The development of computed tomography (CT) technology represented a milestone in the evaluation of the upper urinary tract (UUT) and at present, it constitutes the most up-to-date way of imaging the UUT. This thesis investigated the role of magnetic resonance urography (MRU) in the evaluation of patients with acute flank pain, with obstruction and with high risk of UUT malignancy. It is concluded that MRU achieves comparable results as CT, without exposing the patient to ionizing radiation.
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ABSTRACT

Urolithiasis is a very common disease all around the world with an increasing incidence and prevalence. Acute flank pain due to stone disease is a common health problem. Precise and rapid diagnosis is essential and in negative cases, a possible differential diagnosis should be readily provided. Unenhanced computed tomography (CT) has emerged as the most accurate, rapid and cost effective diagnostic method and has rapidly supplanted other imaging modalities in the evaluation of urinary stone disease.

Urothelial tumors of the upper urinary tract (UUT) are rare, usually presenting as micro- or macrohematuria, can be either symptomatic or asymptomatic. New developments in CT technology have spurred on research into the application of this new technology in the evaluation of the UUT and it soon proved to be superior to other imaging modalities. Nevertheless, the fact that the patient needs to be exposed to radiation is a major drawback and an issue of concern. Initial research into the utility of magnetic resonance imaging (MRI) in the evaluation of the UUT was promising, but the success of CT together with the cost, limited availability and the longer duration of a magnetic resonance urography (MRU) examination, virtually terminated investigations into its feasibility, which is unfortunate as MRU is a safe alternative to CT.

The aim of this thesis was to evaluate the diagnostic performance and feasibility of MRU in the evaluation of the UUT. This thesis had two main parts: the first part involving two reports. In the first study, patients with acute flank pain arriving in the emergency department in Kuopio University Hospital during the period from April 1999 to January 2000 were invited to participate. All patients underwent unenhanced CT, 1.5T MRU and intravenous urography. The diagnostic accuracy of T2- and gadolinium enhanced excretory T1-weighted images of 40 patients was evaluated with respect to the presence, cause, level and degree of obstruction, and these values were compared to the final diagnosis. These results were further evaluated in the second study, where images of the comprehensive MRU (both T1- and T2-weighted sequences, including gadolinium enhanced excretory T1-weighted images) of 49 patients, constituting the whole study population, were compared to the unenhanced CT. The second part (third report) included 20 patients with hydronephrosis of unknown etiology or patients at high risk for UUT malignancy who were scheduled for CT urography (CTU) by an urologist. All recruited patients from January 2014 to December 2015 underwent 3.0T MRU followed by CTU.

The first study concluded that T2 sequences, although highly sensitive for the detection of obstruction and perirenal edema, did not permit the detection of the cause of the obstruction. T1-weighted excretory sequences were superior with sensitivities of 96.2% and 100%, as opposed to
57.7% and 53.8% for T2 sequences when these were interpreted by two independent and blinded observers. Nevertheless, it was also concluded that both sequences supplemented each other. The second study revealed that MRU was at least as accurate as unenhanced helical CT in the evaluation of patients with acute flank pain with sensitivities of 93.8 and 100% for 2 observers compared to 90.6% sensitivity for helical CT. The third study indicated that 3.0T MRU was feasible and comparable to the results of CTU in the evaluation of patients at a high risk of UUT malignancy. Furthermore, visualization of the UUT was more complete with MRU especially when conducted through the acquisition of multiple excretory sequences, which is a new approach on the route to achieving a more comprehensive MRU protocol.

National Library of Medicine Classification:
Medical Subject Headings: Acute Flank Pain; Computed Tomography; Magnetic Resonance Imaging; Urinary Calculi; Urography; Hematuria; Urinary Neoplasms; Cross-Sectional Studies.
TIIVISTELMÄ


Tuloksemme perusteella T2-painotteiset sekvenssit olivat herkkiä osoittamaan obstruktiota ja sen tasoa muttei obstruktion syytä (kahden lukijan sensitiivisyysluvut 57,7% ja 53,8%). T1-painotteiset erityyssekvenssit olivat ylivoimaisia virtsatiekiven osoittamisessa korkealla 96,2%
VIII


Yleinen Suomalainen asiasanasto: Virtsatieden Taudit; Magneettitutkimus; Tietokonetomografia; Kuvaantaminen -- lääketiede
Elämäni rakkaudelle,
päivieni valolle,
iltojeni ilolle.
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Last but not least, my family deserves my deepest gratitude. It has been a long voyage yet we finished it together. Christiina and Rami: you are the sunshine of my life, my pride and joy. You bring so much love and happiness to my life. Amro and Vaiva: your presence fills our life with happiness and joy - you are a constant source of love and delight. Leena, my companion and soul mate, my rock and my safe place, I have enjoyed every day we’ve shared during the past three decades and I look forward to the decades still to come.

Dear reader: I hope you enjoy reading this thesis as much as I enjoyed writing it!

Kuopio, March 2016

Mazen Sudah
List of the Original Publications

This dissertation is based on the following original publications:


The publications were adapted with the permission of the copyright owners.
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<tr>
<td>3D</td>
<td>three-dimensional</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Radiology</td>
</tr>
<tr>
<td>ALARA</td>
<td>as low as reasonably achievable</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
</tr>
<tr>
<td>APD</td>
<td>antero-posterior diameter</td>
</tr>
<tr>
<td>CUA</td>
<td>Canadian Urological Association</td>
</tr>
<tr>
<td>CM</td>
<td>contrast material</td>
</tr>
<tr>
<td>CFU</td>
<td>colony-forming unit</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTU</td>
<td>computed tomography urography</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>ESUR</td>
<td>European Society of Urogenital Radiology</td>
</tr>
<tr>
<td>FLASH</td>
<td>fast low-angle shot</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>IVU</td>
<td>intravenous urography</td>
</tr>
<tr>
<td>KUB</td>
<td>kidney, ureter, bladder X-ray</td>
</tr>
<tr>
<td>MDCT</td>
<td>multidetector computed tomography</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MRU</td>
<td>magnetic resonance urography</td>
</tr>
<tr>
<td>RARE</td>
<td>rapid acquisition with relaxation enhancement</td>
</tr>
<tr>
<td>RI</td>
<td>resistive index</td>
</tr>
<tr>
<td>UC</td>
<td>urothelial carcinomas</td>
</tr>
<tr>
<td>UPJ</td>
<td>ureteropelvic junction</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>UT</td>
<td>urinary tract</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UUT</td>
<td>upper urinary tract</td>
</tr>
<tr>
<td>VUR</td>
<td>vesicoureteral reflux</td>
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1 Introduction

Several conditions or clinical symptoms might necessitate the need to evaluate the upper urinary tract (UUT) e.g. in patients with suspected or known ureteral obstruction or stone disease. Imaging also is needed in certain situations to rule out leakage in the urinary tract following trauma or therapeutic interventions as well as in assessing suspected congenital anomalies, complicated infections or in searching for possible UUT urothelial tumors.

In the history of uroradiology, the progress in imaging has occurred gradually with new developments widening the indications where imaging is advantageous. Soon after the discovery by Roentgen of the X-rays, it became obvious that stones could be visualized in these images. In contrast, visualization of the urinary tract (UT) was more problematic, therefore attempts were made to visualize the course of the ureters in different ways, first by inserting metallic guide-wires through catheters during cystoscopy and later with the development of radiopaque catheters. Better visualization of the ureters was sought by using air as a negative contrast agent but this was soon replaced by X-ray positive liquid contrast agent containing a colloidal suspension of silver which was however found to be highly toxic. Sodium iodide solutions were found to be safer and were further used in retrograde pyelography imaging. Later, these same compounds were found to be excreted by the kidneys and this led to the development of the intravenous urography (IVU) concept, which became popular from the early 1930’s onwards, especially when newer less toxic contrast agents became available (1-3). The introduction of linear tomography further improved the delineation of renal contours and in the interpretation of IVU at different levels of the urinary tract (4).

Angiography was introduced in the 1950’s and was used in the diagnosis, differential diagnosis and preoperative work-out of renal masses (5, 6). The introduction of A-mode still ultrasound (US) was initially reported in the 1950’s, but the true breakthrough was the development of B-mode real time scanning and the progress in probe and image processing technologies, which made US an attractive and safe investigating method (7-9). Nevertheless, the non-dilated UUT cannot be visualized with US and the ureter, even when dilated, lies behind the bowel and is not fully visualized especially in adults.

The introduction of cross-sectional computed tomography (CT) imaging further increased the diagnostic confidence in body imaging and this has extended to the urinary tract since the 1970’s (10-12). Subsequently, the faster imaging made possible by exploiting spiral technology followed by thin section multidetector CT technologies (MDCT) revolutionized many aspects of the diagnostic imaging of the UUT and diminished the role of traditional imaging modalities (Kidney, Ureter Bladder X-ray (KUB), IVU, US).

Imaging of the UUT with magnetic resonance imaging (MRI) started in 1980’s after the report of a new MRI data acquisition technique called RARE (Rapid Acquisition with Relaxation Enhancement) (13). In spite of improved imaging of the kidneys, the diagnostic visibility of the UUT was compromised by the long acquisition time and the T2* effect, due to the high concentration of gadolinium in urine. Rapid 3D sequences together with the introduction of furosemide assisted, enhanced diuresis excretory magnetic resonance urography (MRU) provided a feasible solution to these issues (14, 15).

Indications for imaging of the UUT have continued to evolve. The most common indication for imaging is the evaluation of patients with acute flank pain with unenhanced CT which became the new golden standard in the evaluation of stone disease. Additionally, although rare, possible UUT urothelial tumors constitute a second major indication for imaging including the
evaluation of hematuria or in the evaluation and follow-up of high risk patients. However, in these conditions, imaging of the UUT is challenging (16). The non-dilated slender and contractile structures need uniform maximal opacification. In addition, some form of rapid thin-section imaging, preferably with some dilatation effect, is needed if the UUT is to be properly visualized. Therefore, evaluation of the UUT by imaging depends on both the patient’s age and the clinical situation and the imaging strategies and protocols differ correspondingly. However it should always be remembered that the increased use of more accurate imaging modalities such as CT exponentially increases the radiation dose being administered to patients, therefore wherever possible, a low-dose protocol or safer imaging strategies would be preferable while taking into consideration other factors such as additional costs, availability and local expertise.

