chapter 7

Early detection of upper urinary tract tumors using urography in patients with urothelial cell carcinoma

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Abstract

Purpose: The optimal imaging technique for early detection of upper urinary tract tumors (UUTTs) is unclear. Considering the low radiation and contrast exposure, the feasibility and effectiveness of the first retrograde ureteropyelography (RUP) was evaluated.

Methods: In this retrospective study, a consecutive series of 122 patients with pathologically proven urothelial cell carcinoma (UCC) undergoing a first RUP, with a minimal follow-up of two years were included to evaluate the presence of UUTT. When there was no UUTT diagnosed at baseline or within two years of follow-up, UUTT was considered as absent. Data regarding patient and tumor characteristics, diagnostics, treatment and outcome were retrieved from medical records. The RUP was evaluated by assessing feasibility, sensitivity, specificity, and accuracy. Two scenarios were applied to analyze data from patients with inconclusive results.

Results: In 20 patients (16%), inconclusive results were obtained. In the two years of follow-up in these patients, no UUTTs were diagnosed. In 11 out of 102 evaluable patients (10%) abnormalities were detected; in all a malignancy was diagnosed. The sensitivity was 100%. When inconclusive RUPs were considered as positive findings, the specificity of the RUP was 82%. When inconclusive RUPs were considered as negative findings, the specificity was 100%. The accuracy was estimated as 84% and 100%, respectively.

Conclusion: An initial RUP is a feasible, sensitive, and highly specific diagnostic technique. Considering the low radiation and contrast exposure, it might be an effective diagnostic tool for early detection of UUTTs in patients with pathologically proven UCC.

7 Early detection of upper urinary tract tumors using urography in patients with urothelial cell carcinoma

Introduction

A UUTT can either be found as solitary tumor or diagnosed synchronous with the presentation of a bladder tumor (0.3% - 2.3%), or it can be metachronous at follow-up of primary bladder cancer (2% - 7%). The median time for developing to secondary UUTT is found to be between 2.5 and 7.3 years. For patients with high-grade bladder cancer, most of the upper tract recurrences will occur within five years from treatment of the initial bladder tumor, while patients with low-risk bladder cancer can develop a UUTT up to ten years after the primary bladder tumor.[1,2]
The optimal imaging technique for early detection of UUTTs is unclear. To detect UUTTs at an early stage, different diagnostic strategies for the assessment of the upper urinary tract (UUT) comprise excretory urography, ultrasound, RUP, magnetic resonance urography (MRU) and computer tomography urography (CTU). The current European guidelines advocate CTU as the preferred imaging modality based on level A evidence and proposes RUP as an option for the exclusion of a tumor in the UUT.[3] The American guidelines on asymptomatic microscopic hematuria recommend RUP as an option for those patients who are not candidates for CTU or MRU.[4] Studies comparing the detection rate of RUP with other imaging techniques or studies assessing the diagnostic accuracy of the RUP itself are sparse. After all, RUP promptly provides the urologist with information about potential intraluminal lesions of the UUT in patients presenting with symptoms of hematuria or flank pain, in contrast to the more time-consuming review of a CTU. As renal function can be disregarded, the whole UUT can be safely and fully opacified with contrast. With respect to radiation

exposure, RUP can contribute to superior radiation hygiene as compared to the generally increased clinical utilization of CTU, which has an estimated 10-fold to 50-fold higher effective radiation dose than does the RUP per examination.[5-8]
In this study we evaluated the performance of the initial RUP in patients with pathologically proven UCC, by assessing feasibility, sensitivity, specificity and accuracy. Because of the low incidence of UUTTs we used a design with an enriched population, which was achieved by including only patients with a pathologically proven UCC.

Patients and Methods
Every year more than 500 RUPs are performed in our institution to investigate hematuria and flank pain, or used as an initial diagnostic tool or follow-up for the UUT in patients with non-muscle-invasive bladder cancer. In this retrospective study, we evaluated a consecutive series of patients with pathologically proven UCC, who underwent their first RUP between March 1998 and April 2008 in our center in order to investigate the presence of a UUTT. Patients with a follow up of two years and over were included. By only including patients with a pathologically proven UCC, our study population was enriched for patients diagnosed with a UUTT after investigation using RUP for the indications of hematuria and/or flank pain.

Data regarding gender, age, tumor characteristics, results from RUPs, and use of alternative imaging techniques, treatment, and outcome were collected from the patient's medical records. Data were entered into a separate, anonymous, password-protected database. According to Dutch law, this meant that no further approval from our Institutional Review Board was needed.

