Original Study

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Metastasis Within Three Years from Radical Nephroureterectomy as a Potential Surrogate for Overall Survival

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Abstract

Intermediate clinical endpoints (ICE) help expedite approval of novel treatments. We aimed to identify the most informative ICE for predicting overall survival (OS) after radical nephroureterectomy (RNU) for high-grade upper tract urothelial carcinoma. Distant metastases within 3-years from RNU are the most effective surrogates of OS after RNU and could be useful to expedite earlier results of future studies.

Introduction: The only phase III trial that evaluated the role of adjuvant chemotherapy following radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) was terminated early. Thus, eventual overall survival (OS) surrogacy, as per Prentice, cannot be assessed in this setting. We aimed to identify an intermediate clinical endpoint (ICE) that could serve as an OS surrogate after RNU for UTUC. **Patients and Methods:** We retrospectively analyzed 823 high-grade UTUC patients treated with RNU at 8 tertiary referral centers. We explored the role of any recurrence (aR), defined as recurrence in the urinary tract or in the resection bed as well the presence of distant metastasis (DM), defined as metastatic disease outside the urinary tract and regional lymph nodes, on OS through a time-varying Cox regression analyses fitted at the landmark points of 1, 2, 3, and 4 years from RNU. Models' discrimination was assessed using Harrell's *c* index, after internal validation. **Results:** Median follow-up for survivors was 5.6 years (interquartile range: 2.0-8.8). Overall, 391 and 212 patients experienced aR and DM, respectively. In a time-varying model, aR and DM were predictors of OS: hazard ratio [HR]:1.20, 95% confidence interval [CI]: 1.13-1.28 ($P < .001$) and HR:1.26, 95% CI: 1.18-1.34 ($P < .001$), respectively. Progression to DM within 3 years from RNU was the most informative ICE for predicting OS (*c* index: 0.81; HR: 4.40; 95%CI: 2.45-7.92; $P < .001$), compared to DM within 1, 2, and 4 years (*c* indexes: 0.74, 0.76, and 0.78, respectively). Progression to DM within 3 years from RNU was further found superior for predicting OS compared to aR at any landmark points. **Conclusions:** Progression to DM within 3 years represents a potential OS surrogate for surgically-treated UTUC. This information could help in patient counseling, future study design and expedite results release of ongoing randomized controlled trials.

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Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a relevant albeit uncommon disease, accounting for 5 to 10% of urothelial carcinoma (UC) overall, with an estimated incidence of 2:100,000,[1,2] although recent studies document an increased incidence.[3] The cornerstone of treatment for high-grade (HG) UTUC is radical nephroureterectomy (RNU).[4,5] Notwithstanding, survival outcomes of patients treated with RNU for UTUC remain unsatisfactory[6] and new tools are constantly being investigated to predict patients' prognosis and risk of residual disease after RNU.[7] In this context, novel intermediate clinical endpoints (ICE) are warranted to help expedite approval of novel medications or treatment modalities. For instance, the only trial that investigated the role of adjuvant chemotherapy (AC) for pT2-4 or node-positive disease saw early termination due to the unexpected benefit deriving from AC administration,[8] rendering the evaluation of overall survival (OS) surrogacy, according to Prentice, not possible.[9] In fact, to demonstrate that an ICE can serve as an OS surrogate, data from at least two treatment arms from a randomized controlled trial (RCT) are required.[9] While in the context of neoadjuvant treatments, pathological downstaging, and complete response have been proposed as potential OS surrogates,[10,11] no potential surrogate following RNU has yet been explored. Therefore, the identification of a robust ICE would help to predict long-term survival, overcome the aforementioned issues, and facilitate the completion of clinical trials.

Additionally, there is an ongoing debate on whether early results from phase III trials on progression-free survival should be practice-changing or whether results on OS should be awaited. In UC, this is the case of CheckMate 274 that showed encouraging results from the administration of adjuvant nivolumab in high-risk UC.[12]

In this study, we aimed to identify the most informative ICE after RNU for high grade[13] UTUC that could potentially serve as an OS surrogate.