In this thesis, a comprehensive review of the available literature on imaging of the UUT was performed, focusing on general anomalies and diseases of the UUT as well as reviewing the efficacy and utility of different imaging modalities and strategies. Guidelines were evaluated and the reliability of evidence and the possible biases in major citations were explored. Furthermore, this doctoral thesis focuses specifically on the application of MRU in the evaluation of patients with acute flank pain, patients with obstruction or in high risk patients for UUT malignancy.
2 Review of the literature

2.1 UPPER URINARY TRACT: STRUCTURE AND DEVELOPMENT

2.1.1 Definition
Upper urinary tract-term used in this thesis refers to the anatomical structures involved in the transportation of urine formed by the kidneys into the bladder. This system consists of the calyces, the sac-like renal pelvis, and the ureters (17).

2.1.2 Anatomy
The UUT is located in the retroperitoneum. The most proximal portions of the collecting system are 9 to 11 funnel-shaped minor calyces that surround the individual papillary tips with thin extensions called fornices (17). The major calyces represent the confluence of the minor calyces and unite through their infundibula to form the renal pelvis (Figure 1).

The ureter is arbitrarily divided into three parts: The upper third lies anterior to the psoas muscle. The transition between the renal pelvis and the ureter causes the upper physiologic narrowing. Before reaching the iliac vessels, the ureter passes under the gonadal vessels. The ureter crosses the iliac vessels ventrally causing middle physiologic narrowing and curves laterally in the pelvis. In men, the lower third lies dorsally to the vas deferens, the medial umbilical ligament and superior vesical artery with the anteromedial surface of the ureter covered by peritoneum. In women, the ureter runs posterior to the ovary and then deep to the broad ligament. The uterine artery crosses anteriorly in the rectouterine fold of the peritoneum. The transition of the ureters into the bladder causes the lower physiologic narrowing (18-22).

Each ureter enters the bladder base in a tunnel-fashion diagonally through the thick muscular bladder wall, which is also angled, and therefore prevents the urine from refluxing back into the ureter when the bladder contracts (19-23).
2.1.3 Embryology

The most cranial portion of the nephrogenic cord develops into the pronephros, which consists of a few rudimentary tubules coalescing distally to form the pronephric duct and then it rapidly evolves into the transitionary mesonephric duct, all growing caudally to the cloaca. The ureteric bud during the metanephros phase forms the collecting ducts, calyces, renal pelvis, and ureter. The renal pelvis and major calyces (also known as infundibula) are formed from the first three to six generations of the ureteric bud and the minor calyces develop from the subsequent generation of the branches (24, 25). Distension of the system, probably attributable to the onset of some urine production, results in the coalescence of the first generations of branches (24, 25).
2.1.4 Histology
The collecting system is lined by transitional epithelium or urothelium. The urothelium is thinner in its initial portions in the minor calyces but usually has five or six cell layers in the non-distended pelvis and ureter. It is covered by a superficial layer of large rounded cells, the umbrella cells (17). The urothelium rests on a loose vascularized elastic connective tissue layer, the lamina propria, with an underlying thin muscularis propria. The tunica muscularis of the ureter is composed of longitudinal circular smooth muscle fibers. Finally, the outer layer, the adventitia, is composed of connective tissue with a rich vascular plexus (18, 26).

2.1.5 Physiology
Pacemaker cells located in the most proximal fornix appear to initiate rhythmic peristaltic waves, 2 to 3 per minute, that aid urine movement toward the bladder but also urine flows down the ureter partly by gravity (17). Furthermore a ring of smooth muscle encircles the base of the pyramid compress the papillae creating positive and negative pressures, contributing to papillary fluid movements (17).

2.1.6 Vascularization
The UUT receives arterial branches from several arterial beds at different levels: renal artery, aorta, iliac arteries, gonadal or uterine artery. Additionally, the adventitia of the ureter contains richly branched longitudinal network of vessels. Blood drains out to the renal vein, gonadal vein, internal iliac vein and vesical venous plexus and they usually run in parallel with the arteries.

The proximal ureter joins the renal lymphatics and drains into the paracaval and para-aortic lymph nodes. The middle ureter drains to the iliac nodes. The distal ureter drains into the pelvic lymph nodes (19-22).

2.1.7 Innervation
Pacemaker cells, which are innervated by the autonomic nervous system, are located in the renal pelvis and initiate muscle contractions of the ureter with peristalsis from a cranial to a caudal direction (17, 19-22).

2.2 INVESTIGATING THE UPPER URINARY TRACT
There are two major indications for UUT imaging; 1) to evaluate acute flank pain and 2) to rule out tumors, e.g. in the evaluation of hematuria or in the follow-up of high risk patients for UUT urothelial cancer. Other indications include the evaluation of trauma, fistulae, complex infections, possible UUT obstruction and the assessment of a living kidney donor.

Establishing a diagnosis of the possible UUT-abnormalities or pathologies necessitates a combination of evaluation of clinical symptoms, laboratory tests, radiological, and if indicated, endoscopic or percutaneous interventions. It is important to record the family history or the presence of predisposing risk factors such as diet, obesity, recurrent urinary tract infection, prolonged immobilization, dehydration, medical renal disease, viral illness, trauma, recent urologic procedures, smoking or work-related handling of hazardous materials e.g. chemicals.

2.2.1 Clinical presentation
The most common symptoms relating to the UUT are pain and symptoms of infection. Pain might be triggered by infection or by obstruction of the pelvis and ureter. In acute obstructions, the pain is usually severe and is called renal colic or acute flank pain and often is undulating in nature. Nevertheless, acute obstruction might lead to edema of the kidney with enlargement
resulting in stretching of the renal capsule, and consequently in severe continuous non-colicky renal pain. Pain perception and interpretation are also complicated by the different innervation levels of the UUT, resulting in an overlapping of symptoms. Therefore, symptoms of pain are not solely specific for UUT pathologies. Obstruction of the proximal ureter is perceived as renal pain in the flank and costovertebral angle. Pain caused by the middle or distal ureter projects to the lower abdomen, and this may cause urinary frequency and dysuria. Other symptoms, especially in acute settings, are nausea and vomiting. In non-acute obstructions, the pain might be dull, continuous or intermittent. All of the symptoms can overlap with diseases of other abdominal organs including but not limited to gall bladder, pancreas, gastrointestinal tract or pelvic organs. Finally, some abnormalities also including chronic obstructions might be asymptomatic and found incidentally (27-30).

2.2.2 Laboratory tests
There are no specific blood tests available for pathologies of the UUT are. However, since UUT abnormalities and pathologies might affect kidney function, measurement of markers of renal function is important both for diagnostic and management strategy purposes.

Creatinine is produced from creatine phosphate, a molecule which is a rapidly-available source of energy for the muscles. Creatine is a polar molecule and it is not reabsorbed by renal tubules but almost the entire amount in the glomerular filtrate is excreted by the kidneys. Elevated level of creatinine is an evidence of a renal injury with a decreased ability to filter blood. Creatinine clearance is a more reliable method of evaluating the kidney function but this requires direct creatinine measurements from 24-hour urine collection and blood sample. A more practical method for this purpose is the mathematical estimation of this function by applying the glomerular filtration rate (GFR) formula, which incorporates information about the creatinine level, age, gender and body weight (31, 32).

2.2.2.1 Urine analysis
Test strip pads are widely used and there are a variety of commercially available dipsticks with different impregnated interacting chemical agents. Important information is rapidly available not only on the presence of blood, leucocytes and nitrates, but also on pH, gravity, protein and glucose conferring additional differential diagnostic value to the test. Nevertheless inaccuracies frequently occur. Although automated processes eliminate interpretation subjectivity and have better reproducibility, other potential sources of errors might be related to collection and transport of the sample, receipt and preparation for testing and thus requiring standardized quality assurance (33, 34). Urine microscopic sediment examination provides a more accurate perspective of the possible findings, but it is time-consuming and more expensive. After centrifugation, microscopic specimen analysis is performed using either counting chambers or glass slides (34) with the presence of casts, crystals, white and red blood cells, and bacteria or yeast being evaluated. An excess number of leukocytes probably indicates the presence of an infectious disease somewhere in the urinary tract. Cast sediments are formed by coagulation of albuminous material in the kidney tubules and their excess is usually associated with albuminuria.

The presence of blood in the urine is one of the most important signs indicative of some possible pathology of the urinary tract. Microhematuria is now defined as the presence of ≥ 3 red blood cells per high power field on urinalysis during microscopy (35). Other abnormalities (e.g., pyuria, bacteriuria, contaminants) or obvious benign causes must be absent. Other reasons that could explain hematuria should also be excluded such as “general bleeding disorder or physiological reasons (e.g. strenuous physical exercise) or contamination during menstruation” (34). Macroscopically visible hematuria is an alarming sign that requires prompt evaluation.
2.2.2.2 Urine cytology

Urothelial cells are shed under normal circumstances into urine and can be investigated microscopically after centrifugation, alcohol fixation and staining. Urine cytology is therefore used in the evaluation of hematuria or to follow patients with a known urothelial neoplasia (36). Normal cells have regular appearing monomorphic nuclei. The presence of abnormal cells might be suggestive of malignancy. A highly suspicious or obvious finding in the cytology usually has high specificity (37). On the other hand, low grade cancer cells can cause interpretation difficulties since as many as 20% of high grade cancers can be cytology negative. False positive findings might be attributed to stone disease and inflammation, cytotoxic treatment or radiotherapy (17, 38).

