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# Retrograde Pyelography in the Presence of Urothelial Bladder Cancer Does Not Affect the Risk of Upper Tract Urothelial Cancer: A Retrospective Analysis of a Single-Centre Cohort

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**Keywords**
Bladder cancer · Retrograde pyelography · Upper tract urothelial carcinoma

**Abstract**
***Objective:*** Patients with bladder cancer (BC) are at risk of developing upper tract urothelial carcinoma (UTUC). Therefore, CT urography is recommended for follow-up. To avoid intravenous contrast agents, retrograde pyelography (RPG) is an alternative. However, it is still unclear whether RPG increases the incidence of UTUC. The aim of this study was to investigate the impact of RPG in the presence of BC on the risk of developing UTUC. ***Patients and Methods:*** Retrospectively analysing a total of 3,680 RPGs between 2009 and 2016, all patients with simultaneous BC (group 1) and those without synchronous BC (group 2) during RPG were compared. All patients were risk stratified according to the EORTC bladder calculator. In patients without BC during RPG, risk stratification was based on the worst prior tumour characteristics. ***Results:*** A total of 145 patients with a history of BC were analysed. Of these, 112 patients underwent RPG with simultaneous BC. UTUC developed in 6 of 112 patients (5.4%) and 58.9% (66/112) had high-risk BC according to the EORTC bladder calculator. In the control group, one out of 33 (3%) patients with metachronous high-risk BC developed UTUC. ***Conclusions:*** Using RPG in the presence of BC did not increase the risk of UTUC. Due to the predominant number of high-risk/high-grade tumours, individual tumour biology appears to be the primary driver for the development of UTUC.


## Introduction

Upper tract urothelial carcinoma (UTUC) is less common compared to bladder cancer (BC). The frequency is related to the amount of urothelial surface and results in 5–10% of all urothelial malignancies [1]. Concomitant BC at primary diagnosis of UTUC is found in 17% of cases [2], and up to 41% of the patients have a history of prior BC [3]. Depending on risk factors (e.g., tumour in the trigone and multiple tumours) [4] and the individual patient's risk

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based on the EORTC bladder cancer risk calculator [5], imaging of the upper urinary tract is useful at diagnosis of BC and for follow-up [1, 4, 6]. When imaging is performed, CT urography (CTU) should be the preferred imaging procedure [7, 8], whereas intravenous urography should only be performed if CTU is not available or in case of contraindications [9]. Another alternative to CTU is MR urography [10]. Even though not recommended in actual guidelines anymore, retrograde pyelography (RPG) has been a standard imaging procedure for the upper urinary tract. Although its utilization decreased in the last 3 decades, RPG was still used in 58% of UTUC cases in 2009 [10].

Patients suffering from moderate-to-severe chronic kidney disease are at a higher risk of developing contrast-induced nephropathy when receiving contrast media for CT and are also at high risk for a rare complication called nephrogenic systemic fibrosis which is caused by MRI contrast agents [11]. For this group, RPG remains an alternative in BC follow-up, especially if the individual patient risk for UTUC requires periodic imaging of the upper urinary tract. The aim of this study was to investigate the impact of RPG in presence of a bladder tumour on the risk of developing UTUC.

## Methods

*Data Collection*

Data from our clinical database were queried, and RPG between 2009 and 2016 was analysed. A positive ethics committee vote waiving informed consent of the individual patient was present (Ethics Committee of the Medical Faculty of the University of Duisburg-Essen – 17-7746-BO). In the first step, we searched for all RPGs performed in this period. The second step identified all patients with a history of BC within the first group. The third step contained a search for matching between RPG and BC to identify all patients with simultaneous documentation of RPG and BC in our clinical database. By comparing the last group to the surgical and medical reports, all patients with RPG in the presence or absence of synchronous BC were identified.

*Procedures*

All RPGs and/or simultaneous transurethral resections of the bladder (TUR-BT) were performed at our institution after written informed consent. When indicated, DJ-stenting or ureterorenoscopy (URS) was performed in some patients.

