Urothelial Cell Carcinoma

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chapter 6

Opacification in the distal and middle part of the ureter by retrograde ureteropyelography is superior compared to CT-urography

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Abstract

Objective Opacification is required for the optimal evaluation of intraluminal lesions in the upper urinary tract (UUT) with different types of contrast urography. In retrograde ureteropyelography (RUP) and contrast enhanced CT urography (CTU), we compared the degree of opacification of both studies within the same patient throughout the UUT, using a semi-qualitative assessment in a single center cohort study.

Material and methods Paired images of 100 UUT were included in the study. CTU images obtained by late phase CTU (29 UUT) and multiphase CTU (71 UUT) were compared with RUP (100 UUT). Opacification was determined in four segments (renal pelvis and calyces, proximal, mid and distal ureter). Opacification was graded as: 0: No filling of the segment with contrast; 1: Incomplete filling of the segment with contrast; 2: (Nearly) complete filling with contrast. Two independent observers scored the grade of opacification using a 3-point scale. A paired simple T-test was performed to consider the significance of the differences.

Results The mean opacification score of the RUP was significantly higher compared to CTU in all segments of the ureter (proximal ureter RUP versus CTU 1.74 versus 1.13, p<0.001, mid ureter 1.90 versus 1.02, p<0.001 and distal ureter 1,73 versus 1,02, p<0,001). No significant difference was found in mean opacification of the renal pelvis and calyceal system (RUP 1,87 versus CTU 1,78, p=0.072). No differences in the numbers of non opacified segments between late phase CTU and multiphase CTU were found.

Conclusion In this study the opacification of the UUT by CTU is imperfect compared to RUP in all segments of the ureter but not in the renal pelvis and calyceal system. The next area under discussion to investigate is if RUP is superior in detecting lesions in the ureter.

6 Opacification in the distal and middle part of the ureter by retrograde ureteropyelography is superior compared to CT-urography

Introduction

The urographic phase will add important information on the imaging of the intraluminal part of the UUT provided that the whole tract is opacified. Different urographic imaging modalities aim at optimal opacification throughout the UUT. Traditionally IV urography was practiced though has largely been replaced by CTU recommended by the European Association of Urology as the preferred imaging modality detecting synchronous and metachronous upper urinary tract tumors in patients with confirmed muscle invasive bladder tumor.[1-7]

RUP has never been used routinely although it has the advantages not using intra venous (IV) contrast and has low radiation exposure. On the other hand it may be more invasive for the patient as cystoscopy is needed to perform the examination. With Magnetic Resonance (MR) no iodinated contrast is needed for opacification in the T2-weighted hydrographic sequences.[8]

For diagnostic performance CTU and MR with use of gadolinium have the advantage of the attenuation of tissue of the UUT whereas RUP has not. Only a small number of studies refer to opacification as a prerequisite to detect lesions. Apparently, opacification is an important issue to deal with facing the numerous studies on what is the best CTU protocol to achieve optimal opacification.[7,9-12] Nevertheless, there is no generally accepted protocol for CTU. Studies comparing the degree of opacification on different imaging techniques are lacking.

To determine the difference in the degree of opacification in CTU and RUP, we assessed the opacification of the UUT semi-qualitatively in patients who underwent CTU as well as RUP in a retrospective single center cohort study. Depending on the results there may be a justification for further investigation to compare these techniques on lesion level.

Materials and Methods

Paired images (CTU and RUP) of the UUT were included in a retrospective study. The clinical indications for using both RUP and CTU in the same patient were diverse: a unilateral technically insufficient RUP or a persistent suspicion of a malignancy after a negative RUP who underwent a CTU or vice versa. Impaired renal function was an exclusion criterion. CTU images obtained by late phase CTU (29 UUT) and multiphase CTU (71 UUT) were compared with RUP (100 UUT). One radiologist and one urologist scored the degree of opacification in four segments of the UUT by CTU and RUP independently, respectively. Patient demographics, indication for the upper tract imaging, date of the study were drawn from the medical records. A general informed consent was obtained for the anonymous use of imaging data prior to this study.