Material and Methods

Study Population

Overall, 823 patients treated with RNU for non-metastatic HG UTUC at eight tertiary referral centers between 1992 and 2016 were identified. Patients with a prior history of UC, either of the lower or upper urinary tract, were excluded because this invariably alters the risk of recurrence following surgery.[14] All patients were followed up according to the European Association of Urology (EAU) guidelines for UTUC.[4] The administration of platinum-based AC was left at the discretion of the treating physician.

Variables' Definition, Outcomes, Covariates, and Follow-up

Demographic data were collected for each patient and included age at RNU, gender, American Society of Anesthesiologists (ASA) score.[15] The pathological stage was reported according to the American Joint Committee on Cancer (AJCC) Tumour, Node, Metastasis (TNM) classification (8th edition).[16] Pathological report at RNU specimen included tumor grade according to the 1973 and 2004/2016 World Health Organization (WHO) classification,[17] presence of necrosis, presence of lymphovascular invasion (LVI), defined as the unequivocal presence of tumor cells in the lymphatic vessels and in vascular walls,[18] and positive soft tissue margins, defined as the presence of neoplastic cells at inked areas of soft tissue at RNU specimen.[19] Follow-up after RNU was conducted in accordance with institutional protocols and current EAU guidelines on UTUC.[4]

The outcome of the study was OS, defined as the absence of death from any cause.[20] To assess this endpoint, we relied on a time-dependent analysis where the entry point of the study (time zero: t_0) was represented by the time of RNU. OS was assessed from this time point to death from any cause. Any recurrence (aR) was defined as any radiological evidence of tumor recurrence after RNU regardless of the presence of symptoms and included urothelial recurrence in the urinary tract or in the resection bed, as well the presence of distant metastasis (DM), while the latter was defined solely as the documented presence of metastatic disease outside the urinary tract and regional lymph nodes.[4] Similarly, time to aR and DM were computed from the time of RNU. For the purpose of the study, we also considered the age at RNU, ASA score, pathological tumor (pT) stage, lymph node invasion (pN), presence of necrosis, presence of LVI, surgical margins status, and AC as potential confounders.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges (IQR), while categorical variables were reported as frequencies and proportions. First, to prove that aR and DM have a different impact on OS depending on timing of their occurrence, we relied on a multivariable Cox regression where aR and DM were treated as time-varying covariates. Second, to evaluate when this occurrence was more informative for predicting OS, we tested the associations of aR and DM within 1, 2, 3, and 4 years with the risk of death from any cause using multivariable Cox regression analyses, fitted at the landmark points of 1, 2, 3, and 4 years after RNU. All analyses were adjusted for age at RNU, gender, ASA score, pT stage, pN stage, necrosis, LVI at RNU specimen, surgical margin status, and AC administration. The discriminative ability of each model for predicting OS was assessed using Harrell's *c* index, computed after internal validation. A sensitivity analysis was carried out by including only patients that received AC after RNU. Statistical analyses were performed using Stata 14 (StataCorp MP, College Station, TX, USA). All tests were two-sided, with a significance level set at $P < .05$.

Table 1 Descriptive Characteristics of 823 Patients Who Underwent Radical Nephroureterectomy (Rnu) for High Grade Upper Tract Urothelial Carcinoma (UTUC) at 8 Tertiary Referral Centers Between 1992 and 2016.

Variable	Overall, n = 823
Median age (IQR)	69 (60 - 76)
Gender, n (%)	
Male	519 (63%)
Female	304 (37%)
ASA score, n (%)	
1	269 (33%)
2	387 (47%)
3	161 (20%)
4	6 (1%)
pT, n (%)	
pTa/pT1	202 (25%)
pT2	140 (17%)
pT3/pT4	481 (58%)
pN, n (%)	
pN0	664 (81%)
pN+	159 (19%)
Tumor Necrosis, n (%)	
Absent	659 (80%)
Present	164 (20%)
Lymphovascular invasion, n (%)	
Absent	602 (73%)
Present	221 (27%)
Surgical margins status, n (%)	
Negative	734 (89%)
Positive	89 (11%)
Adjuvant Chemotherapy, n (%)	
None	677 (82%)
Yes	146 (18%)

Abbreviatons: ASA = American Society of Anesthesiologists; IQR = interquartile range; pT = pathological T stage; pN = pathological N stage.