2.2.3 Ureterorenoscopy

Endoscopy constitutes one of the most important diagnostic and therapeutic urological tools. The last few decades have witnessed considerable technical advances due to appearance of more flexible and miniaturized endoscopic equipment with improvements in the accessories have resulted in the incorporation of this procedure into routine urological practice. Consequently together with the increased surgical skills, this has changed many of the procedures’ indications with improved patient outcome. The retrograde approach has been expanded, for example, to the investigation of pyelocalyceal diverticulum, infundibular stenosis, or in patients with urinary diversions, urolithiasis, as well as UUT tumors are all conditions which can now be managed with this methodology (39, 40).

The initial inspection of the distal and middle ureter can be performed with a semi-rigid ureteroscope to evaluate the presence of any unanticipated pathology in the distal ureter as well as it passively dilates the ureteral orifice (41). This is followed by the placement of a safety wire to maintain access to the UUT. A ureteral access sheath is placed over the working guidewire to minimize the risk of ureteral trauma. The use of a ureteral access sheath has been demonstrated to facilitate ureteral re-entry and optimize overall success with intrarenal ureteroscopic surgery (42). A flexible ureteroscope is inserted through a sheath into the collecting system. Actively deflecting flexible ureteroscopes increase the access rate to the lower pole.

Currently available flexible ureteroscopes have working channels of at least 3.6 Fr size. This allows the use of instruments up to 3 Fr, such as biopsy forceps or stone-retrieval devices, while still permitting adequate irrigation (39). It is possible to collect a sample of tumor tissue for diagnosis and to assess treatment options using laser technologies (43, 44). Furthermore, promising initial results were obtained with the use of high frequency endoluminal US during ureterorenoscopy, as it increases the diagnostic accuracy and improves tumor staging (45, 46).

Historically, renal stones larger than 2 cm were managed with percutaneous nephrolithotomy, shockwave lithotripsy, or a combination of both and, in rare instances, with an open procedure. The holmium laser has come to dominate intracorporeal lithotripsy since it has thin and flexible laser fibers, making them ideal for passing through the working channel of a flexible ureteroscope (47, 48).
2.2.4 Imaging of the upper urinary tract

2.2.4.1 Plain film of the abdomen

Traditional plain X-ray of the kidney, ureter and bladder (KUB) had an important role in the initial evaluation of acute flank pain and is obtained routinely prior to the injection of contrast material before urography. One of the limitations of this technique is the scattering of radiation due to relatively large beams not fully removed by the use of grids. This translates into reduced subject contrast by creating a background intensity unrelated to the overlying anatomy (49).

The main roles of KUB nowadays are to determine the presence of calcifications along the urinary tract and in the follow-up of radiopaque urinary tract stones (50) (Figure 2). Although the majority of UT stone are radiopaque, the sensitivity and specificity of KUB were reported to range from 44-70% and 80-87%, respectively (51-53). The detection of stones is hampered by the superimposition of bony structures, phleboliths and bowel contents. Detection is also related to stone size and location, especially small stones tend to be less accurately visible on KUB (54).

![Figure 2. Male patient (18 yr.) with acute left flank pain symptoms. MR urography showed obstructing stone in the upper third of the ureter (not shown). Limited left sided plain film of the abdomen showed the 1 cm stone to be readily visible (between two arrows) facilitating monitoring and treatment planning.](image)

2.2.4.2 Ultrasound

Ultrasound (US) is the first line investigation of choice in the evaluation of the UUT in children and pregnant women. US is a safe, rapid, noninvasive, repeatable and cost-effective examination and is also an ideal screening method of fetal UT anomalies (55, 56). In older children and adults, the visibility of the non-dilated ureters is limited because of the retroperitoneal location behind the bowels. US promptly detects dilatations in the pelvicalyceal system, yet not all dilatations are obstructive and conversely, not all obstructions necessarily lead to dilatation. Differentiating these conditions by applying gray scale ultrasound alone might prove difficult. Doppler duplex US with measurement of the resistive index (RI) in the intrarenal arteries might be helpful in differentiating these conditions (57, 58). Frequently obstruction leads to intrarenal vasoconstriction with a consecutive increase of the RI above the upper limit of 0.7 or a 10% difference between the affected and the non-affected contralateral kidney. In addition, the presence or absence of normal symmetrical ureter jet is reported to be helpful in the evaluation of obstruction (59). A Doppler “twinkling” artifact can be seen as a rapidly alternating red and blue color signal behind certain stationary objects, giving the appearance of movement. While a twinkling
artifact is commonly associated with nephrolithiasis and reported to be helpful, it was also found to exhibit a relatively high false-positive rate and conflicting positive predictive values (60-62).

Overall, US is operator dependent, highly sensitive but nonspecific (63). Furthermore US can provide no information on the functional severity of obstruction as this does not correlate with the degree of dilatation of the pelvicalyceal system. An extrarenal pelvis is a condition known to mimic mild obstruction and furthermore mild obstruction can be misdiagnosed in a well-hydrated normal person (63).

Renal cysts in the renal sinus area are subdivided into parapelvic and peripelvic cysts. The former originates from the adjacent parenchyma and they protrude into the renal sinus while the latter have a lymphatic origin and originate extraparenchymally within the sinus itself. US is not able to differentiate between these two types of cysts by etiology but occasionally both might simulate hydronephrosis. On the other hand, the potentials for false negative US scan might be attributed to the presence of solid material such as calculus, blood clot, or pus in the pelvicalyceal area (63).

The sensitivity of US in the direct visualization of UUT tumors is unacceptably low (64). Therefore, US examination is usually only applied in very low tumor-risk patients to exclude the presence of secondary signs of UUT pathology such as an obstruction or any other major finding.

In acute flank pain, US is able to recognize larger stones in the pelvicalyceal, ureteropelvic and vesicoureteral junctions. However, the direct visibility of stones is considerably limited in the ureter. Furthermore, direct measurement of stone size is a prerequisite to the management decisions and is not always reliable at US (65). Therefore, US is usually applied in conjunction with KUB.

2.2.4.3 Intravenous urography

Intravenous urography is an investigation of the UT consisting of serial X-ray acquisitions after the intravenous injection of contrast material, thus visualizing the UUT as iodine-based contrast material is excreted by the kidneys. The “urographic imaging sequence is designed to optimize depiction of specific portions of the urinary tract during maximal contrast material opacification” (66) and should be tailored to answer the individual clinical situation.

In order to optimize visualization and minimize artefacts, bowel preparation is usually recommended prior to IVU, especially for patients with chronic constipation (67, 68). Nevertheless, the value of routine bowel preparation is questioned with no definite benefits detected (69, 70).

Initially, a KUB is always obtained before the administration of contrast agent to visualize the presence of possible calcifications along the UT, which consequently might be obscured by the contrast agent. Tomographic views at the level of kidneys, pelvicalyceal region and/or ureters are obtained when necessary or when feasible to better delineate the anatomical structures or to localize suspected findings with better confidence. After the bolus injection of contrast material (1–3 minutes), nephrographic and, if needed, tomographic views of the kidneys might provide better demarcation of the renal contours (66).

Progression of excretory function of the kidneys is further evaluated by a KUB obtained at 5 minutes after the administration of contrast material. If there are no contraindications, e.g. obstruction, arterial aneurysms, recent abdominal surgery, trauma, renal transplant or severe abdominal pain, a compression device is applied to compress the ureters against the sacrum (66, 71). Compression improves calyceal distension especially in heavy patients and those with a large girth (72). After 5 minutes of compression, a collimated image to the kidneys is obtained for the evaluation of the renal calyces and collecting systems and further tomographic and/or bilateral oblique views are appropriate for the evaluation of the pelvicalyceal anatomical details.
and the PU junction (73). After acquisition of all necessary images, the compression is released at 15 minutes after the administration of contrast, and immediate KUB is obtained to evaluate the ureters. Fluoroscopy complements the visualization of different segments during peristalsis with appropriate spot views obtained as needed. The prone urogram improves the visibility of the entire UUT and obtaining an additional KUB was found to be cost-effective, even when only a few retrograde pyeloureterography studies are avoided (74). An oblique view of the bladder helps to evaluate the distal ureters, especially if the bladder is filled with excreted contrast that obscures the visibility. If an obstruction is present, then delayed images should be obtained until opacification to the level of obstruction can be identified or until it is determined that renal excretion is insufficient for adequate opacification (66).

By following the excretory function of the kidney, it is possible to evaluate the severity of obstruction. The directive criteria used in clinical studies (66, 75) to evaluate the severity of obstruction are described in Table 1.

<table>
<thead>
<tr>
<th>Severity of Obstruction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Obstruction</td>
<td>No distension of the intrarenal collecting system or ureter; no delay in excretion; absence of columnization</td>
</tr>
<tr>
<td>Mild Obstruction</td>
<td>Ureter visualized as a persistent column of signal intensity or contrast material, proximal to the level or cause of obstruction on the symptomatic side; mild prominence of the renal pelvis; the whole urinary tract is visualized on 15-min urogram</td>
</tr>
<tr>
<td>Moderate Obstruction</td>
<td>Enlargement of the calyces with blunting of the calyceal fornices, but the intruding shadows of the papillae, although flattened, are still readily seen; delayed urogram</td>
</tr>
<tr>
<td>Severe Obstruction</td>
<td>Increasingly dense nephrogram with markedly delayed excretion; obvious dilatation of the ureter; dilatation and rounding of the calyces with obliteration of the papillae</td>
</tr>
</tbody>
</table>

The total acquisition of the full standard IVU delivers a high radiation dose to the patients and at present, it is usually unnecessary. A better evaluation of the kidney parenchyma can be obtained with US or with other cross-sectional modalities, and thus obviating the need for nephrographic and nephrotomographic views. In the acute setting, no compression is needed and especially in young individuals, one view pre- and post-contrast KUB might prove sufficient. Tomographic views can be reduced or eliminated by obtaining an oblique view only on the side affected or suspected. Therefore, the IVU is planned individually with special focus on delivering minimal radiation dose in accordance with the ALARA principal (= As Low As Reasonably Achievable).

The indications for IVU have been systematically challenged over the past years, with a significant body of evidence now supporting the view that IVU should no longer be applied as a screening test in patients with recurrent UTI, hypertension and bladder outflow obstruction (76-78).