CT Urography Acquisition Technique

The CT scans were obtained on a 16-row multidetector CT (MDCT) scanner (SOMATOM Sensation 16, Siemens Medical Solutions, Erlangen, Germany), on a 64-row MDCT scanner (SOMATOM Sensation 64, Siemens Medical Solutions, Erlangen, Germany) or on a Dual Source MDCT scanner (SOMATOM Definition, Siemens Medical Solutions, Erlangen, Germany). IV contrast (Visipaque 270/320, GE Healthcare) was administered by means of a power injector (Stellant, Medrad, Warrendale, PA, USA). Technical parameters of the CT are provided in table 1. All abdominal scans were obtained during a single breath-hold, from diaphragm to pubic bone with the patient in supine position. Initially a single bolus of 120 mL of IV contrast material was administered at a rate of 3.5 mL/sec. Patients underwent an unenhanced scan, a contrast-enhanced scan in a corticomedullary and/or nephrogenic phase, and an excretory scan obtained approximately 300 seconds after contrast administration. Twenty nine UUT images were included using the late phase excretory CTU protocol. A multiphase contrast injection CTU protocol was used in 72 UUT. Prior to scanning, the patients were asked to drink 500 mL of water. An unenhanced scan was obtained followed by IV contrast administration using a multiphase infusion protocol. The first contrast injection phase consisted of a bolus of 45 mL at a rate of 2.5 mL/sec, followed by slow infusion of contrast (0.1 mL/sec) during a period of 220 seconds. After this a second bolus of 70 mL at 3.0 mL/sec was administered, followed by 40 mL of saline at 3.0 mL/sec. Contrast-enhanced scanning of the abdomen was started about 300 seconds after the start of the administration of the first contrast bolus and about 60 seconds after administration of the second bolus, thus yielding both a corticomedullary and excretory phase (multiphase) in a single scan.

CT Urography Reconstruction and Interpretation

All axial images were transferred to a dedicated workstation (Rogan-Delft, Veenendaal, the Netherlands). Maximum-intensity-projections (MIP) or coronal and/or sagittal reconstructions were not routinely generated by the radiology technician. However, additional reformatting (including MIP, multiplanar reformations, and Volume Rendering) was performed by the reading radiologist if requested, using a 3D post-processing server (AquariusNET, TeraRecon, San Mateo, Ca).

RUP Technique

One hour preceding 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 - 6 French open end vascular catheter (Cook Medical) was introduced into the ureteral orifice. After a blank radiographic shot a few milliliters (< 10mL) of diluted contrast agent (Telebrix ®: saline 0.9%; 1 : 1) was injected in the catheter under low pressure. Fluoroscopy of the entire UUT was performed; with detailed imaging of the renal pelvis and potential abnormalities. Subsequently the performing urologist assessed the images of 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).

	Tube Voltage	Collimation	Rotation Time	Pitch	Reconstruction
16 MDCT	120 kV	16 × 1.5 mm	0.5 sec	1.25	3.0 / 1.5 mm
64 MDCT	120 kV	24 × 1.2 mm	0.5 sec	1.00	2.0 / 1.5 mm
Dual Source CT	120 kV	24 × 1.2 mm	0.5 sec	1.05	2.0 / 1.5 mm

Table 1 Scan parameters for multiphase CTU protocol on various scanners.

Opacification Analysis

To assess opacification, the UUT was divided in four segments: 1) The renal pelvis and calyceal (collecting) system; 2) The proximal ureter from the ureteropelvic junction to the iliac crest; 3) The middle ureter from the iliac crest to the inferior sacroiliac joint ; 4) The distal ureter from the inferior sacroiliac joint to the ureterovesical junction the lower sacral bone all according to Kekelidze et al.[10]

The opacification was graded as follows: 0: No filling of the segment with contrast; 1: Incomplete filling of the segment with contrast; 2: (Nearly) complete filling with contrast. The density of contrast material was not scored. Thus, in case of CTU, no minimal Hounsfield Unit was defined as cut-off for opacification. For assessment of the RUP this was not an issue.

