D, Ruether D, Flaig T, Baranda J, Lang J, Plimack E, Sangha R, Heath E, Merchan J, Quinn D, Srinivas S, Milowsky M, Wu C, Gartner E, Zuo P, Melhem-Bertrandt A, Petrylak D: EV-101: a Phase I study of single-agent enfortumab vedotin in patients with nectin-4-positive solid tumors, including metastatic urothelial carcinoma. *J Clin Oncol* 38(10): 1041-1049, 2020. DOI: 10.1200/JCO.19.02044
- 24 Rosenberg J, O'Donnell P, Balar A, McGregor B, Heath E, Yu E, Galsky M, Hahn N, Gartner E, Pinelli J, Liang S, Melhem-Bertrandt A, Petrylak D: Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol* 37(29): 2592-2600, 2019. DOI: 10.1200/JCO.19.01140
- 25 Powles T, Rosenberg J, Sonpavde G, Loriot Y, Durán I, Lee J, Matsubara N, Vulsteke C, Castellano D, Wu C, Campbell M, Matsangou M, Petrylak D: Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 384(12): 1125-1135, 2021. DOI: 10.1056/NEJMoa2035807
- 26 Liu L, Yuan H, Wang Q, Li C: Effects of different organ metastases on the prognosis of stage IV urothelial carcinoma of the bladder. *J Oncol* 2022: 1-12, 2022. DOI: 10.1155/2022/8594022
- 27 Chen W, Wu Z, Xiao Y, Wang Q, Yu D, Cai J, Zhou C: Prognostic value of site-specific metastases and therapeutic roles of surgery and chemotherapy for patients with metastatic renal pelvis cancer: a SEER based study. *Technol Cancer Res Treat* 20: 153303382110049, 2021. DOI: 10.1177/15330338211004914
- 28 Bajorin D, Dodd P, Mazumdar M, Fazzari M, McCaffrey J, Scher H, Herr H, Higgins G, Boyle M: Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 17(10): 3173-3181, 1999. DOI: 10.1200/JCO.1999.17.10.3173
- 29 Li J, Wang S, Lu K, Chen C, Cheng C, Hung S, Chiu K, Hsu C, Yang C: First-line chemotherapy response is associated with clinical outcome during immune checkpoint inhibitor treatment in advanced urothelial carcinoma: a real world retrospective study. *Anticancer Res* 43(3): 1331-1339, 2023. DOI: 10.21873/anticancer.16281

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