RUP Technique
All RUPs were performed during cystoscopy in an outpatient setting or preceding transurethral resection of a bladder tumor to check the UUT for a UUTT, performed under regional or total anaesthesia. One hour prior to performing the RUP, the patient was given 500 mg of ciprofloxacin orally. The patient was placed in lithotomy position. All procedures were performed with a flexible or rigid cystoscope. After inspection of the bladder mucosa, the tip of a 5-French or 6-French open-end vascular catheter (Cook Medical) was introduced into the ureteral orifice. After a blank radiographic shot, a few milliliters (< 10 ml) of diluted contrast agent (Telebrix 35: saline 0.9%; 1 : 1) was injected in the catheter under low pressure. Fluoroscopy of the entire UUT was performed, along with detailed imaging of the renal pelvis and potential abnormalities. Subsequently the performing urologist assessed the images from the fluoroscopy and reported the results in the patient's file. The fluoroscopy studies were performed using a Siemens Polydoros SX 65/80 X-ray tube (Siemens Medical Solutions, Erlangen, Germany).

Reference standard
In the follow-up of patients with a treated high-risk bladder tumor or a UUTT, the UUT is evaluated regularly with radiological examination and cytology of the urine for at least five years.[3] In case of suspicion of recurrent disease found in upper tract imaging and/or in cytology results, or in case of the patient is presenting directing symptoms, a ureterorenoscopy will be performed, and consequently resection or biopsy of the suspected mass will be conducted. Eventually histology will confirm the presence of a missed malignancy. In this study we used two years of follow up as cut off; malignancies diagnosed after this period were considered as newly developed lesions which were not present at the time of the first RUP.

Statistics
Descriptive statistics were applied to describe patient and tumor characteristics. All failed RUPs were evaluated and the feasibility of RUP was assessed. In the successfully performed RUPs, the sensitivity, specificity, as well as the accuracy was calculated for RUP in terms of diagnosing a UUTT. To analyze patients with inconclusive results two different scenarios were applied. In one scenario all inconclusive RUPs were considered as positive findings on the RUP and the other scenario inconclusive RUPS were considered as negative findings on the RUP. Data analyses were performed using IBM SPSS statistics version 20.

Results
Between March 1998 and April 2008 a total of 156 patients, with a pathologically proven UCC, underwent their first RUP. Of these patients 122 were in follow up for two years or more. Males were four-fold more present than females, and the mean age was 64 (23-87) years. The characteristics of the patients and their urinary tract tumors are found in table 1.

In 20 patients (16%), inconclusive results were obtained. In 20 of these patients, the attempted RUP failed because of technical difficulties. In

Characteristic		Number
Sex	male	97 (79.5%)
	female	25 (20.5%)
Mean age (years)		64 (range 23 – 87)
Tumor stage	0	6 (4.9%)
	a	73 (59.8%)
	1	26 (21.3%)
	2	7 (5.7%)
	3 / 4	0
	Unknown	10 (8.1%)
Tumor grade	0	3 (2.5%)
	1	31 (25.4%)
	2	53 (43.4%)
	3	28 (23.0%)
	Unknown	5 (4.1%)
Concomitant CIS	Yes	11 (7.1%)
	No	145 (92.9%)
Multifocal	Yes	30 (24.6%)
	No	92 (75.4%)

Table 1 Characteristics of patients and their tumors (N=122)