Statistic Analysis

To compare the mean opacification between CTU and RUP in the four segments of the UUT a paired sample T-test was performed using PSAW-Statistics-18. Differences were considered significant with $p<0.05$ (two tailed test).

Results

Imaging data from 63 patients, a total of 100 UUT paired imaging sets, were available for comparison in opacification score on a one to one base. The mean opacification score of RUP was higher than the opacification score of CTU in every single part of the ureter. The difference in opacification score was most evident in the mid and distal ureters; mid RUP mean 1.90 versus CTU mean 1.02 ($p< 0.001$) and distal RUP mean 1.73 versus CTU mean 1.02 ($p< 0.001$). No significant differences in opacification in the collecting system were seen between CTU mean 1.78 and RUP mean 1.87 ($p=0.072$) (Figure 1). There were no significant differences between opacification score and numbers of non opacified segments between the excretory CTU versus the multiphase CTU (tables 2 and 3). Typical examples of RUP and CTU are presented in Figures 2 and 3.

Discussion

We retrospectively evaluated the opacification grade of two different techniques based on urography. We have shown that there is a significant difference in opacification grade between CTU and RUP in all three

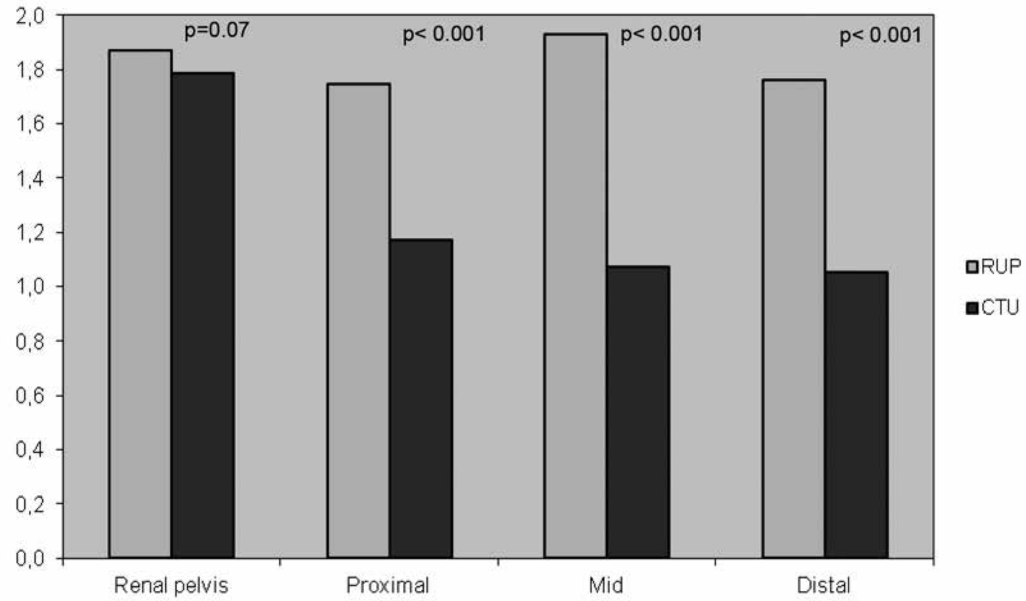

Figure 1 Mean opacification scores by RUP and CTU (100 UUT)

Segment of UUT	RUP (100)	Excretory CTU (29)	Multiphase CTU (71)
Pyelum-calyces	1.87	1.86	1.77
Proximal Ureter	1.74 *	1.24	1.08
Middle Ureter	1.90 *	1.17	0.96
Distal Ureter	1.73 *	1.10	0.99
* p < 0.001 versus CTU. All others NS.			

Table 2 Mean opacification scores by RUP and CTU

Segment of UUT	RUP (100)	Excretory CTU (29)	Multiphase CTU (71)
Pyelum-calyces	3 (3%)	1 (3%)	1 (1%)
Proximal Ureter	3 (3%)	7 (24%)	18 (24%)
Middle Ureter	2 (2%)	8 (27%)	28 (38%)
Distal Ureter	3 (3%)	10 (34%)	28 (38%)

Table 3 Number of non-opacified segments by RUP and CTU (percentage)

segments of the ureters in favor of the RUP. No significant difference in opacification grade was assessed in the renal pelvis and collecting system.