*Histopathological Characteristics and Risk Classification*

Histopathological characterization was performed by dedicated uropathologists. Risk classification (low risk, intermediate risk, and high risk) was evaluated using the EORTC bladder calculator, which provides a more differentiated risk profile, since other clinical factors (number of tumours, tumour size, recurrence rate, and T-stage) are considered in addition to grading [5]. For each patient, an individual risk constellation was assessed by collecting data from BC according to the EORTC bladder calculator, BC at diagnosis, BC at RPG, and worst BC throughout follow-up.

*Statistical Analysis*

Clinical and demographic parameters of the patients participating in this study were analysed descriptively (Table 1a/b, 2). Descriptive analyses were done assessing median and by calculating percentage values. All statistical analyses were performed using SPSS® (IBM, Armonk, NY, USA) and Microsoft Excel® (Microsoft, Redmond, Washington, USA). The Cochran-Mantel-Haenszel test as well as the $\chi^2$ test and the Fisher's exact test was applied. The Wilcoxon sign-rank test was used for comparative significance determination of the ages. The significance level for empirically found $p$ values was chosen at $2\alpha < 0.05$ in all cases.

All $p$ values were presented purely exploratively, and therefore they were not adjusted. The reporting of the results followed Standards of Reporting of Diagnostic Accuracy (online suppl. Table 1; see www.karger.com/doi/10.1159/000519898 for all online suppl. material).

## Results

Between 2009 and 2016, a total of 3,680 RPGs were performed in 2,190 patients at our institution. Of these, 145 patients with a positive matching for RPG and prior or simultaneous BC were identified. One hundred and twelve patients presented with synchronous BC at the time of RPG (group 1). Median follow-up in group 1 was 68.5 months.

Eighty-six patients (76.7%) were male and 26 patients (23.3%) were female. Mean age at diagnosis of BC was 65.9 years (Table 1a). Ninety-three patients (83%) had a non-muscle-invasive BC (NMIBC) and 19 (17%) patients had muscle-invasive BC (MIBC) at the first diagnosis. At the time of RPG, 90 patients (80.4%) were diagnosed with NMIBC and 22 patients (19.6%) with MIBC. Grading at the time of diagnosis was low grade in 47 patients (42%) and high grade in 65 patients (58%); BC grading at the time of RPG was low grade in 59 patients (53%) and high grade in 53 patients (47%). More than half of the cohort (58.9%) was classified as high-risk according to the EORTC bladder calculator at the time of RPG. Of the EORTC high-risk patients, 54 individuals had the highest risk constellation with high risk according to the EORTC bladder calculator, high-grade BC at the time of diagnosis, and high-grade BC at the time of RPG (Table 1a/b). Median number of RPG was 1.

Another 33 patients with a history of prior BC but without a tumour at time of RPG were identified and used as the control group (group 2). Before RPG, 10 patients (30.3%) and 23 patients (69.7%) had a history of low-

**Table 1.**

**a** Patient characteristics – group 1

| | |
|---|---|
| Patients with a history of BC, *n* | 112 |
| Age (median), years | |
| Age at diagnosis of BC | 65 |
| Age at diagnosis of UTUC | 66 |
| Sex, *n* (%) | |
| Male | 86 (76.7) |
| Female | 26 (23.3) |
| T-stage at diagnosis of BC, *n* (%) | |
| Ta | 57 (50.9) |
| Tis | 7 (6.25) |
| T1 | 22 (19.6) |
| T1 + Tis | 7 (6.25) |
| T2 | 14 (12.5) |
| T3 | 4 (3.6) |
| T4 | 1 (0.9) |
| Grading at diagnosis of BC, *n* (%) | |
| Low grade | 47 (42) |
| High grade | 65 (58) |
| T-stage at time of RPG, *n* (%) | |
| Ta | 71 (63.4) |
| Tis | 7 (6.2) |
| T1 | 11 (9.8) |
| T1 + Tis | 1 (0.9) |
| T2 | 20 (17.9) |
| T3 | 1 (0.9) |
| T4 | 1 (0.9) |
| Grading at time of RPG, *n* (%) | |
| Low grade | 59 (52.7) |
| High grade | 53 (47.3) |
| Risk classification (bladder calculator) at time of RPG, *n* (%) | |
| Low risk | 10 (8.9) |
| Intermediate risk | 36 (32.2) |
| High risk | 66 (58.9) |
| Max. T-stage before RPG, *n* (%) | |
| Ta | 49 (43.8) |
| Tis | 10 (8.9) |
| T1 | 30 (26.8) |
| T2 | 18 (16) |
| T3 | 4 (3.6) |
| T4 | 1 (0.9) |
| Max. grading before RPG, *n* (%) | |
| Low grade | 38 (33.9) |
| High grade | 74 (66.1) |

