Author’s response to reviews

Title: Impact of double J stenting or nephrostomy placement during transurethral resection of bladder tumour on the incidence of metachronous upper urinary tract urothelial cancer

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Author’s response to reviews:

Luebeck, 13-January-2020

Dear Professor Gummlich,

Dear Professor Sundi,

Hereby we would like to thank you and the reviewers for the thorough review of our manuscript “Impact of double J stenting or nephrostomy placement during transurethral resection of bladder tumour on the incidence of metachronous upper urinary tract urothelial cancer” and the efforts to improve it. We revised our manuscript accordingly and would like to re-submit it for publication to your valuable journal “BMC Cancer”.

We addressed the reviewers’ comments point-by-point (see below) and highlighted all changes in yellow in the manuscript.

The manuscript underwent a professional editing by “Proof-Reading-Service.com”. All authors have
made a significant contribution to the findings and methods in the paper. Further all authors have read and approved the final draft. There are neither financial interest nor any other potential competing interest. The current work has not already been published and has not been submitted simultaneously to any other journal. Dr. Mario W. Kramer takes on the responsibility of the present work as the corresponding author.

We believe that the current topic is of wide interest and would be glad if you could find the present manuscript suitable for publication. We are looking forward to your answer.

Yours sincerely,

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Editor
Comment 1: Please consider using Fisher's exact comparison test for variables when event rates are very low (<10).
Response 1: We thank the editor for this important remark. We performed Chi square and Fisher’s exact test primarily. Now we indicated it with “§” or “#” in the Tables 4-6, respectively. We also added a comment to the Material and Methods Section (page 6 line 12-13): “…and Fisher’s exact test (event rates <10) were…” We also added this information in the Methods section of the abstract (page 2 lines 11-12).

Reviewer #1
Comment 1: The authors excluded "histologies other than BCa". This statement is somewhat vague. Do the authors mean they only included urothelial carcinoma of the bladder? Did the authors include variant urothelial histologies or exclude these as well?
Response 1: Thank you for this comment. We excluded all patients with benign histologies and other malignant histologies such as squamous cell carcinoma or adenocarcinoma. Variants of urothelial cancers were not excluded. We expanded this definition in the cohort description accordingly (page 5 lines 15-18): “Histologies other than BCa, (such as benign histologies, squamous cell carcinoma, adenocarcina; n = 419 patients) were excluded from the analysis. Variants of urothelial cancers were included.”.

Comment 2: The authors included "patients who received their initial diagnosis of BCa prior to 2008". Did the authors account for any upper tract manipulation prior to 2008 in patients who were diagnosed prior to 2008?
Response 2: We thank the reviewer for this remark. Due to the retrospective character of our study, information about an earlier upper urinary tract manipulation was not assessable. This lack of
information would be anticipated in a prospective trial. We also see this as a limitation and added a respective statement in the discussion (page 12 lines 12-13).

Comment 3: The authors should include indications for upper tract intervention. They also do not mention in the methods when the DJ stent or nephrostomy was placed. The reader must infer from the introduction that DJ stents were placed at the time of surgery.
Response 3: Thank you for this comment. Indications for DJ stenting or nephrostomy placement were based on the surgeon’s individual decision. There were no standard operating procedures. Assumed main indications were hydronephrosis (DJ or nephrostomy) or a resection close to the ureteral orifice (DJ). However, as this was not explicitly assessable in the majority of the OR reports, we were not able to include this information in our statistical analysis.
In total, 19.2% of all patients underwent DJ stenting or nephrostomy placement during TURBT and 13.2% of all patients had a hydronephrosis at the time of TURBT (Table 1).
All patients who received a nephrostomy tube presented with hydronephrosis at the time of TURBT. The parameter hydronephrosis was not associated with a metachronous UUTUC (Table 4).
The drainage of the upper urinary tract took place at the time of TURBT. We added this information in the Methods section (page 5 lines 23-24).

Comment 4: What was the typical imaging regimen for their patients? How were the UUTUC diagnosed?
Comment 5: The authors should provide a definition of "metachronous" in the methods.
Response 4 and 5: Thank you for this point. The criteria for the diagnosis metachronous UUTUC were: (I) UUTUC diagnosis >3 months from diagnosis of BCa and (II) clear radiological findings on CT or MRI scan or a respective histopathological result. We added a definition of metachronous UUTUC in the Methods section (page 6 lines 6-7).