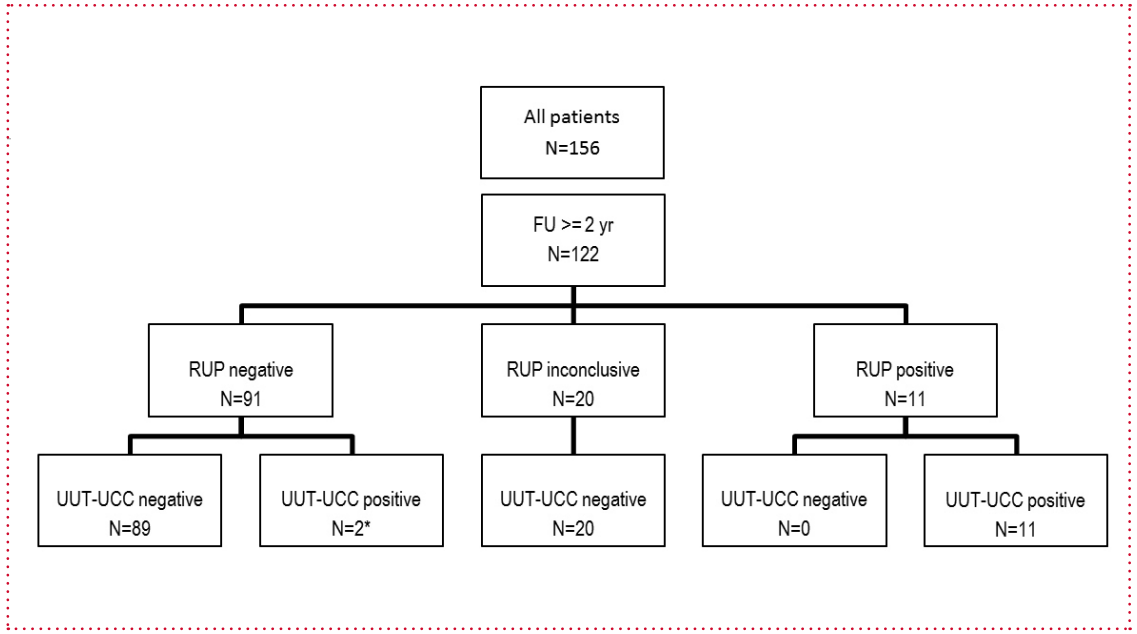

Figure 1 RUP results in 122 patients with follow up (FU) two years or more. *Time from examination to diagnosis: 52 and 65 months, respectively. There were considered as newly developed lesions

Subject	Result RUP	Diagnosis	Classification	Additional	Treatment
1	Contrast defect renal pelvis	Renal cell carcinoma left	T3N0M0	URS	Nephrectomy
2	Contrast defect renal pelvis	UCC renal pelvis left	T1G2NxM0	URS	Nephro-ureterectomy
3	Contrast defect renal pelvis	UCC renal pelvis left	T1G2NxM0	CT	Nephro-ureterectomy
4	Contrast defect upper pole calyx	UCC renal pelvis left	T3G2NxM0	URS	Nephro-ureterectomy
5	Tumor upper pole calyx	UCC renal pelvis left	TaG3NxM0	CT	Nephro-ureterectomy
6	Contrast defect upper pole calyx	UCC renal pelvis right	TaG2NxM0	none	Nephro-ureterectomy
7	Contrast defect upper pole calyx	UCC renal pelvis right	TaG2NxM0	CT	Nephro-ureterectomy
8	Complete stop ureter	UCC ureter right	TaG2NxM0	URS	Partial ureterectomy
9	Contrast defect upper pole calyx	UCC renal pelvis right	T1G3NxMx	URS	Nephro-ureterectomy
10	Contrast defect renal pelvis	UCC renal pelvis right	T2G3NxM0	URS	Nephro-ureterectomy
11	Contrast defect ureter	UCC ureter right	TxGxNxMx	URS	Endoscopic coagulation
URS – ureterorenoscopy; CT – computed tomography; UUT – upper urinary tract; UCC – urothelial cell carcinoma					

Table 2 Patients with abnormalities on retrograde ureteropyelography (RUP)

fourteen cases out of 20 an orifice could not be identified because of a tumor. Other reasons for failure in performing the RUP were hematuria and prostatic enlargement which impeded smoothly entering of the orifices with a catheter. In 18 of 20 patients, alternative imaging was performed, with intravenous pyelography (IVP) in 10 patients, CTU in 7 patients, and with both in one patient. In the two years of follow-up in these patients, no UUTTs were diagnosed.
In 11 out of 102 evaluable patients (10%), abnormalities detected on the RUP prompted treatment and/or further examinations (Table 2). In both scenarios regarding the inconclusive RUPs this led to a sensitivity of 100%. When the inconclusive RUPs were considered as positive findings on the RUP, the specificity of the RUP was 82%. When the inconclusive RUPs were considered as negative findings on the RUP, the specificity was 100%. The accuracy was estimated as 100% and 84%, respectively.

Discussion

This study shows the feasibility and effectiveness of a RUP for initial evaluation of the UUT in an enriched, consecutive population of unselected patients with histologically proven UCC. Of 122 patients who underwent their first RUP, 20 (16%) showed inconclusive results. In 11 (10%) out of 102, evaluable RUPs abnormalities were detected. In all 11 patients a malignancy was diagnosed. Taking into consideration two scenarios of estimating the inconclusive RUPs the sensitivity was 100%, the specificity was 82% and 100% and accuracy was 84% and 100%, respectively.

The concern about feasibility of the RUP performed in an outpatient setting has been mentioned earlier. McFarlane and collegues presented a failure rate of 11%. In almost two-thirds of patients this was because of failure to visualize the ureteric orifce.[9] Our results on effectiveness were comparable to the sparse available figures in the literature.[10]
Cowan and colleagues compared RUP and multidetector CTU in a retrospective study of a selected high-risk group of 106 patients with macroscopic hematuria, after investigation with an IVP and flexible cystoscopy. For the RUP they reported a sensitivity and specificity of 96% and 97%, respectively.[11] Another retrospective study by Lee and colleagues assessed the diagnostic performance of the MRU by using RUP as a reference in 35 patients with suspected malignancy in the UUT. In this study for RUP the sensitivity and the specificity were 53% and 97%, respectively.[12] The lower sensitivity was partly due to the presence of subtle, small, or flat

upper urinary tract lesions. Additionally, as the RUP examinations were not all performed by the same urologists, the interpretation of these studies remains operator dependent.