BC, bladder cancer; RPG, retrograde pyelography; UTUC, upper tract urothelial carcinoma.

**b** Grading and T-stage of UTUC in group 1

| T-stage UTUC, *n* | Low grade | High grade |
|---|---|---|
| *UTUC with previous intermediate-risk BC* | | |
| Ta | 0 | 0 |
| Tis | 0 | 0 |
| T1 | 0 | 0 |
| T2 | 0 | 0 |
| T3 | 0 | 2 |
| T4 | 0 | 0 |
| *UTUC with previous high-risk BC* | | |
| Ta | 0 | 1 |
| Tis | 0 | 0 |
| T1 | 0 | 1 |
| T2 | 0 | 1 |
| T3 | 0 | 1 |
| T4 | 0 | 0 |

UTUC, upper tract urothelial carcinoma; BC, bladder cancer.

grade and high-grade BC, respectively. Mean age at time of RPG was 61.6 years, and 22 patients were male (64%) and 11 female (36%) (Table 2). Median follow-up in group 2 was 88.6 months. Median number of RPG was 2.

In group 1, 6 patients were diagnosed with UTUC during follow-up (5.4%). Mean age at diagnosis was 65.8 years, and median time elapsed from diagnosis of BC to UTUC was 49 months. Median number of RPG in these patients was 5. In all patients, we found high-grade BC, and 4 patients were classified as high risk (66.7%) and 2 patients as intermediate risk (33.3%). Three patients (50%) had the highest risk constellation (Table 2). Five patients (83.3%) had invasive disease (≥pT1) at the time of UTUC diagnosis (Table 1a/b).

In group 2, 1 patient developed UTUC during follow-up (3%). The age at diagnosis was 68 years. The time from RPG to UTUC was 5 months and 57 months from diagnosis of BC to UTUC. The patient had a high-grade and high-risk BC, and the T-stage of the UTUC was pTa low grade (Table 2).

In group 1, a total of 24 patients (21%) were identified in whom a DJ-stenting was performed in the presence of a BC. Of these patients, 5 patients subsequently developed UTUC, accounting for 83% (5 out of 6) of all UTUCs in this group. Compared to group 2, these findings are significant ($p < 0.0003$). Additionally, 6 patients in group 1 had URS (plus DJ-stenting), and 3 of these patients presented with subsequent UTUC at follow-up.

In group 1, pathological T-stage in patients developing UTUC was pT1 ($n = 1$), pT1/pTis ($n = 2$), pTis ($n = 1$), and pTa ($n = 2$) at the first diagnosis of BC and pTa ($n = 1$), pT2 ($n = 2$), and pT4 ($n = 3$) as the maximal tumour stage. The only UTUC patient in group 2 always had a pTa tumour. Univariate analysis showed that a higher tumour stage (OR 2.145; 95% CI: 1.42–3.25) as well as the maximal tumour stage (OR 2.126; 95% CI: 1.192–3.792) increased the risk of developing UTUC.