Results

Study Population Characteristics

Baseline characteristics of the patient population are reported in Table 1. The median age at RNU was 69 years (IQR: 60-76), 519 (63%) of the patients were male. Overall, 202 (25%) patients had pTa or pT1 disease, 140 (17%) had pT2, and 481 (58%) had pT3 or pT4; lymph node invasion was found in 159 (19%) individuals. Surgical margins were positive in 89 (11%) cases. A total of 146 (18%) patients received AC.

Survival Analysis: Time-varying Models

Median follow-up for survivors was 5.6 years (IQR: 2.0-8.8). Overall, 276 patients died from any cause, whereas 391 and 212 experienced aR and DM, respectively. To explore the differential effect on OS of aR and DM, these variables were treated as binary covariates whose effect varied with time. On a time-varying Cox regression, aR (hazard ratio [HR]: 1.20, 95% confidence interval [CI]: 1.13-1.28) and DM (HR: 1.26, 95% CI: 1.18-1.34) were both associated with OS (both $P < .001$), revealing a different effect on OS based on their occurrence during follow up, as summarized in Table 2. This demonstrated that in the case of recurrences, either in the forms of aR or DM, an augmented risk of dying persists for each unit time increase.

Landmark Analysis

Having demonstrated that, we performed a landmark analysis at different time points to investigate the prognostic role of progression to aR or DM during follow-up, as depicted in Figure 1. At the landmark points, 606, 439, 327, and 235 patients were alive and not censored. *Supplementary Table 1* shows the number of patients and events at each landmark point.

On multivariable Cox regression analysis, aR within 3 years from RNU (HR: 3.19; 95% CI: 2.06-4.95; $P < .001$) was the most informative ICE relative to aR within 1, 2, and 4 years (*c* indexes: 0.73, 0.75, and 0.77, respectively). Similarly, progression to DM within 3 years from

Table 2 Univariable and Multivariable Cox Regression Analyses Predicting Overall Survival, Including Any Recurrence and Distant Metastasis as Time-Varying Covariates.

	Univariable analysis			Multivariable analysis		
Covariate	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.02	1.01,1.03	.001	1.02	1.01,1.03	.003
Gender						
Male	1			1		
Female	0.94	0.73,1.21	.627	0.87	0.68,1.13	.295
ASA score						
1	1			1		
2	0.92	0.68,1.24	.573	1.05	0.77,1.44	.741
3	1.74	1.24,2.44	.001	1.90	1.34,2.68	<.001
4	1.13	0.35,3.63	.836	1.15	0.36,3.68	.819
pT						
Ta/T1	1			1		
T2	1.29	0.81,2.04	.285	1.26	0.79,1.99	.332
T3-4	2.42	1.63,3.59	<.001	1.91	1.28,2.85	.001
pN						
Negative	1			1		
Positive	2.18	1.62,2.93	<.001	2.18	1.62,2.93	<.001
Tumor Necrosis						
Absent	1			1		
Present	1.25	0.92,1.68	.152	1.18	0.88,1.60	.271
LVI						
Absent	1			1		
Present	1.21	0.91,1.61	.195	1.33	0.99,1.77	.056
Surgical margins status						
Negative	1			1		
Positive	1.63	1.17,2.27	.004	1.84	1.32,2.58	<.001
AC						
None	1			1		
Yes	1.26	0.94,1.69	.127	1.12	0.83,1.51	.444
Any recurrence	1.20	1.13,1.28	<.001			
Distant Metastasis				1.26	1.18,1.34	<.001

Abbreviations: AC = adjuvant chemotherapy; ASA = American Society of Anesthesiologists; CI = confidence interval; HR = hazard ratio; LVI = lymphovascular invasion; pT = pathological T stage; pN = pathological N stage.

RNU (HR: 4.40; 95% CI: 2.45-7.92; $P < .001$) was found to be the most informative ICE for predicting OS, with a *c* index of 0.81, compared to DM within 1, 2, and 4 years (*c* indexes: 0.74, 0.76 and 0.78, respectively), as summarized in Table 3. The 3-year DM-free rate was 71% (95% CI: 67%-74%); among patients who recurred within 3 years from RNU the OS rate was 34% (95% CI: 25%-42%) vs. 81% (95% CI: 77%-84%) of those who recurred later than 3 years from surgery.