Comment 6: The number of patients with metachronous UUTUC is very low (only 8 patients) which severely limits the power and conclusions of the manuscript.
Response 6: We agree with the reviewer here. This limitation is pointed out in the limitations paragraph (page 12 line 17).

Comment 7: The authors claim that all UUTUC in stented patients occurred on the same side as the stent; however, 2 patients received bilateral stents and only developed UUTUC on a single side. Assuming that both upper tracts are receiving equal exposures in the same patient, can the authors rationalize why UUTUC only developed on a single side in these patients?
Response 7: Thank you for this remark. In our study cohort 13.5% of the patients received a DJ stent either retrogradely, anterogradely or together with a nephrostomy tube (Table 1). In contrast, only 1.3% (8/637) patients developed a metachronous UUTUC. That means, not every DJ stent resulted in a metachronous UUTUC. This might also be the explanation why the patients with bilateral stenting did not develop a bilateral UUTUC. Our statistical analysis indicates a statistically significant association between DJ stenting and development of a metachronous UUTUC. It does not assume that every DJ stent leads to an UUTUC. We added an explanatory sentence on page 9 lines 24-25.

Comment 8: It would be helpful to know how many patients went on to receive cystectomy considering about 27% were pT2 at initial diagnosis.
Response 8: We thank the reviewer for this important remark. Subsequent radical cystectomy or systemic therapy was not recorded in our dataset. This was added as a limitation of our study (page 12 lines 14-15). See also Comment 2 by Reviewer #2.
Comment 9: Why did the authors choose to perform Chi-square versus logistic regression when determining associations? Logistic regression seems like the more logical choice of statistical test when determining predictors of UUTUC.
Response 9: Thank you for this remark. The tested variables were mostly dichotomous/categorial. Logistic regression may be necessary when aiming to predict outcome from a continuous predictor variable, which was not the case here. Additionally, for logistic regression the event rates should be >25. Hence, we opted for the statistically simpler and more comprehensible calculation: Chi square and Fisher’s exact test.

Comment 10: Can the authors provide a median time from stent placement to UUTUC development?
Response 10: We thank the reviewer for his comment. Table 2 indicates a median time from stent placement (=diagnosis BCa) to UUTUC of 28.2 months (patients # 4, 5, 9, and 16). We added this information on page 7 lines 20-21.

Comment 11: Also, were the stents only placed perioperatively?
Response 11: Thank you for this comment. The DJ stents were placed at the time of TURBT (see Comment and Response 3). In the study of Kiss et al. the timing of DJ stenting (before vs. during vs. after TURBT) did not impact the rate of metachronous UUTUCs [9].

Comment 12: Did any of the patients receive additional upper tract manipulation during their follow-up?
Comment 12: We thank the reviewer for this important remark. There was no information about subsequent upper urinary tract manipulations during follow-up. We added this as a limitation on page 12 line 15.

Comment 13: The authors should specify how stents were managed as this may impact outcomes. For example, perhaps chronic indwelling stents were more likely to develop UUTUC.
Response 13: Thank you for this argument. Usually the DJ stents are being removed in external outpatient clinics, thus we do not have valid data about the stent dwell time. This was added as a limitation on page 12 lines 13-14. However, in the study by Kiss et al. there was no statistically significant difference in the stent dwell time in patients with vs. without a metachronous UUTUC (49 vs. 42 days) [9].

Comment 14: The authors claim that DJ increases the risk of metachronous UUTUC. This claim was derived from univariable Chi-square test which does not account for any confounders. Further models would need to be constructed to account for possible confounding variables (such as stage and grade) with multivariable regression. Unfortunately, due to the very few number of events, I think this would not be possible.
Response 14: We agree with the reviewer in this point. However, as stated by the reviewer, due to the low incidence of metachronous UUTUC in our series multivariable Cox regression did not seem feasible. For Cox regression the event rates should ideally be >10 per parameter. But our study includes only 8 events (metachronous UUTUC). Thus, we performed only univariate analyses: Chi-square, Fisher’s exact test and log rank test.