Razavi and colleagues critically appraised and compared the diagnostic performance of imaging modalities that are used for the diagnosis of upper urinary tract malignancies in current available literature. The retrieved sensitivity/specificity for the detection of UUTT for CTU, MRU, IVP, and RUP were 96%/99%, 69%/97%, 80%/81%, and 96%/96%, respectively. However the heterogeneity between the studies and the mostly retrospective character give wide confidence intervals.[10]

Advantages of RUP comprise less radiation exposure, a negligible risk for contrast induced nephropathy (CIN), the more complete opacification of the distal ureters, and an extremely low risk for an allergic reaction to urinary contrast material. From the ALARA (As Low As Reasonably Achievable) point of view, patients who have undergone RUP are exposed to doses comparable to a conventional anterior-posterior abdominal X-ray examination with approximately 0.25 mGy, which is at least 50 times less than the corresponding dose from an abdominal multiphase CT scan (16 mSv in 2-phase and 22 mSv in 3-phase CTU).7,8 Optimum results of the CTU are largely depending on the technique used. For both the detection of intraluminal lesions as ureteral and renal pelvis wall thickening a minimum of two accurate planned scanning phases after administration of contrast are required.[12,13] To delineate irregular areas of the upper tract, even more subtle lesions than detectable on conventional CTU, post-processing 3 D reconstruction techniques are very helpful. Consequently the additional imaging sets can be performed real time for immediate evaluation.[14] Besides the increased exposure of radiation necessary in multiple phase scanning the increase of the volume of IV administered contrast material in split bolus CTU protocols (in order to save scanning phases) is a concern to pay attention to.[7,15,16,17] In our cohort, three patients needed additional imaging with CTU to establish definitive diagnosis while in 111 (91%) patients a CTU was avoided. Radiation has a proven carcinogenic potential, although the exact risks for developing cancer are not clear yet, and as the patients at risk for a UUTT are often over 65 years of age, the problem with radiation might be of minor importance.[7]

With respect to the IV-contrast administration for CTU, there is increasing awareness of CIN. The major risk factor for developing CIN is preexisting renal impairment.[15,18,19] Moreover, diabetes mellitus, heart failure, and dehydration also contribute to the risk of CIN. These comorbidities are especially rather common in the population with UCC.[15,18,20] Another potential advantage of the RUP is the more entire opacification of the distal ureter. As the incidence of more distally located UUTTs is higher than tumors located in the mid or proximal ureter this might be important for clinical practice.[21,22] To overcome the problem of the incomplete opacification of the distal ureters in CTU various protocols have been developed.[23,24]
As disadvantages of the RUP can be mentioned its invasiveness and variation in patient factors (e.g. anatomy and pathology of the bladder or clarity of the urine), which can lead to inconclusive results. Notwithstanding its invasiveness, the RUP entails collection of urine for cytology from each UUT separately.

Strengths and weaknesses of the study

One of the strengths of this study is its description of the feasibility of the RUP for detection of UUTT in daily practice. The use of an enriched design allowed us analyzing a relatively small group of patients with a rather uncommon tumor. A disadvantage of this design was that the positive predictive value and the negative predictive value could not be calculated. The retrospective character of the study, however, implies a drawback. Since not every patient underwent a URS a two years period of the follow-up was chosen as a reference standard for detecting UUTT. To overcome the difficulty in the analysis with the inconclusive RUPs the specificity and accuracy in two different scenarios were reported.
As missing a UUTT can lead to progression of T-stage and lymph vascular invasion and consequently to worse prognosis a high sensitive test is crucial.[25] Our study showed that no lesions were missed on the evaluable RUPs. Consequently RUP can positively contribute to diagnosing a UUTT, in addition to the use of other intravenous contrast and radiation demanding imaging modalities.

Conclusion

RUP is a feasible urographic technique and an initial RUP is very sensitive, specific, and highly accurate in early detecting of UUTTs in patients diagnosed with UCC of the bladder or upper urinary tract. Taking the increasingly important issues as radiation hygiene and contrast exposure

into account a more prominent role for RUP among other imaging modalities may be justified. Considering which technique for urography should be used advantages and disadvantages of every single imaging technique should be outweighed in the individual patient.

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part 3
General discussion