The investigation of acute flank pain is a major indication for IVU in order to rule out or confirm UUT stones. However, in contrast to other imaging techniques such as CT, MRI and US, it is time consuming and exposes the patient to contrast and radiation with lower sensitivities. Unenhanced CT has supplanted IVU and become the golden standard in imaging acute flank pain. Nevertheless, some limited IVU projections may occasionally be performed in the post-
therapeutic evaluation of stone disease that has been discovered with other imaging modalities, if the potential radiation dose is expected to be less than that at of low-dose CT (66).

The evaluation of hematuria is another major indication for IVU. The rapid technological development in cross-sectional imaging modalities such as MDCT and MRI rapidly proved more accurate than IVU. Therefore, nowadays MDCT-urography is the first line imaging modality for high risk patients for malignancy. Furthermore, major traumatic conditions are nowadays routinely evaluated by structured CT, since it provides a better image quality and a depiction of any damage to the kidneys or to the UUT. The benefits of IVU have been further questioned in a report showing that around half of the patients have to undergo additional subsequent imaging after IVU. In these further evaluations, as many as one third of these patients were found to have additional or different results (79). Other occasional indications for IVU could be the evaluation of possible postoperative iatrogenic injury/complications to the UUT after major surgeries to the abdomen or pelvis. Nevertheless, CT or MRU are more accurate in the detection of even small amounts of contrast extravasation after an injury and furthermore provide differential diagnostic information.

In the recently revised practice parameter for the performance of excretory IVU the joint American College of Radiology (ACR) and collaborating medical specialty societies published potential indications for the use of excretory IVU, with indications for the examination including, but not limited to, the following: (80)

1. Evaluation of patients with suspected or known ureteral obstruction
2. Assessment of the integrity of the urinary tract following trauma or therapeutic interventions, especially when cross-sectional imaging is inappropriate or unavailable.
3. Assessment of the urinary tract for suspected congenital anomaly, when thought to be more appropriate than cross-sectional imaging
4. Assessment of the upper urinary tract (renal collecting systems and ureters) for urothelial lesions that may explain hematuria and for identification of urinary tract abnormalities that may predispose to infection, especially when cross-sectional examinations using US, CT, or MRI are either unavailable or felt to be inappropriate for the clinical circumstance.
5. Follow-up of patients with recurrent renal/ureteral calculi, with a limited number of images obtained pre- and post-contrast administration. These kinds of limited studies may reduce the patient’s radiation burden compared with repetitive CT studies.

In institutions with expertise and sufficient CT capacity, IVU is no longer performed in adults. In pediatric populations, the use of IVU is not recommended and might be used only in these rare circumstances in which IVU remains a diagnostic option, i.e. if MR is not available and/or US and voiding cystourethrography (VCUG) yield insufficient information in view of the required treatment (81).
2.2.4.4 Retrograde pyelography
When the noninvasive diagnostic procedures are occasionally contraindicated (e.g. severely compromised renal function), are likely to be equivocal or fail to demonstrate the level and possible intrinsic etiology of ureteral obstruction, then a retrograde pyelography may be performed. Moreover, retrograde pyelography might be an option when there is a need to collect urine for cytological analysis from each ureter separately during cystoscopy. Usually the procedure is conducted under local anesthesia, but general anesthesia may also be used, especially in children. A catheter is advanced under fluoroscopy or X-ray control. The catheter is introduced into the pelvis or ureter as needed. A KUB is usually obtained before the direct injection of contrast via the catheter and tilting of the patient might be helpful to evenly distribute the contrast material into the UUT and to evaluate possible strictures.

Pyelovenous backflow of urine and contrast material occurs when the contrast is injected under increased pressure and escapes the collecting system. A fornicial rupture is a possible theoretical complication. Therefore, every effort must be made to ensure that contrast is introduced under low pressure. Other complications of the procedure include ureteral perforation and infection.

2.2.4.5 Antegrade pyelography
Cross-sectional imaging techniques have dramatically reduced the need for antegrade pyelography imaging. Retrograde pyelography covers most of the possible previously mentioned indications but occasionally cannot be performed e.g. in ureteral diversions or stenosis. Historically, a needle is introduced through the kidney to the pelvicalyceal cavity and through which the contrast medium is injected. Furthermore, antegrade puncture is an essential component of the UUT urodynamic testing (Whitaker test) (82). Nowadays, the antegrade pyelography procedure is usually performed through a pyelostomy catheter inserted in order to release the obstruction to determine the level and possible cause of obstruction. Meticulous attention should be paid to prevent pyelovenous backflow especially in possible UTI.

2.2.4.6 Reflux studies
Vesicoureteral reflux (VUR) in children is a known risk factor for renal scarring with potential consequent renal damage. “Overall, of the children who present with a UTI, it is likely that between 30% and 40% have VUR. VUR in girls ranged from 17% to 34% and in boys from 18% to 45%” (83). Therefore, the exact evaluation and classification of the reflux grade and severity are important. Nevertheless, there is a lack of good evidence and of randomized controlled trials assessing the clinical effectiveness of the investigations of UTI for long-term renal outcomes (84, 85), especially when the risk of long-term consequences from childhood UTI seems to be very low (86). The detection of VUR was usually considered to be an important element in the investigation of UTI yet routine imaging was not found to lead to a reduction in recurrent UTIs or renal scarring (85, 87).

The imaging of VUR is currently performed by three different diagnostic imaging modalities:

a. Micturating/voiding cystourethrogram
Micturating/voiding cystourethrogram (MCUG) constitutes the most widespread method for examination for VUR and is the most frequently performed pediatric fluoroscopic examination in Europe (88); it remains the procedure of choice for evaluating possible urethral valves, therefore it is the preferred first examination for VUR in boys, whenever there is a need to specifically evaluate the urethra or the bladder. Digital pulsating fluoroscopic techniques with fluoroscopic screen image saving reduces the number of exposures or totally replaces them, achieving therefore a considerable reduction in the ionizing radiation dose (89-91).
After catheterization of the bladder, the contrast material is installed into the bladder under fluoroscopic guidance, with oblique or lateral views of the bladder as needed. The presence of VUR is documented and graded during the peak of voiding. In male children, also the lateral view of the urethra is obtained without the presence of indwelling catheter.

b. Radionuclide cystography
Radionuclide cystography can be divided into direct and indirect techniques. In direct cystography, the tracer is instilled into the bladder through an indwelling catheter and the entire filling and voiding phases are recorded. The popularity of direct radionuclide studies is mainly attributable to the lower gonadal radiation dose than needed with X-ray MCUG, yet with comparable sensitivities for the detection of VUR. Nevertheless, due to the poor resolution, it does not reveal the same anatomical details or morphological changes such as the urethral valves or developmental anomalies in the same manner as X-ray MCUG and furthermore, grading of reflux is less reliable (92, 93).

Indirect cystography requires the intravenous administration of the tracer which is excreted through the kidneys and usually performed after a renogram (94). Children are asked to void a full bladder and the active micturition is recorded. The indirect technique is less sensitive than direct cystography. Residual tracer activity in the ureter and pelvicalyceal system might hamper interpretation as well as the need for cooperation tend to limit its use in younger children. Bladder filling volume cannot be controlled which might result in lower sensitivities. Radionuclide studies are frequently used in the follow-up of patients with VUR.

c. Voiding urosonography
The basic principal of voiding urosonography (VUS) is similar to MCUG, yet without the use of ionizing radiation which makes it attractive for investigating infants and young children. The urinary tract is first scanned at baseline and then the bladder is filled with saline under sterile conditions through an indwelling catheter and rescanned with US. Contrast material is inserted into the bladder and the UT is scanned in real time also during voiding. The reflux of contrast and dilatation of ureters and pelvicalyceal system are noted. The grading of VUR is similar to the international Grading system (see 2.3.9.; Figure 3).

The available evidence supports the belief that VUS possesses superior diagnostic performance, being reliable, feasible and radiation safe for children and as a suitable alternative for detecting VUR, (85). VUS is becoming increasingly popular and is recommended to be primarily performed in follow-up studies or as the primary reflux examination modality in girls (95-99). The examination had comparable sensitivity as direct radionuclide cystography and higher sensitivity than MCUG (98), although there are some reservations on the possible false positive results which usually does not affect clinical management (100, 101).

The introduction of more stable second generation ultrasound contrast agents have improved the diagnostic yield of this examination, yet they are still only available for off-label use with VUS. The visualization of the entire urethra requires training and seems impractical in clinical practice (95). Nevertheless, encouraging results have been reported about its successful use for evaluating the urethra (102). Inadequate visualization of the bladder or one of the kidneys on US or possible allergy to the contrast agent components are shortcoming of this technique (95).
Figure 3. Four month old female infant with a history of pyelonephritis. Contrast enhanced gray scale voiding urosonography shows severe contrast reflux with dilatation of all of the intrarenal cavities of the right kidney (long arrow) and loss of papillary impression in some calyces (short arrows) consistent with a grade 4 reflux.

2.2.4.7 Positron emission tomography/computed tomography
Although 18F-FDG is the radiopharmaceutical most frequently used in PET, FDG is not a useful tracer for the detection of primary tumors of the urinary tract because of its renal excretion (103). Therefore, the utility of FDG PET in the detection of urinary tract tumors is thought to be limited to distant metastases (103). Recently, efforts have been made to eliminate tracer from the UUT with the help of forced diuresis. Furthermore, only limited experience is available on the use of Choline PET/CT in the evaluation of UUT tumors. Preliminary results suggest that PET/CT is a promising tool for the primary detection and staging of UUT with a high positive predictive value (103, 104).

2.2.4.8 Isotope-scintigraphy
Renal scintigraphy is performed with radioisotopes. It allows the quantitative evaluation of renal function and diuresis renography can help in the differentiation between urinary obstruction and unobstructed dilatation (105). The tracer is allowed to accumulate in the collecting system for 20 minutes and this is then followed by intravenous furosemide administration. Washout of the tracer from the kidney and the collecting system is evaluated by the drug-induced elevation of urine flow or alternatively, the unaffected flow (106, 107).