Reviewer #2
Comment 1: The average f/u of 12-15 months is a bit short to assess for metachronous UTUC.
Response 1: Thank you for this remark. The median follow-up of our cohort was 14.9 months from initial BCa diagnosis and 12 months from urinary drainage of the upper urinary tract. We also
acknowledge that the comparative study by Kiss et al. [9] has a longer median follow-up of 36 months. Nonetheless we do believe that a median follow-up around one year subsequent to a manipulation of the upper urinary tract is sufficient enough to detect manipulation-related UUTUCs. However, we added this short follow-up as a limitation in the manuscript (page 12 lines 17-18).

Comment 2: Furthermore, how many patients had further therapies, such as cystectomy, chemotherapy, or immunotherapy? This would all obviously be important to the survival analysis, but would likely also impact disease occurrence in the upper tract.
Response 2: Thank you for this important remark. Due to the retrospective character of the study we do not have valid data about consecutive systemic therapies (chemotherapy or checkpoint inhibition) as most of them would be applied in external outpatient clinics. Subsequent radical cystectomy was also not recorded in our dataset. We also added this as a limitation of the study (page 12 lines 14-15).

Comment 3: How were synchronous and metachronous defined? Since these were not cystectomy patients, is there a hard "cut-off" period after which new UTUC would be considered metachronous (as was done in the Kiss et al. study - Ref #9)? There needs to be a more defined time point or event that will help differentiate synchronous vs. metachronous lesions. Presumably, this would also impact the analysis. I was eventually able to find the 3-month cutoff at the bottom of Table 2. Why was 3 months chosen? Did all patients have full upper tract imaging at the time of their initial bladder cancer diagnosis to evaluate for UTUC? If not, you might find some UTUC at follow up imaging that was really synchronous. Were positive upper tract cytologies considered as evidence of UTUC, or just imaging?
Response 3: We thank the reviewer for this comment which is similar to the comments 4 and 5 by Reviewer #1.
The criteria for the diagnosis metachronous UUTUC were: (I) UUTUC diagnosis >3 months from diagnosis of BCa and (II) clear radiological findings on CT or MRI scan or a respective histopathological result. Positive cytological findings were not considered as definite evidence of UUTUC.
Not every patient was screened for an UUTUC at the time of BCa diagnosis by default. Also the EAU guidelines do recommend a full upper urinary tract imaging only for selected BCa patients (tumours located in the trigone, multiple- or high-risk tumours; [EAU guidelines on “Non-muscle invasive Bladder Cancer”, www.uroweb.org]).
In our opinion, an UUTUC that was diagnosed within the first 3 months after the TURBT was most certainly already present during the TURBT (synchronous UUTUC). Thus, we defined 3 months as a cut-off for synchronous vs. metachronous UUTUC.
We added a definition of metachronous UUTUC in the Methods section (page 6 lines 6-7) and the lack of a standardized screening for an UUTUC as a limitation (page 12 line 16).

Comment 4: This statement is based off of studies with small cohorts, so I would caution against making a broad statement against a long-considered best-practice procedure (stenting when close to or resecting a UO) without proper studies to evaluate it: "Taken together, the rate of postoperative vesicoureteral obstruction rate during TURBT close to ureteral orifice is acceptably low. Thus, DJ stenting to protect the ureteral orifice might be abdicable.”
Response 4: We thank the reviewer for this important comment. We now attenuated this statement:” Taken together and based in the aforementioned studies [12,16-17], the rate of postoperative vesicoureteral obstruction rate due to a TURBT close to the ureteral orifice seems to be low and thus DJ stenting to protect the ureteral orifice eventually abdicable. However, these studies include only small cohorts. Larger cohorts are certainly needed to support this assumption.” (page 12 lines 4-8).
respective histopathological result. We added a definition of metachronous UUTUC in the Methods section (page 6 lines 6-7).

Comment 6: The number of patients with metachronous UUTUC is very low (only 8 patients) which severely limits the power and conclusions of the manuscript.

Response 6: We agree with the reviewer here. This limitation is pointed out in the limitations paragraph (page 12 line 17).

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