Although there are ways to improve our CTU protocol, these results indicate that RUP is superior in opacification of the UUT, especially of the middle and lower segments of the ureters. Predominantly this can be explained by the retrograde character of the RUP whereby contrast is injected in the ureter under direct vision of the urologist. For optimal opacification additional contrast administration can be provide instantly.
There are a number of reasons that can be mentioned for the generally less opacification grade of the UUT in our CTU cases. First the delay between contrast injection and scanning may have been relatively too short. In six patients there was a relatively wide renal pelvis, without signs of obstruction, which was not fully opacified at the start of scanning. In these cases opacification could have been simply improved by adding a scan in a later phase in which more excretion would have been achieved. Secondly, although detection of lesions was not the subject of this study the presence of a lesion influenced the opacification grade negatively in seven CTUs by obstructing the proximal part of the ureter.
Various techniques and protocols have been investigated with the intention to improve opacification in CTU. Abdominal compression, infusion of saline and/or furosemide, oral intake of water, and adjusting scan delay following contrast administration will increase the opacification grade and are subsequently discussed. Abdominal compression will improve proximal distension and increases the number of completely opacified segments, especially with a longer scan delay of 300 seconds.[13] However, in a more recent study by the same investigators comparing the effect of abdominal compression, IV saline, and different imaging delays on both opacification and distension of the entire urinary tract, showed no significant effects with regards the opacification of the lower ureteral segments.[14] Previously, it has also been shown that administration of 250 mL of IV saline 10-15 minutes before CTU significantly improved opacification of the proximal urinary tract.[14] According to Sanyal et al a low dose of furosemide gives a significantly better result than saline infusion.[15] A third study showed no benefit of the combination of IV saline and furosemide compared to IV furosemide alone.[16] In a recent study by Portnoy et al there was no difference in the opacification of the UUT segments using 250 mL saline IV with or without furosemide IV.[17] Our study is in concordance with the results of Portnoy et al, in lack of complete opacification in all segments of the ureters irrespectively of the CTU protocol used. Recently the effect of oral hydration and contrast volume on renal enhancement and UUT opacification was evaluated. It was found that oral hydration with an intake of 1000 mL of water 30-45 minutes prior to scanning significantly reduced the attenuation of excreted contrast, but did improve the continuous opacification of the UUT and probably increased diagnostic confidence.[18] In our CTU protocol half of that amount of oral fluid (500 mL) was given. A longer scan delay after contrast injection is another factor to improve UUT opacification. Kemper et al applied test images to individually establish urographic timing after low dose furosemide administration. For optimal opacification, a median scan delay of 420 second was found.[19] We applied a relatively shorter scan delay of 300 seconds in our protocol.

On opacification score of RUP there are no series in literature. The several retrospective series reported on the assessment of the opacification grade of the CTU all reported a minor opacification grade of the distal ureter unless all effort to optimize the supply of contrast and the distension of the ureter. Kekeledze et al divided each UUT in four segments and used a 3-pointscale for the score of opacification. Unopacified segments were seen in 13% of middle and 21% of distal ureters.[10] Sanyal et al studied various CTU protocols to investigate the best ureteric delineation. The ureter was divided in three segments and a 4-scale was used. The mean opacification score with furosemide in the distal ureters was significantly better than with saline, supine and prone positioning (2.89 versus 1.87 and 1.83 respectively).[15]

Patel et al used a 4-pointscale to score the opacification in multi detector CT. They have shown a high degree of correlation between ureteral opacification and distention and therefore promote using a high volume of low-concentration IV contrast agent, preprocedural per oral hydration, IV furosemide administration, and IV saline infusion. Unless these efforts the distal ureter remain less opacified according to the three separate readers with opacification score of 2.63 to 2.83 (score of 3 is 100% opacification).[20]