Sensitivity Analysis

Finally, to confirm our results, we repeated the same analyses in patients who received AC [n = 146 (18%)] which confirmed DM within 3 years from RNU as the best potential candidate for OS surrogacy (*c* index: 0.82, *Supplementary Figure 1, Supplementary Table 2)*.

Discussion

RCTs with the primary endpoint of OS are the gold standard for evaluating effectiveness of interventions in the oncological setting. However, factors such as long follow-up time, risk of early termination, and higher cost of trials render implementation of novel interventions cumbersome. From a trial design standpoint, it has been demonstrated that the use of ICEs can shorten by approximately 1 year the time to approval of novel therapies.[21] Moreover, having an early predictor of OS can serve many purposes also in a clinical setting, such as for patient counseling and early identification of poor prognosis. The latter would act as a sentinel, prompting administration of second-line therapies, or enrollment in a trial evaluating novel treatments.

For the management of UTUC, there are still concerns regarding the administration of neoadjuvant chemotherapy.[22] In this setting, as a proxy of OS, pathological complete and partial responses have been investigated.[10,11] Nevertheless, no potential surrogate has yet been investigated in the postoperative setting. Additionally, since the only trial that evaluated the role of AC after RNU has been terminated

Figure 1 Kaplan-Meier estimates illustrating landmark analyses for overall mortality-free survival, according to the development of any recurrence (navy blue) and distant metastasis (red). Dashed lines denote the subgroups of patients who experienced recurrence or distant metastasis from surgery till the landmark time point.