**Table 2.** Patient characteristics – group 2

| | |
|---|---|
| Patients with a history of BC, *n* (%) | 33 (100) |
| Age (median), years | |
| Age at diagnosis of BC | 61 |
| Age at diagnosis of UTUC (*n* = 1) | 68 |
| Sex, *n* (%) | |
| Male | 22 (66.7) |
| Female | 11 (33.3) |
| T-stage at diagnosis of BC, *n* (%) | |
| Ta | 14 (42.5) |
| Tis | 8 (24.2) |
| T1 | 8 (24.2) |
| T1 + Tis | 1 (3) |
| T2 | 2 (6.1) |
| T3 | 0 |
| T4 | 0 |
| Max. T-stage BC before RPG, *n* (%) | |
| Ta | 12 (36.4) |
| Tis | 10 (30.3) |
| T1 | 9 (27.3) |
| T1 + Tis | 0 |
| T2 | 2 (6.1) |
| T3 | 0 |
| T4 | 0 |
| Max. grading before RPG, *n* (%) | |
| Low grade | 10 (30.3) |
| High grade | 23 (69.7) |
| T-stage UTUC, *n* (%) | |
| Ta | 1 (100) |
| Tis | 0 |
| T1 | 0 |
| T2 | 0 |
| T3 | 0 |
| T4 | 0 |
| Risk classification (bladder calculator) according to the worst BC before RPG, *n* (%) | |
| Low risk | 2 (6.1) |
| Intermediate risk | 8 (24.2) |
| High risk | 23 (69.7) |

BC, bladder cancer; RPG, retrograde pyelography; UTUC, upper tract urothelial carcinoma.

## Discussion

The aim of the present retrospective study was to investigate whether RPG in the presence of BC leads to an increased occurrence of UTUC. The rationale of this study was to evaluate if RPG can be used as an alternative imaging procedure to clarify the upper urinary tract under certain clinical conditions (e.g., severe chronic kidney disease) that do not allow intravenous contrast agents. However, the importance of CTU as the gold standard for the evaluation of the upper urinary tract is not questioned.

Kiss et al. [12] investigated the impact of DJ-stenting prior to cystectomy as a risk factor for UTUC. Compared to patients treated with nephrostomy, the incidence of UTUC was significantly higher (13 vs. 0%). Based on these data, retrograde manipulation of the upper urinary tract has to be viewed critically. In particular, patients with BC and hydronephrosis are at an increased risk for UTUC, since the manipulation takes place adjacent to tumour tissue, which increases the likelihood of mechanical cell spillage. This hypothesis is indirectly supported by the fact that retrograde manipulation (URS) in the presence of UTUC increases the risk of subsequent BC [13]. Urothelial injury can promote the adherence and implantation of tumour cells, and mechanical as well as chemical methods can damage the urothelial layer, as demonstrated in several studies investigating the attachment of cancer cells to the urothelium [14]. Therefore, the traumatic potential of all retrograde procedures of the upper urinary tract needs to be seen in this context. RPG is less traumatic than DJ-stenting, and this fact may have influenced the UTUC rate in the work of Kiss et al. [12] while our cohort showed no increase in UTUC compared to the literature. Nevertheless, it is noticeable that in 5 of the 6 patients who developed UTUC in group 1, DJ-stenting and in 3 cases additional URS were performed in the presence of BC in addition to the RPG. This is in line with the observations of Kiss et al. [12] and underlines the hypothesis that not only the manipulation of the upper urinary tract but its invasiveness could influence the risk of UTUC development.

Sountoulides et al. [15] showed in a meta-analysis of 5 studies (3,309 individuals) that ureteral stenting in patients with bladder cancer to protect the ureteral orifice during TUR-BT was associated with a higher likelihood of metachronous UTUC compared with no stenting (OR: 3.49, 95% CI: 1.43–8.48) and no upper urinary tract drainage (OR: 3.37, 95% CI: 1.49–7.63). No difference with regard to metachronous UTUC was observed between stent and nephrostomy (OR: 3.07, 95% CI: 0.41–22.98). For the same outcomes, no difference was noted for patients with hydronephrosis [15].