2.2.4.9 Computed tomography (CT)
Computerized tomography was first described in 1973 by Hounsfield and Ambrose (108, 109). Measurements of X-ray transmission through a subject at many positions and at a sufficient number of angles can be used to determine attenuation differences between different tissues. The reconstructed slices are divided into a matrix of 3-dimensional rectangular voxels displayed as image slices.

The first CT generations were slow and susceptible to artefacts. Improved body CT quality, requiring continuous rotations became possible with the advent of helical CT technique that eliminated the interscan delays and gaps. The table with the patient is moved smoothly through the gantry as rotation and data collection continue (49). Tube heating during thin slice acquisitions was a major limitation of the technique. Further advances in CT technology resulted in the introduction of MDCT. Advanced and more efficient computer and software technologies made it possible to acquire, handle and generate an enormous amount of data rapidly, consequently allowing increased number of rows in the MDCT (110). The more recent evolution of newer dual-energy CT technology is attracting increased interest since substance behavior “at two different energies can provide information about tissue composition and provide improved tissue characterization” (111).
Dual-energy CT can be used to distinguish different substances such as iodine, calcium, and uric acid crystals from soft tissues (111). Furthermore, dual-energy CT has the potential to reduce the radiation dose in CTU examinations by omitting the unenhanced scan by the use of virtual unenhanced images which are generated from the excretory phase after the removal of the iodine pixels (112, 113).

a. Unenhanced CT
Almost since its inception, it had been well-known that CT could reveal almost all UUT stones (114). Older non-helical CT scanners usually obtained scans consisting of 10-mm-thick sections with a 1-second scanning time and a 1-second interscan delay from the top of the kidneys to the bladder base. This impractical approach with a long scanning time and variations due to breathing soon changed with the introduction of helical CT technology. Rapid acquisition of thin reconstructed scans with no possible interslice gaps resulted in superior stone detectability. The first report about the use of unenhanced CT for the evaluation of acute flank pain and suspected UUT stone disease demonstrated the superiority of CT in the detection of UUT stones compared to IVU (115). Further studies consistently confirmed the high accuracy of unenhanced CT not only in the detection of stones but also of obstruction and these were accompanied by good interobserver agreement (54, 116-124). Furthermore, 3D software reconstructions were found useful in the evaluation, interpretation and illustration of findings from multiple perspectives (125-127). Unenhanced CT rapidly became the primary test of choice and the golden standard in the initial evaluation of suspected urinary colic with excellent scientific evidence (126-128). In addition to the superiority of unenhanced CT in the direct visualization of UUT stones, the presence of secondary signs can be used to make the diagnosis of a recently passed stone (114).

The majority of patients (mean of 83%) with ureteral stones will have some degree of hydronephrosis and or hydroureter which together with perinephric high stranding and vesicoureter-junction edema have a strong predictive value for the presence of ureteric stone (129). However, the presence of hydronephrosis does not predict the need for intervention (130). Another limitation of CT includes the inability to evaluate the excretory function of the kidneys and consequently no information is available on the degree of obstruction (131). Nevertheless, there is no convincing evidence that these parameters can be used to guide patient treatment or determine prognosis (114).

One limitation of unenhanced CT is related to the use of radiation which can be minimized using low-dose radiation protocols (132). On the other hand, unenhanced helical CT offers not only rapid evaluation of patients presenting with acute flank pain without the risks associated with the use of intravenously administered contrast media (127), but also reliably confirms or rules out the presence of UUT stones and offers differential diagnostic information (127, 133).

b. Pitfalls
Numerous pitfalls may be encountered in the interpretation of unenhanced CT images. Some stones can be visualized in the bladder. Typically in a full bladder, the stone will be localized centrally at the bottom of the bladder. Nevertheless, this is not always straightforward and occasionally it is difficult to differentiate between passed stones and ureteral stones in the intramural part of the bladder i.e. a stone lodged at the ureterovesical junction (Figure 4), particularly if bladder has not been fully distended. In such problematic cases, patients should be scanned in the prone position so that a stone that has already passed into the bladder will move freely to the opposite side while impacted stones will not change their position (124).
Figure 4. Axial unenhanced CT image in a 30 year old male patient with acute onset of flank pain showing an 8 mm stone protruding into the bladder at the level of ureterovesical junction as its position is not central and not leaning on the posterior wall of the bladder. The dilated ureter can be seen behind the obstructing stone.

The ureter may be obscured between bowel loops and the iliac vessels and cannot be reliably followed, especially in slim patients in whom there is a paucity of retroperitoneal fat. Gonadal vein thrombosis is a rare disease which can resemble hydroureter (127). Therefore, the continuity with the renal pelvis should always be verified. Occasionally, a gonadal vein phlebolith might be misinterpreted as a ureteral stone (117) and therefore continuity of a calcification within the ureteral lumen should be established by viewing sequential images. Pelvic phleboliths are common findings and differentiating those from a ureteral stone might occasionally be difficult. In these cases, the presence of central lucency or the comet-tail sign, which is a tapering soft-tissue structure extending from a pelvic calcification and corresponding to the non-calcified portion of the pelvic vein might aid in the differential diagnosis (134, 135).

Peripelvic cysts might be difficult to differentiate from pelvicalyceal dilation at unenhanced CT and in such cases, imaging might be repeated during the excretory phase after the administration of contrast material.

Perinephric stranding of fat on the side of clinical symptoms, most probably due to the so-called renal backflow mechanisms (pyelovenous, pyelolymphatic, pyelotubular, pyelointerstitial, or pyelosinus types) (136, 137). Stranding is a useful sign of acute obstruction and constitutes a common finding and it is important that it should be differentiated from the more focal, non-linear perinephric fluid collections, likely representing extravasated urine as a result of fornicial rupture (127, 138).

The soft-tissue rim sign is a strong indicator that a calcification along the course of the ureter is a stone, and represents inflammatory reaction of the ureteric wall thickened by edema as a reaction to the presence of the impacted stone (139). On the other hand, the absence of this sign does not completely rule out the possibility of a ureteral stone and furthermore, a rim might be present in up to 8% around phleboliths.

The use of protease inhibitors to treat human immunodeficiency viral disease has led to the increasing prevalence of crystal deposition, resulting in the formation of urinary tract stones that are nonopaque on CT scans (127, 140). The presence of secondary signs of obstruction together with the medical history should raise concerns of this possibility. An excretory phase CT should then be performed to confirm the diagnosis.

In vitro studies have indicated that the fragility and the chemical composition of urinary calculi can be determined by CT (141-143). The considerable overlap in the attenuation values precludes an accurate characterization of stone composition with single source CT while dual energy scanner techniques are theoretically and practically more promising but need to be further
evaluated in vivo, yet still require further optimization to increase the number of stone groups that can be accurately identified (112, 144-146).

c. CT urography

After the introduction of the rapid MDCT technology, it became clear that this new imaging modality is more accurate than IVU in the initial workout of a wide range of UUT pathology (79, 147-151). Images from a MDCT scan are reconstructed into thin slices which can be viewed in any orientation with similar image quality. Completely isotropic resolution in 16- to 64-slice CT can be achieved using 0.5- to 0.625-mm slice thickness. According to the ESUR, “resulting images have high noise levels unless the tube load is increased considerably. In most clinical situations, a near-isotropic resolution with 1.0- to 1.5-mm effective slice thickness suffices for high-quality images created in any plane using multiplanar reconstruction” (152).

Investigations into the accuracy of CTU for the evaluation of possible UUT malignancy soon proved CTU to be a very sensitive and specific method with a pooled sensitivity of 96% (range 88-100%), and pooled specificity of 99% (range 93-100%) (153). Furthermore, direct comparison confirmed the superiority of CTU over IVU in terms of sensitivity and specificity (153, 154).

In order to reduce confusion in the terminology, the European Society of Urogenital Radiology’s (ESUR) CTU Working Group has proposed that CTU should be defined as “a diagnostic examination optimized for imaging the kidneys, ureters and bladder. The examination involves the use of MDCT with thin-slice imaging, intravenous administration of a contrast medium, and imaging in the excretory phase” (152).

The ESUR guideline comprehensively addresses all aspects of CTU based on extensive literature review and on the expertise of leading researchers in this field.

First, hydrating the patient is beneficial in reducing possible contrast induced nephropathy, especially in an otherwise dehydrated or not well hydrated patient, and at the same time provides negative bowel contrast medium. Usually one liter of water is slowly ingested during a period of 20-60 minutes before the CTU examination or alternatively a maximum of 500 ml slow intravenous drip-infusion of 0.9% saline may be used in patients who cannot tolerate oral hydration. Nevertheless, the ESUR guideline also concludes that the net benefit of intravenous saline bolus hydration is probably minimal and thus its routine use is not advocated. Bowel preparation with positive contrast will inevitably interfere with the interpretation, especially in the demonstrative quality of reformatted images and is not recommended. In diuretic-enhanced CT urography, the patients are asked to empty their bladder before the start of the CTU examination (155), although the ESUR guideline offers no detailed guidance on this issue. The use of compression pads is a routine practice in IVU and consequently it was thought that this maneuver could well be transferred to the CTU protocol. However after evaluating the available evidence, the ESUR guideline did not advocate the use of compression.

Patients are scanned in the supine position. Prone position is not advocated to be used routinely (156-158) but can be used in special cases e.g. to reduce layering effects of the contrast medium, especially when the renal collecting system is dilated (152).

The amount of contrast medium used at CTU has varied in the various publications and is dependent on the protocol being used. Ideally, and as recommended by the ESUR guideline: “the volume of contrast material (CM) should be adapted to the CM concentration and the patient’s weight (e.g. 1.7–2.0 ml/kg of 300 mg/l/ml CM or 1.4–1.6 ml/kg of 370 mg/l/ml CM), while adaptation of the injection rate to the patient’s weight (e.g. 0.04 ml/s/kg) ensures a constant injection duration which is optimal for MDCT” (152, 159).