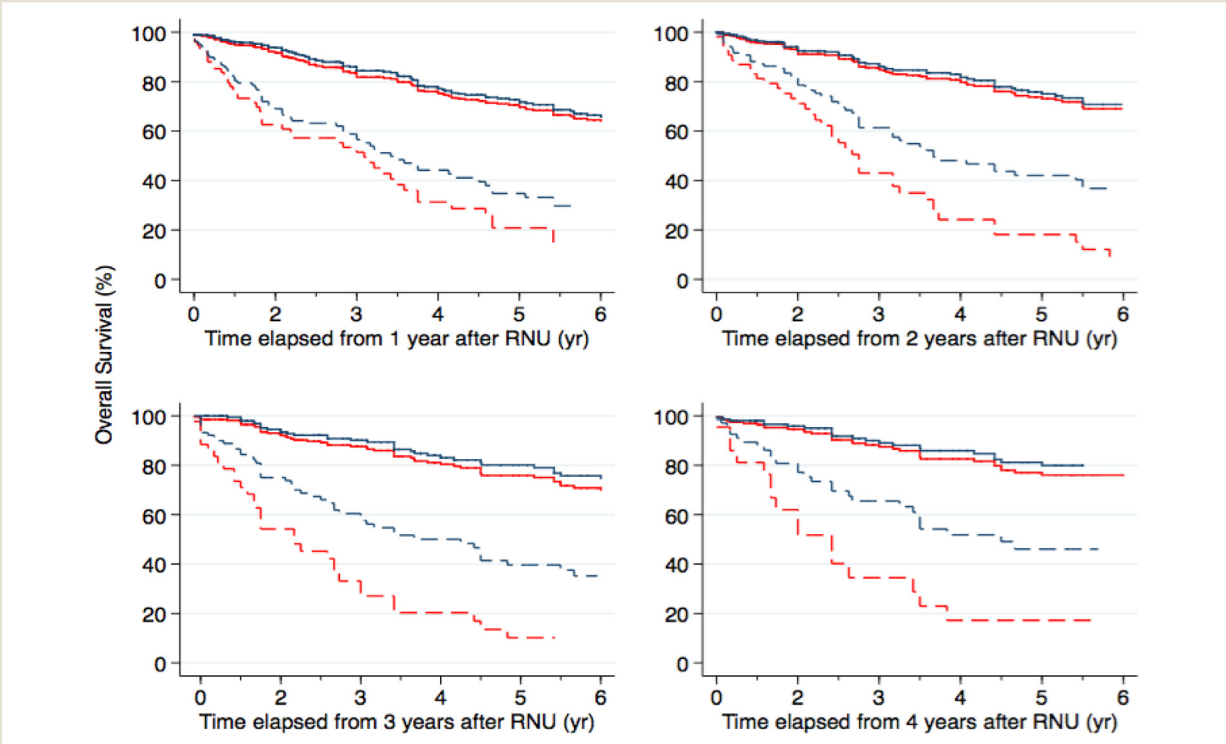

Table 3 Multivariable Cox Regression Analyses Predicting Overall Survival, at Different Landmark Points Evaluating the Impact of Different Intermediate Endpoints.

Model	HR	95% CI	*P* value	*c* index
aR				
1 y	2.96	2.18,4.03	<.001	0.73
2 y	2.93	2.02,4.23	<.001	0.75
3 y	3.19	2.06,4.95	<.001	0.79
4 y	3.31	1.91,5.76	.001	0.77
DM				
1 y	3.03	2.12,4.33	<.001	0.74
2 y	3.86	2.47,6.04	<.001	0.76
3 y	4.40	2.45,7.92	<.001	0.81
4 y	6.51	2.86,14.8	.001	0.78

Abbreviations: aR = any recurrence; CI = confidence interval; DM = distant metastasisHR: hazard ratio.

early, surrogacy, as per the Prentice criteria,[9] cannot be assessed. Our study stands out in this regard as the first that explored potential OS surrogates. We evaluated the role of aR (a combined endpoint including bladder, local, and distant recurrence) and progression to DM as potential proxies of OS. From our analyses, it emerged that DM represents the best candidate as a surrogate endpoint and its role deserves to be investigated more. This is in line with other neoplasms, where distant progression has been demonstrated to be a surrogate for OS.[23-25]

Most cases of UTUC occur in the pyelocaliceal cavities, with the remaining 25% occurring in the ureter.[26] Similar to bladder cancer, the disease multifocality is a common feature in patients diagnosed with UTUC, with the disease being present in the bladder in 17% of patients at initial investigations.[27-29] Since the presence of a history of prior bladder cancer denotes a poorer prognosis in patients with a neoplasm of the upper tract,[30] we decided to exclude these individuals from our analysis. This renders our patient population more reflective of the real natural history of the disease and allows for a realistic assessment of ICEs in the postoperative setting.

Clinically, the management of UTUC is based on disease risk stratification, whereby UTUC is sub-divided into low- and high-risk tumors based on factors such as disease focality, size, cytology, and abdominal imaging. RNU with bladder cuff excision is the standard treatment

of high-risk UTUC.[4] Subsequently, stringent follow-up with imaging, cytology, and cystoscopy is mandatory to identify early metachronous bladder tumors, local recurrence, and distant metastases.[31] Novel practices surrounding RNU such as perioperative chemotherapy,[32-34] immunotherapy,[7,35] adjuvant radiotherapy,[36] and postoperative bladder instillation[37] are starting to be investigated and implemented, albeit with sporadic evidence and few RCTs. During follow-up, the timely identification of recurrence within a certain time point could lead to better patient counseling and potential earlier enrollment in clinical trials. According to our study, patients recurring within 3 years of RNU are at high risk of dying from any cause during follow-up.

From a trial design standpoint, recurrence within 3 years from RNU could be used to power neoadjuvant or adjuvant trials evaluating the impact of novel therapies on the recurrent disease after surgery. Additionally, in the context of salvage therapies, the timing of recurrence, whether within or later than 3 years of surgery can serve as a stratification factor.

While previous studies have demonstrated the role of response to NAC as a potential OS surrogate,[10,11,22] to the best of our knowledge this study is the first of its kind in the postoperative setting. An ICE linked to surgical outcomes is essential to evaluate the effectiveness of peri-procedural interventions We found that progression to metastatic disease within 3 years of RNU is a strong predictor of OS and this could also result in reduced RCT-related costs and improved prognosis at the population level for the individuals that would receive novel medications earlier.