Miest et al. [16] found no difference in UTUC incidence between DJ-stenting and nephrostomy before radical cystectomy but a higher rate of subsequent UTUC when hydronephrosis was present. Compared to Kiss et al. [12], median duration of follow-up was longer (52 vs. 36 months), and many upper tract recurrences in the cohort of Miest et al. [16] occurred after 36 months. Additionally, median follow-up in the nephrostomy group was only 20.4 months. Therefore, the results of Kiss et al.

[12] were discussed as caused by an observation period that is too short [16]. Although nephrostomy in the presence of a bladder tumour seems more attractive in terms of the risk of UTUC, it should not be forgotten that this may, in return, disrupt the integrity of the urinary tract and promote tumour spillage in the retroperitoneum [17].

Looking at the RPG itself, it seems unlikely to accidentally seed cells in the upper urinary tract: before intubating the ureteral ostium, the ureter catheter is flushed with contrast agent to avoid artefacts (bubbles) so that there is no intraluminal space left in the catheter which could be filled with urine. Additionally, presupposing a normal upper urinary tract function, the contrast agent as well as introduced cells should flow out within minutes, making it harder to adhere to the urothelium. Additionally, the viability of tumour cells also decreases depending on the concentration of the contrast agent and the exposure time [18]. There is also evidence for cytologic persistence of cancer cells in high-grade BC after TUR-BT and serial bladder washes [19]. Applied to our cohort, there was a higher likelihood of tumour cells in urine and spillage when performing RGP because most RPGs were performed before TUR-BT and without serial bladder washes, but no increase in the risk to UTUC was observed either in the entire cohort or in the high-grade subgroup.

In our study, 5.4% of the patients in group 1 developed UTUC. The rate of UTUC in patients with prior BC shows a wide range in the literature from 0.8 to 21%, and grading as well as risk classification has found to impact the risk [20–24]. About 10% (9.6–11.1%) of NMIBC patients classified as high risk develop UTUC in the follow-up [21,23]. The major part (83%) of our cohort (group 1) was NMIBC. About 55% were classified as high risk, and almost half of the patients (47%) had a high-grade BC when RPG was performed. Therefore, we suggest that not RPG in presence of a BC, but predominantly the tumour characteristics took the most influence on the UTUC rate in our cohort. This is reinforced by the fact that 5 of the 6 (83%) UTUC patients were classified as high risk, resulting in a UTUC rate of 8.1% (5 of 62 patients) in this subgroup, which is a lower rate compared to the above literature. Even among the 54 patients with the highest risk constellation (high-risk bladder calculator, high-grade BC at diagnosis, high-grade BC at RPG, and high-grade BC at follow-up), only 2 patients (3.7%) developed UTUC over time. This assumption is supported by a comparable UTUC occurrence in the control group (RPG in absence of BC) of 3%.

In our opinion, urothelial carcinoma should be regarded as a panurothelial disease. It was shown that the biological profiles are similar regardless of the tumour location (bladder, ureter, and renal pelvis) [25, 26]. Our results confirm this assumption to the extent that 83% of UTUC cases had high-risk BC, suggesting a relationship with tumour biology. In addition, univariate analysis underlined BC tumour stage as a potential risk factor for developing UTUC, highlighting the need for structured follow-up: in our cohort in which CTU was not used, 5 patients already had invasive (≥pT1) disease and 3 patients were diagnosed late (pT3 disease).

Our study is subject to several limitations. First, the study design was unicentric and retrospective, and the statistical analysis was univariate and descriptive. Second, the study cohort as well as the control group was relatively small. On the different side, follow-up was rather long.

## Conclusion

The use of RPG in the presence of BC did not increase the risk of UTUC substantially. Due to the predominant number of high-risk/high-grade tumours, individual tumour biology appears to be primarily responsible for the development of UTUC.

## Statement of Ethics

The study received ethical approval of the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (17-7746-BO). All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and after written informed consent of every patient in this study.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

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## Author Contributions

L.P., B.H., and S.T. contributed to conceptualization. L.P., C.K., and S.T. contributed to data analysis. L.P., C.K., A.P., J.H., H.R., T.S., J.P.R., U.K., C.D., B.H., and S.T. contributed to writing and critical review.

## Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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