The normally functioning kidneys excrete most of the iodine-containing contrast agents rapidly (160). Consequently high endoluminal concentrations of contrast material may cause CT beam hardening artefacts, a pitfall which can impair the assessment of pelvicalyceal details on standard abdominal window settings (155). Therefore, image evaluation at CTU necessitates
evaluation not only with normal abdominal window settings, but also with wide window settings to achieve maximum urothelial surface visualization (161).

Inspired by the advances in MRU protocols, and in an attempt to achieve uniform opacification, distension and less concentrated contrast filling of the UUT, nowadays it is routinely recommended to administer a low-dose diuretic infusion (furosemide 0.1 mg/kg) 1-2 minutes prior to the injection of contrast agent (152). There is one report claiming that opacification of the UUT was more visible with a fully distended bladder one hour after oral hydration (162). Furthermore, opacification was shown to be better achieved with furosemide than with saline (163). A low dose of furosemide is usually safe but should be withheld in some patients, including those with allergy to furosemide or other sulfa drugs and patients with a systolic blood pressure of less than 90 mm Hg.

There are no randomized trials on CTU nor is there any universally accepted first line routine CTU imaging protocol. Most of the currently published data falls within evidence categories III–IV (152). Malignancy of the UUT is uncommon and various scanning techniques for CTU have been described, mainly driven by the effort to limit and minimize the radiation exposure (to be discussed in a subsequent chapter) in relation to the risk of malignancy. (152, 164, 165). Nevertheless, more recently, a growing consensus has developed on the importance of enhanced venous phase vs. the excretory phase and therefore highlighting the superiority of triple phase protocol (166).

Indications and imaging techniques for CTU continue to evolve. At present, there are two popular protocols and three strategies recommended by the available ESUR guideline to investigate the UUT by CTU, depending on the clinical settings and the risk of malignancy.

The first popular CTU protocol is the single-bolus 3-phase technique. After hydration, a low-dose unenhanced CT is acquired from the top of kidneys to the base of the bladder, followed first by low-dose diuretic and 1-2 minutes later by injection of contrast agent. The imaging strategy after the administration of contrast material is controversial with different protocols available aimed mainly to detect or rule out possible malignancies. Thus, no scientific evidence is available on the superiority of any particular specific protocol. Contrast enhanced abdominal scan can be obtained during the corticomedullary phase (25–35 s delay after start of contrast injection) or at nephrographic (delay of 90–110 s) or with a combination of nephrographic-corticomedullary phase (so-called dose-efficient or arterial-nephrographic-corticomedullary) after splitting of the contrast injection into two or three bolus in some modified protocols. The third excretory phase (240–480 s delay) is the most important scan with the purpose of achieving excellent endoluminal opacification, preferably with some UUT dilatation. Even better results have been reported if acquisition is further delayed to 720 s for improved depiction of the lower ureter while opacification of other UUT segments are not sensitive to any time delay. When low-dose furosemide is administered, the excretory phase delay may be reduced to an average of 450 s (152).

The other CTU protocol is called the split-technique and it utilizes considerably different protocols for the contrast bolus. The main concept lies in the administration of one bolus of contrast agent followed by variable delays of 480–1,000 s (recent practices report a 600-660 s delay) prior to the injection of a second contrast bolus. After a constant delay of 90–120 s from the second bolus, an abdominal scan is acquired and as the first injected contrast is already excreted, the acquisition contains combined nephrographic and excretory phases in one scan, therefore reducing the radiation dose. Further modifications of the split-bolus technique includes triple-bolus contrast injection for the acquisition of combined corticomedullary-nephrographic-excretory phase data some 510 s after start of the first bolus, with or without low-dose diuretics (152).

The ESUR guideline further stresses the need for individual evaluation of excretory phase delays which can be easily monitored by obtaining a low-dose single axial image through the level of mid-ureter. In the case of obstruction, the test image is repeated (usually only 2-3 times).
If both ureters are opacified, then scanning can begin and thus ensure best opacification of both ureters. This technique is of limited use in high-grade obstruction or in patients with decreased renal function (152).

Imaging strategies and protocol selection must take into consideration the individual evaluation of the patient’s clinical presentation. The unenhanced scan can be omitted with dual-energy CT or with the split-bolus technique if the indication for CTU is a benign cause. In high risk patients, the administration of a somewhat higher radiation dose might be justified and the 3-phase technique is applicable. For other indications, an unenhanced and combined nephrographic-excretory scan may be more appropriate (152).

2.2.4.10 MR urography
- Technique and implementation
MRU-protocol includes both heavily T2-weighted imaging sequences and T1-weighted excretory sequences. Breath-hold heavily T2-weighted sequences are usually obtained with either thick-slab single-shot fast spin-echo or similar thin-section techniques (167). Additionally 3D heavily T2 respiratory-triggered sequences can be used to obtain thin-section data (167). These so-called static fluid sequences (occasionally called MR hydrography) rapidly reveal all fluid filled structures and are highly sensitive in the detection of obstruction and its level, irrespective of kidney function. Nevertheless, when no obstruction is present, the depiction of the UUT anatomical structures is poor. Furthermore these sequences alone are not always sufficient to determine the cause of an obstruction. Per oral hydration and enhanced diuresis might improve UUT visibility, yet the presence of fluids in close vicinity, e.g. in the bowel, might hamper image interpretation (165, 167, 168). An oral negative contrast agent is helpful in reducing the signal from bowel contents but is not a prerequisite for MRU (167).

Gadolinium enhanced T1-weighted excretory MRU complements T2-weighted sequences. In normally functioning kidneys, gadolinium-based contrast agents are rapidly excreted, allowing the urine to appear bright because of the T1 relaxation-time shortening effect of gadolinium. Concentrated gadolinium might have an undesirable signal-reducing T2* effect, which is usually overcome by hydration, enhanced diuresis or by reducing the gadolinium dose. Nevertheless, visualization of the UUT is poor without the use of pharmacologically enhanced diuresis, which also provides distension of the UUT (14, 169, 170). Pharmacologically enhanced diuresis may not necessarily improve the distribution of excreted gadolinium and might result in fluid-fluid levels in the dilated pelvicalyceal system, either through the excess amount of gadolinium resulting in T2* effect at the posterior aspect of the pelvicalyceal system, or by the presence of excreted gadolinium in the dorsal parts of the pelvicalyceal system and non-visualization of the more anterior parts (171). The acquisition of high-resolution 3D-gradient-echo sequences enables the rapid evaluation of the UUT and the excretory function of the kidneys in a fashion similar to IVU.
-Pitfalls and limitations

Imaging of the UUT with MRI is challenging and as with other imaging modalities, MRU has its strengths and weaknesses. MRI is susceptible to various artifacts including chemical shift mis-registration, wraparound, phase-encoded motion and susceptibility artefacts, which might be more prominent at higher field strengths (172, 173). Furthermore, standing wave and conductivity artifacts are observed in obese subjects or ascites patients at 3T imaging strengths (172). Therefore, a good knowledge and experience of both normal anatomy and artefacts are a prerequisite for correct image interpretation. MRI is a lengthy examination and requires good patient cooperation. Breath-hold ultrafast sequences and the use of parallel imaging reduces imaging time and are useful to obtain high quality images and hence help reduce movement artifacts (174, 175). It is also beneficial to raise the arms over the head during coronal imaging to prevent the so-called wraparound artifact (172). It is essential to be familiar with these various artefacts, as well as to those related to the enhanced excretion of urine such as void lines and turbulence artefacts, especially in the dilated pelvis. It is also recommended to image the UUT routinely in both axial and coronal planes during the excretory phase (167), as an artefact seen in one plain will not be usually visualized in the second.

The inability to visualize calcifications is considered as a limitation to the use of MRU in the evaluation of UUT stone disease. Indeed, a possible stone is visualized as a partial or complete intraluminal filling defect which is nonspecific and needs to be differentiated from a blood clot or a tumor. Nevertheless, a clot is usually hyperintense in the unenhanced sequence and it does not enhance after the administration of contrast and additionally the margins of the soft-tissue abnormality are usually irregular compared with the well-defined margins of calculi (167). This contrasts to the situation with a tumor that will usually enhance. Therefore, any MRU protocol should include both T2- and T1-weighted sequences and the latter should apply both pre- and postcontrast sequences. A failure to do so might result in misinterpretations, but even then, occasionally severe edema might be misinterpreted as a possible tumor (176). Different results from the literature should be interpreted with caution because of the variability of sequences in use and selection bias. Not all studies evaluating the performance of MRU use both T1- and T2-weighted sequences and as previously mentioned, T2-weighted sequences alone are insufficient if one wishes to evaluate the cause of an obstruction (177).

MRU has another limitation; it can cause a slight underestimation of the size of ureteral stones compared to the images obtained with CT and IVU. Furthermore, according to the published results, small ureteral stones can be occasionally missed in chronic obstructions, especially when the secondary signs of acute obstruction are absent and therefore there is no suspicion of a stone disease. Additionally MRU is insensitive in the detection of small calyceal stones and therefore cannot reliably evaluate the actual stone disease-burden of the calyceal system, but, it should be stressed that small stones are rarely of clinical importance.

-Applications

MRU has been demonstrated to be superior to IVU in the detection of UUT stones (176). MRU was found to be at least as accurate as helical CT in the evaluation of patients with acute flank pain. Furthermore, the presence of secondary signs of obstruction, such as the perirenal edema on the side where there are symptoms, are highly suggestive of an acute obstruction and are better visualized with MRU than CT. Nonetheless CT has gained greater acceptance: CT is a widely available, accurate and rapid imaging modality in the evaluation of acute flank pain and stone disease. MRU is an acceptable substitute in cases where the use of radiation is not desired such as in special patient populations like children, young adults and pregnant patients. A comprehensive MRU protocol does make it possible to evaluate the renal parenchyma, the UUT, the surrounding structures and if needed, also the renal vasculature. This “one-stop evaluation” approach is possible with MRU, which has the additional advantage of not exposing the patient...
to radiation. Furthermore, MR is superior to CT in that it provides better tissue contrast resolution and greater sensitivity for contrast enhancement (178). For these reasons, MRU has become the secondary investigation of choice after US in pediatric UUT imaging. The European Society of Paediatric Radiology - uroradiology task force and the ESUR paediatric working group have recommended to always consider MRU, when available, as a secondary investigation after US in applicable situations, with the main principle being to avoid CT whenever possible (179). The few accepted major indications for CTU in children are severe urinary tract trauma, complicated/equivocal urolithiasis (if high level US + KUB are not conclusive and if there is an expected therapeutic impact) (81).