With that being said, our results are hypothesis-generating and need validation in future studies. Besides its strengths, there are a few limitations that should be addressed. The main limitation of our study is its retrospective and multicenter design, resulting in selection biases that partially mitigate our findings. Thus, even if all patients were followed up in compliance with the current EAU guidelines for UTUC, there might be some unaccounted variability in our analyses. However, albeit recognizing these as limitations, the retrospective and multicenter design of our study makes our findings more generalizable and more applicable to different health care settings and, in addition, given the rarity of the disease, the only way to collect robust data is to rely on multi-institutional collaborations.

Conclusions

We found that progression to DM within 3 years of RNU, represents the most informative ICE for the prediction of OS in patients with HG UTUC. This information can be useful for i) patient counseling, ii) the implementation as an endpoint for future trial design, iii) potentially expedite earlier results release of ongoing RCTs, and iv) the stratification of metastatic patients upon entering a trial based on time from RNU to recurrence, as either earlier or after 3 years from surgery.

Clinical Practice Points

- Overall survival (OS) after radical nephroureterectomy (RNU) for high-grade upper tract urothelial carcinoma (UTUC) is still poor.
- Intermediate clinical endpoints (ICE) help expediting approval of novel treatments or therapies to improve patients' survival.
- We aimed to identify the most informative ICE after RNU for high-risk UTUC which could serve as potential surrogate for OS after RNU.
- We found that progression to distant metastases (DM) within 3 years from RNU represent the most effective OS surrogate after RNU.
- Progression to DM within 3 years from RNU could be useful for i) patient counseling, ii) implementing future studies, and iii) expediting earlier results of ongoing randomized controlled trials in order to improve patients' survival.

Credit Authorship Contribution Statement

Alberto Martini: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Chiara Lonati:** Investigation, Data curation, Writing - original draft, Writing - review & editing. **Andrea Necchi:** Resources, Writing - review & editing, Supervision. **Matthew D. Galsky:** Resources, Writing - review & editing, Supervision. **Guillaume Ploussard:** Resources, Writing - review & editing, Supervision. **Giuseppe Fallara:** Resources, Writing - review & editing, Supervision. **Antony Pellegrino:** Resources, Writing - review & editing, Supervision. **Claudio Simeone:** Resources, Writing - review & editing, Supervision. **Nazareno Suardi:** Resources, Writing - review & editing, Supervision. **Stefania Zamboni:** Resources, Writing - review & editing, Supervision. **Wojciech Krajewski:** Resources, Writing - review & editing, Supervision. **Giuseppe Simone:** Resources, Writing - review & editing, Supervision. **Alberto Briganti:** Resources, Writing - review & editing, Supervision. **Francesco Montorsi:** Resources, Writing - review & editing, Supervision. **Agostino Mattei:** Resources, Writing - review & editing, Supervision. **Shahrokh F. Shariat:** Conceptualization, Resources, Writing - review & editing, Supervision. **Marco Moschini:** Conceptualization, Writing - review & editing, Visualization, Supervision, Project administration.

Disclosure

A. Necchi reports Honoraria from Roche, Merck, Astra- Zeneca, Janssen Pharmaceuticals, has served as consultant or advisor for Merck Sharp & Dohme, Roche, Bayer, Astra- Zeneca, Clovis Oncology, Janssen Pharmaceuticals, Incyte, BioClin Therapeutics, Seattle Genetics, Astellas Pharma, has received research funding from Merck Sharp & Dohme (Inst), AstraZeneca (Inst) and Travel funding from Roche, Merck Sharp & Dohme, AstraZeneca, Janssen Pharmaceuticals, outside the submitted work. M.D. Galsky has served as consultant for BioMotiv, Janssen, Merk, Dendreon, Glax- oSmithKline, Lilly, Astellas, Genetech, BMS, Novartis, Pfizer, EMD Serono, AZ, Seattle Genetics, Incyte, Aileron Therapeutics, Dracen, Inovio Pharmaceuticals, NuMab, has received research funding from Janssen, Merk, Dendreon, Novartis, BMS, AZ, Genentech/Roche and owns stock of Rappta Therapeutics, outside the submitted work. The other authors have no conflict.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.03.007.