So far no clinical study has addressed the value of contrast enhancement of pelvic and ureteral wall in the detection of tumors in the UUT using CTU, to exclude the need for opacification to identify lesions. However, in recent reports the importance of 3D reconstructions have been discussed in order to identify subtle ureteral wall thickening and strictures which can easily be overlooked on tomographic images. The authors state that lack of opacification is the main reason for missing these lesions on coronal images. Filling of the entire ureter in 3D reconstructions allow visualization of the ureter and accentuate filling defects, thickening of the wall and stenosis.[21] Although RUP is completely dependent on opafication its superior performance in the distal ureter may play a favourable role in the diagnosis and follow up of high risk non muscle invasive bladder cancer. For 75% of the tumors in the UUT are actually situated in the distal and middle segment of the ureter. The majority of these tumors are non muscle invasive tumors, which can therefore easily be missed by CTU, especially with low-dose CTU protocols.[22,23] Thereby optimal opacification of the RUP is lacking in the potential risk of contrast-induced nephropathy compared to CTU.[24] And RUP has a much lower radiation exposure which may be prudent nowadays with increasing utilization of medical imaging using radiation exposure.[25]

Another potentially important advantage of the creation of opacification in RUP, which we didn't investigate though, is its dynamic character. It allows waiting for peristalsis of the ureter through which the bolus of contrast is pushed throughout the entire UUT. The eventual decision for using RUP or CTU in daily practice will depend primarily on the accuracy of the used technique for the specific indication. But factors like radiation exposure, invasiveness, risk of contrast-induced nephropathy and costs play an increasingly important role. Unless the advantage of a paired comparison of two urographic modalities this study has several limitations due to its retrospective character. As two separate readers assessed the RUP and the CTU this will result in an intra observer bias concerning the scoring of the opacification. Thereby the reader of the RUP is dependent on the skills of the different operators and of the stored selection of the stills of this dynamic study. The opacification might be even improved with skilled operators only. Owing to the lack of a standardized opacification score scheme or a standardized subdivision of the UUT we decided to use the same Keklidze practiced in his study in 2010.[10] Using a 3-point scale instead of a 4-point scale forces differences in scores more clear but ignore fine distinction.

The remaining question of our study is if the superior opacification of the ureter by RUP will lead to detection of more clinically relevant lesions compared to CTU, particularly in the distal part. To answer this question a prospective head-to-head study where CTU is compared to RUP on a lesion level must be performed. Ureterenoscopy should then be considered as the golden standard.

Conclusion

In this study the opacification of the upper urinary tract by CTU is imperfect compared to RUP in all segments of the ureter but not in the renal pelvis and calyceal system. Adjustment of the applied technique and protocol, based on the proven advancements mentioned in literature, could lead to greater opacification of the ureters of the CTU. The subject of further investigations will be the question if superior opacification leads to better detection of lesions, particularly in the distal ureter.

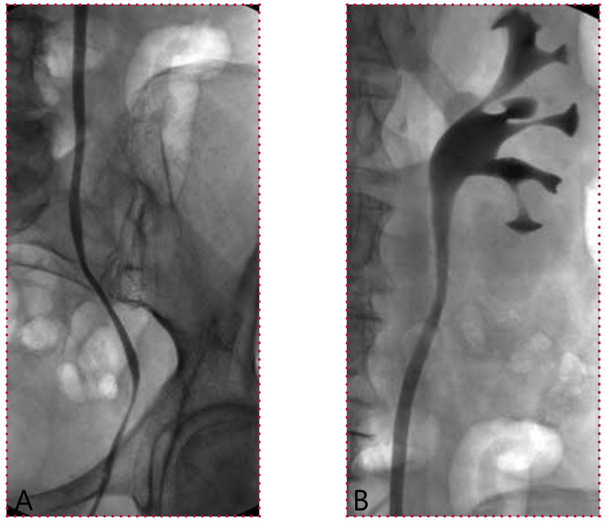

Figure 2 Normal retrograde ureteropyelography (RUP) with complete opacification.
A. Lower and middle segment of the ureter.
B. Proximal segment of the ureter and collecting system.

Figure 3 Normal CT urography (Maximum Intensity Projection, multiphase CTU) with complete opacification.

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Chapter 6