The comprehensive MRU protocol always includes both T2 and T1 breath-hold sequences in coronal orientation as a minimum. Heavily T2- weighted thin slices can also be obtained in the axial orientation since these may assist in the interpretation. A T2 fat suppressed sequence may be helpful in the identification of edema and is recommended in symptomatic patients. Thick slabs are not usually necessary, yet these sequences can be conducted very quickly and these can reveal the presence and level of obstruction and allow the physician to concentrate on these problems. Furthermore, obtaining numerous sequences watched at loop helps in evaluating peristalsis and in the detection of possible strictures. Unfortunately, there is very limited experience and few reports available about this technique, since it requires the introduction of oral, contrast negative agents in order to achieve better visualization of the UUT. T2 sequences can show acceptable diagnostic accuracies in the evaluation of a range of pathologies including ureteral stones and tumors (114, 180-184). Another study reported high, (97%), sensitivity of MRI combined with KUB and ultrasound in the detection of various causes of obstruction (185).

After the administration of diuretics and contrast agent, a thin slice breath hold 3D sequence is obtained in corticomedullary and nephrographic phases, including axial orientation of both upper abdomen and pelvis. Excretory phase T1 3D sequences are obtained at least at 5 and 10 minutes, although it is possible that imaging of maximum distension and more complete opacification might require both coronal and axial orientations taken at 15 minutes (167). In cases of obstruction and delayed contrast excretion, the patient can be removed from the imaging room and the examination continued at later stage e.g. at hourly intervals.

-Contrast dose
The dose of gadolinium used in MRU is empirical and complies with the abdominal imaging practices. Usually a dose of 0.1 mmol/kg body weight is sufficient although this might still induce T2* artefacts. Although T1 relaxation times of soft tissues generally increase with a higher magnetic field strength, the relative T1 shortening effects of gadolinium remains unchanged, leading to more pronounced contrast enhancement and consequently to a higher contrast to noise ratio and improved lesion contrast and conspicuity (172), but this might be at the expense of the appearance of a T2* effect with the increasing field strength. Therefore a reduction in the contrast dose might be needed at 3T MRU. There is very limited experience with MRU at 3T with only one report using 0.05 mmol/kg body weight gadobenate dimeglumine, a contrast with higher T1 relaxitivity (171, 173). With 1.5 T magnets, half the dose is also considered sufficient (171).

-MRU results
The first reports of gadolinium enhanced excretory urography were promising and MRU was claimed to be superior to IVU. The T1 excretory protocol included prolonged respiratory gated sequences with a non-unified protocol (15, 176). Subsequently, breath-hold sequences were found to be more accurate than respiratory triggered sequences (174). This might explain why a few small stones and tumors were misinterpreted. These results also stress the importance of applying a comprehensive protocol which includes not only T2 and T1 sequences, but also a
high quality T1 gadolinium enhanced sequence of the whole UT area during the venous phase to evaluate the presence or absence of pathological enhancement, since this can help in the diagnosis of a possible tumor.

Takahashi et al reported that the “sensitivity, specificity and accuracy of MRU to detect upper urinary tract malignancy were 74.3%, 96.8% and 93.7% for reviewer 1, and 62.9%, 96.3% and 91.7% for reviewer 2, respectively” (186). This study deserves an in-depth evaluation as it is frequently cited in the literature: the patient population was heterogeneous and it did not represent the usual populations examined with CTU. Urinary tract surgery was performed on 25 patients, and these interventions included cystectomy and nephroureterectomy and renal transplantation. Of the 91 MRU examinations done, in 76 there was a relative contraindication to CTU or excretory IVU due to contrast allergy or since an estimated value of GFR less than 45 ml per minute per 1.73 m2 was arbitrarily considered as a relative contraindication (GFR 30 to 45 in 44 patients, 15 to 30 ml in 13 and less than 15 in 6). Therefore due to the selection bias, these results cannot be used for comparison with CTU. Furthermore when 13 patients with ureteral stents or nephrostomy tube were excluded from the analysis, then the values of sensitivity, specificity and accuracy were improved to 86.2%, 99.5% and 97.7% for reviewer 1, and 72.4%, 97.9% and 94.6% for reviewer 2. In fact, MRU performed especially well in the group of patients with severely compromised renal function, which is a known limitation of all excretory studies.

In a retrospective study, MRU was compared to retrograde pyelography/ureteroscopy for the exclusion of UUT malignancy (187). MRU was found to have comparable accuracy, with a high negative predictive value of 92%. This study included full comprehensive T2 and T1 sequences, yet apparently with only one excretory phase sequence taken with a 5-10 minute delay.

The feasibility of MRU at 3T was reported retrospectively by Childs et al (173). The protocol involved full comprehensive T2 and T1 sequences but included only one axial and coronal excretory phase sequence at 5 minutes after the administration of gadolinium. One hundred percent visualization of the UUT was achieved in 83.1% of the collecting systems and 73.8% of ureters. In addition, if patients with stents or compromised contrast excretion due to chronically obstructed kidneys were excluded, then 100% visualization could have been achieved in 88.5% of collecting systems and 81.4% of ureters. Although artefacts were not uncommon, they did not interfere with the interpretation in most cases. Overall, out of 7 patients with stones, 5 were correctly diagnosed with MRU. Susceptibility artefacts due to metallic clips after surgery were a major limitation to the visibility of the UUT and one ureteral stone was missed because of this limitation. Another small calyceal stone was missed with MRU but it was less than 3 mm in diameter and apparently was of no clinical significance. Single urothelial strictures in 3 patients were missed in the initial interpretation but were visualized in the retrospective analysis. Four upper tract urothelial lesions were present in 2 patients and were properly evaluated by MRU. In a third patient, a relapse of a laser ablated tumor was detected 7 months after MRU when ureteroscopy was also negative. In addition, a large number of benign findings were visualized by MRU. Therefore, although the number of tumor events was limited, it seems that in that study, MRU had been reliable in both the detection and evaluation of UUT.

Another retrospective study compared image quality between CTU and MRU and assessed the diagnostic confidence between the two techniques in patients with hematuria (188). CTU was performed with diuretics and the split bolus technique. MRU was performed with 1.5T field strength with T2 and only one T1 excretory MRU sequence in the coronal plane with a delay of 10 min. Unfortunately, the failure to perform a complete comprehensive MRU examination biases this study in favor of CTU. As expected, CTU provided better visibility of urothelial structures and allowed for greater diagnostic confidence.

There is no reliable evidence where the true performance of a comprehensive MRU protocol would have been compared with CTU in the same patient population (Figure 5). It is clear that excretory phase imaging at 5-10 minutes is not always sufficient and the imaging of opacification
is incomplete. Therefore, one can postulate that the reliability of MRU can be improved by taking repeated excretory phase sequences at longer durations.

Figure 5. MR excretory urography maximum intensity projection images at 5 min (image A), 10 min (image B) and 15 minutes (image C) shows comparable visibility of the whole upper urinary tract as compared to CT urography (image D).

2.2.4.11 Radiation exposure issue

The selection of the most suitable investigation protocol depends not only on availability but also on individual estimation of the risk/benefit ratio for each patient. Exposure to medical ionizing radiation relies on justification and optimization concepts and given that there is no consensus on the optimal radiation dose, every effort is always made to perform these investigations according to the ALARA principal (189, 190).

In a pediatric patient, the life expectancy is long, therefore it is reasonable that in this population all forms of ionizing radiation should be avoided whenever possible as in general, radiation risks in children are 2-3 times higher than in adults (191, 192). In many studies, it has been stated that radiation induced cancer risks were “related to radiation dose and appeared to be greatest for children irradiated early in life, and risks for solid tumors persisted throughout life” (191).

Radiation doses from IVU reports depend widely not only on patient characteristics but also on radiation parameters in use and local protocols, with effective doses varying from 1.5 to 15 mSv. (193-195). On average, doses of 2.5 mSv will be delivered if the patient undergoes an IVU examination with a six-exposure protocol (194).

CT examinations result in approximately 1.5-2 times higher radiation risk than for IVU (157, 195). In CT, the radiation dose can be reduced by adopting different mechanisms: low dose protocols can be used including low mAs and even a lower tube voltage. A recent study described the reduction of effective dose by more than 65% by applying the 100-kV protocol and by more than 76% with the introduction of the 80-kV protocol (196). Furthermore, all modern MDCT scanners use automatic tube-current modulation protocols, which can achieve a 10-30% reduction from usual doses.

The issue of radiation reduction has been extensively discussed in the literature (197), and it has been reported frequently that dose reduction is possible without suffering any significant degradation in image quality (198-202). A radiation dose as low as 0.48 mSv could be achieved if one used an ultra-dose unenhanced CT compared with 4.43 mSv conventional dose which is already comparable to a KUB (203). By applying unenhanced CT for the diagnosis of stone disease greater than 3 mm in diameter, it was shown that there was no statistically significant difference in sensitivity even with a 50% or 75% dose reduction. Therefore a protocol with reduced dose should always be considered e.g. in patients undergoing follow-up of a previously detected stone or to evaluate therapy. (204-206).
Patients should be always individually evaluated and whenever radiation is deemed undesirable, MRU, if available, should always be considered as a suitable and valid substitute for both IVU and CTU.