References

1. Deuker M, Stolzenbach LF, Collà Ruvolo C, et al. Upper Urinary tract tumors: variant histology versus urothelial carcinoma. *Clin Genitourin Cancer*. 2021;19(2):117–124. doi:10.1016/j.clgc.2020.11.004.
2. Lwin AA, Hsu CH, Chipollini J. Urothelial carcinoma of the renal pelvis and ureter: does location make a difference? *Clin Genitourin Cancer*. 2020;18(1):45–49.e1. doi:10.1016/j.clgc.2019.10.023.
3. Almås B, Halvorsen OJ, Johannesen TB, Beisland C. Higher than expected and significantly increasing incidence of upper tract urothelial carcinoma. A population based study. *World J Urol*. 2021:1–7 0123456789. doi:10.1007/s00345-020-03576-3.
4. Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma : 2020 Update. *Eur Urol*. 2021;9:80–81. doi:10.1016/j.eururo.2020.05.042.
5. Veccia A, Antonelli A, Checcucci E, et al. Segmental ureterectomy for upper tract urothelial carcinoma: a systematic review and meta-analysis of comparative studies. *Clin Genitourin Cancer*. 2020;18(1):e10–e20. doi:10.1016/j.clgc.2019.10.015.
6. Kenigsberg AP, Meng X, Ghandour R, Margulis V. Oncologic outcomes of radical nephroureterectomy (RNU). *Transl Androl Urol*. 2020;9(4):1841–1852. doi:10.21037/tau.2019.12.29.
7. Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature*. 2021;595(7867):432–437. doi:10.1038/s41586-021-03642-9.
8. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet*. 2020;395(10232):1268–1277. doi:10.1016/S0140-6736(20)30415-3.
9. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;3. doi:10.1177/009286159603000230.
10. Martini A, Daza J, Poltiyelova E, et al. Pathological downstaging as a novel endpoint for the development of neoadjuvant chemotherapy for upper tract urothelial carcinoma. *BJU Int*. 2019:665–671. doi:10.1111/bju.14719.
11. Singla N, Christie A, Freifeld Y, et al. Pathologic stage as a surrogate for oncologic outcomes after receipt of neoadjuvant chemotherapy for high-grade upper tract urothelial carcinoma. *Urol Oncol Semin Orig Investig*. 2020;38(12):933.e7–933.e12. doi:10.1016/j.urolonc.2020.04.025.
12. Bajorin DF, Witjes JA, Gschwend J, Schenker M. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab vs placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma (MIUC). *J Clin Oncol*. 2021;39(6_suppl):391.
13. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs-Part B: prostate and bladder tumours. *Eur Urol*. 2016;70(1):106–119. doi:10.1016/j.eururo.2016.02.028.
14. Kuroiwa K, Inokuchi J, Nishiyama H, et al. Impact of previous, simultaneous or subsequent bladder cancer on prognosis after radical nephroureterectomy for upper urinary tract urothelial carcinoma. *J Urol*. 2019;202(6):1127–1135.
15. Owens WD, Felts JA, Spitznagel EL. ASA Physical status classifications: a study of consistency of ratings. *Anesthesiology*. 1978;49(4):239–243. doi:10.1097/00000542-197810000-00003.
16. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol*. 2018;73(4):560–569. doi:10.1016/j.eururo.2017.12.018.
17. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of tumours of the urinary system and male genital organs—Part A: Renal, penile, and testicular tumours. *Eur Urol*. 2016;70(1):93–105. doi:10.1016/j.eururo.2016.02.029.
18. Novara G, Matsumoto K, Kassouf W, et al. Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract : an international validation study. *Eur Urol*. 2010;57(6):1064–1071. doi:10.1016/j.eururo.2009.12.029.
19. Colin P, Ouzzane A, Yates DR, et al. Influence of positive surgical margin status after radical nephroureterectomy on upper urinary tract urothelial carcinoma survival. *Ann Surg Oncol*. 2012;19(11):3613–3620. doi:10.1245/s10434-012-2453-9.
20. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non–muscle-invasive bladder cancer: recommendations from the international bladder cancer group. *J Clin Oncol*. 2016;34(16):1935–1944. doi:10.1200/JCO.2015.64.4070.
21. Chen EY, Joshi SK, Tran A, Prasad V. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. *JAMA Intern Med*. 2019;179(5):642–647. doi:10.1001/jamainternmed.2018.8351.
22. Martini A, D M, Falagario UG, et al. Neoadjuvant versus adjuvant chemotherapy for upper tract urothelial carcinoma. *Urol Oncol Semin Orig Investig*. 2020;38(8):684.e9–684.e15. doi:10.1016/j.urolonc.2020.03.008.
23. Martini A, Pfail J, Montorsi F, Galsky MD, Oh WK. Surrogate endpoints for overall survival for patients with metastatic hormone-sensitive prostate cancer in the CHAARTED trial. *Prostate Cancer Prostatic Dis*. 2020;23(4):638–645. doi:10.1038/s41391-020-0231-5.
24. Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong Surrogate of overall survival in localized prostate cancer. *J Clin Oncol*. 2017;35(27):3097–3104. doi:10.1200/JCO.2017.73.9987.
25. Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. *Eur J Cancer*. 2019;106:196–211. doi:10.1016/j.ejca.2018.11.012.
26. Craig Hall M, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: A 30-year experience in 252 patients. *Urology*. 1998;52(4):594–601. doi:10.1016/S0090-4295(98)00295-7.
27. Cosentino M, Palou J, Gaya JM, Breda A, Rodriguez-Faba O, Villavicencio-Mavrich H. Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma. *World J Urol*. 2013;31(1):141–145. doi:10.1007/s00345-012-0877-2.
28. Xylinas E, Rink M, Margulis V, Shariat SF. Multifocal carcinoma in situ of the upper tract is associated with high risk of bladder cancer recurrence. *Eur Urol*. 2012 Published online. doi:10.1016/j.eururo.2012.02.042.
29. Li WM, Shen JT, Li CC, et al. Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. *Eur Urol*. 2010;57(6):963–969. doi:10.1016/j.eururo.2009.12.032.
30. Martini A, Lonati C, Montorsi F, et al. The role of prior bladder cancer on recurrence in patients treated with radical nephroureterectomy. *Clin Genitourin Cancer*. 2021:S15. doi:10.1016/j.clgc.2021.12.006.
31. Rouprêt M, Babjuk M, Compérat E, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. *Eur Urol*. 2018;73(1):111–122. doi:10.1016/j.eururo.2017.07.036.
32. Liao RS, Gupta M, Schwen ZR, et al. Comparison of pathological stage in patients treated with and without neoadjuvant chemotherapy for high risk upper tract urothelial carcinoma. *J Urol*. 2018;200(1):68–73. doi:10.1016/j.juro.2017.12.054.
33. Meng X, Chao B, Vijay V, et al. High response rates to neoadjuvant chemotherapy in high-grade upper tract urothelial carcinoma. *Urology*. 2019;129:146–152. doi:10.1016/j.urology.2019.01.058.
34. Hosogoe S, Hatakeyama S, Kusaka A, et al. Platinum-based neoadjuvant chemotherapy improves oncological outcomes in patients with locally advanced upper tract urothelial carcinoma. *Eur Urol Focus*. 2018;4(6):946–953. doi:10.1016/j.euf.2017.03.013.
35. Necchi A, Martini A, Raggi D, et al. A feasibility study of preoperative pembrolizumab before radical nephroureterectomy in patients with high-risk, upper tract urothelial carcinoma: PURE-02. *Urol Oncol Semin Orig Investig*. 2022;40(1):10.e1–10.e6. doi:10.1016/j.urolonc.2021.05.014.
36. Hahn AW, Giri S, Pathak R, Bhatt VR, Martin MG. Effect of adjuvant radiotherapy on survival in patients with locoregional urothelial malignancies of the upper urinary tract. *Anticancer Res*. 2016;36(8):4051–4055.
37. Fang D, Li XS, Xiong GY, Yao L, He ZS, Zhou LQ. Prophylactic intravesical chemotherapy to prevent bladder tumors after nephroureterectomy for primary upper urinary tract urothelial carcinomas: a systematic review and meta-analysis. *Urol Int*. 2013;91(3):291–296. doi:10.1159/000350508.