2.3 ABNORMALITIES OF THE UPPER URINARY TRACT

2.3.1 Congenital abnormalities

Ureteral duplications are the most common congenital abnormalities of the ureter. The embryonic development of UUT is genetically coded and three main classes of molecules are expressed during its development i.e. transcription factors, growth factors, and cell adhesion/extracellular matrix proteins (17, 207). Disturbances in these mechanisms may lead to a range of anatomical variants and congenital abnormalities, with the most common being duplication variants usually accompanied by ectopic insertions. Ureteral atresia is rare.

Duplication may be either incomplete or complete (208) and in addition, it may be asymptomatic or accompanied by a variety of complications. Incomplete duplications are believed to be due to the premature split of the ureteric bud, while the complete type is attributable to its duplication. Unilateral duplications are more common than the bilateral type while triplications are extremely rare. In ureter duplication, “the ureter draining the upper pole moiety system often drains into an ectopic ureterocele located inferomedial to the insertion of the lower pole ureter. Classically, the ureterocele of the upper pole ureter results in obstruction, while abnormal insertion of the lower pole ureter results in vesicoureteral reflux” (209-211).

The ureters arise from the Wolffian ducts. The ureter of the lower renal pole arises inferiorly and is initially incorporated into the developing bladder. It ascends during bladder growth and is inserted both superiorly and laterally to the ureter of the upper renal pole. This relationship in insertion is called the Weigert-Meyer rule. The ureter of the upper pole remains with the Wolffian duct. Its insertion is located in the bladder or wherever remnants or derivatives of the Wolffian duct are found (212). In boys, most extravesical insertions are suprasphincteric, conversely, in girls they occur beyond the sphincter (212). Other usual ectopic ureteral orifices in females tend to be in the vagina or perineum; in boys they are usually found in the seminal vesicle or ductus deferens. An extravesicular ectopic orifice usually gradually develops into a stenosis, preventing urine from flowing freely (208, 213).

The most common complications of complete duplication are a vesicoureteral reflux, ectopic ureterocele, ectopic ureteral insertion (Figure 6) and ureteropelvic junction obstruction of the lower pole (213, 214). Ureteral atresia results in an absent or multicystic dysplastic kidney, which may involute.
Figure 6. Three month old female infant with a history of urinary tract infections. Imaging revealed a complete duplication of the severely dilated and tortuous right ureter of the functional upper pole. Preoperative MR urography (left image MIP reconstruction of the 3D T1 late excretory sequence (1 hr. after contrast)) showed the anatomical details of the dilated upper pole and duplicated ureter as well as the clinically important information on the most distal stenotic and ectopic anterior insertion (right-sided T1 3D source image).

2.3.2 Ureteropelvic junction stenosis
The etiology of ureteropelvic junction (UPJ) obstruction is still controversial. Several causes or their coexistence have been postulated. The possibility that crossing vessels are an etiologic factor is widely acknowledged, but in addition, an aperistaltic ureteral segment, an intrinsic luminal narrowing, an excessive local collagen deposition, a periureteral fibrosis or an insertional abnormality have been postulated (211, 215, 216). In some cases, no specific cause for UPJ obstruction may be detected. Most commonly, the etiology can be traced to an anteriorly crossing artery. In particular, the lower pole segmental artery and vein have been implicated in UPJ obstruction (215).

2.3.3 Ureteric stenosis
Congenital ureteric strictures are rare (217). Ureteral valves can be associated with strictures; in severe strictures, the smooth muscle layer is replaced by fibrous tissue (218). Vascular compression is thought to interfere with the muscularization process and can be associated with coexistent renal abnormalities (219).

2.3.4 Ureteral diverticula
Ureteral diverticula are exceedingly rare and may present as an incidental finding or with a secondary complication. They can result from a blind-ended bifid ureter or, they can be a true congenital saccular diverticulum, occurring at any portion along the ureter. These conditions can be associated with congenital anomalies or complex abdominal or pelvic abnormalities. On the other hand, acquired diverticula represents mucosal herniation, e.g. in the setting of chronic distal obstruction (220, 221).

2.3.5 Calyceal diverticula
These nonsecretory outpouchings are lined by transitional cell epithelium and communicate with the main collecting system through a narrow channel, allowing for passive filling with urine and consequently they predispose to intradiverticular stone formation (222, 223). Calyceal diverticula predominates in the upper pole calyces and are considered to be congenital in etiology. Calyceal diverticula are classified as type I, when communicating with a minor calyx or an
infundibulum (Figure 1 and 7), or type II, when emanating from the renal pelvis or a major calyx (222). Type II diverticula are larger, tend to be symptomatic, and are located in the central part of the kidney (222).

Figure 7. A 3 month old male infant with urosepsis and multiple right kidney abscesses in the ultrasound image. The etiology behind kidney abscesses was later shown to be due to multiple type 1 calyceal diverticulae (arrows).

2.3.6 Ureterocele
An ureterocele represents a cystic dilatation of the intravesical segment of the terminal ureter as a response to the congenital stenosis of the meatus. It has been postulated that ureterocele formation may be related to the timing of absorption of the mesonephric (Wolffian) duct into the urogenital sinus during embryology (224).

The outer wall of ureterocele is composed of bladder epithelium below which lies the inner wall of ureteral epithelium, with connective tissue and muscle fibers in between these structures. Ureteroceles may be either simple or ectopic (208, 225). Ectopic ureterocele can manifest in different ways i.e. the most common forms: stenotic or sphincteric ureteroceles or the uncommon forms: sphincterostenotic-, blind-, nonobstructed-, pseudoectopic- and cecoureterocele variants (225). For simplicity, the American Academy of Pediatrics has classified ureteroceles as intravesical (entirely within the bladder (Figure 8), or ectopic (some portion is situated permanently at the bladder neck or in the urethra) (226).

Figure 8. CT Urography in axial and coronal planes of a 25 year old male patient with dysuria symptoms and compromised renal function due to bilateral intravesical ureterocele and a left sided secondary megaureter.
2.3.7 Megaureter
Megaureter is a term indicating the presence of an enlarged ureter (≥7 mm) with or without concomitant dilatation of the upper collecting system (208, 227). “Primary megaureter is an inherently compound term that includes all cases of megaureter due to an idiopathic congenital alteration at the vesicoureteral junction” (227). Secondary megaureters are a consequence of vesicoureteral reflux (VUR) or of an outlet obstruction such as ureteroceles, urethral strictures and valves or elevated bladder pressure due to neuropathy or other acquired causes of obstruction (227, 228). The primary nature of the megaureter is confirmed by excluding secondary causes. Smith classified megaureters into four categories: obstructed, refluxing, refluxing with obstruction, and non-refluxing/non-obstructing, later subdivided into primary and secondary categories by King (229, 230). Megaureter is further classified according to its morphological appearance (Pfister–Hendren classification): type I involves the distal ureter without associated hydronephrosis; type II extends to both ureter and pelvis; type III is associated with severe hydronephrosis and ureteric tortuosity (231). The classical description of the obstructed megaureter is a ureterovesical functional obstruction without stricture but with an aperistaltic segment. Megaureters might be asymptomatic but this condition is usually associated with a high rate of urinary tract infection (UTI). Other consequences include decreased renal function and pain (227).

2.3.8 Retrocaval ureter
A retrocaval ureter is a rare anomaly caused by the persistence of the posterior cardinal vein during embryonic development. The right ureter passes posteriorly to the inferior vena cava and then medially anterior to it before resuming its normal pathway to the pelvis. A retrocaval ureter has been also described to be associated with a double inferior vena cava anomaly, which is an extremely rare condition (232). Usually, a retrocaval ureter is found incidentally or in the third or fourth decades of life, with symptomatic upper ureteric obstruction (233).

2.3.9 Vesicoureteral reflux
VUR represents back-flow of urine from bladder to the UUT. This condition can be asymptomatic with a spontaneous resolution but might predispose to UTI, renal scarring and nephropathy (234). VUR may arise as a prenatal hydronephrosis during the fetal development. Bilateral and high grade VUR are more frequent among boys. The vesicoureteral reflux can be divided into two categories: primary, when children have a defect or dysfunction in the valve-like mechanism of the bladder that normally prevents urine from flowing backward or it can occur in association with other anomalies; secondary when it is due to a urinary tract malfunction, often caused by infection, or with the presence of lower urinary tract obstruction of urine flow.

The classification of VUR is based on both the reflux of contrast material and on the severity of the pelvicalyceal and the ureteric dilatation according to the international Grading system (235, 236) (Table 2). The most severe reflux during the peak of voiding determines the grade of VUR.
Table 2. Classification of vesicoureteral reflux.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>Contrast only in the ureter</td>
</tr>
<tr>
<td>2</td>
<td>Contrast in the renal pelvis but with no significant pelvic dilatation. Calyces not dilated.</td>
</tr>
<tr>
<td>3</td>
<td>Contrast in the renal pelvis associated with mild or moderate renal pelvic and calyceal dilatation. Mild dilatation and/or tortuosity of ureter</td>
</tr>
<tr>
<td>4</td>
<td>Contrast in the renal pelvis associated with significant both renal pelvic and calyceal dilatation. Complete blunting of fornices but maintenance of the papillary impressions in the majority of calyces. Tortuous ureter with moderate dilatation.</td>
</tr>
<tr>
<td>5</td>
<td>Contrast in the renal pelvis associated with significant gross both renal pelvic and calyceal dilatation. Tortuous ureter with gross dilatation. Papillary impressions no longer visible in the majority of calyces.</td>
</tr>
</tbody>
</table>

2.3.10 Hydronephrosis
Prenatally "pelviureteric obstruction is the most common cause of hydronephrosis with reported incidences of 39–64% and reflux accounting for a third (33%) and vesico-ureteric obstruction 9–14%" (237). Most detected dilatations are classified as mild in nature with favorable outcome (237).

The measurement of the antero-posterior diameter (APD) in the transverse plane of the renal pelvis is the most widely studied parameter for assessing hydronephrosis prenatally. An APD measurement of 4-5 mm is often be regarded as a suitable threshold for considering the APD to be abnormal (238). Postnatal hydronephrosis is evaluated using the numerical grading system proposed by the Society for Fetal Urology (239) (Table 3). The finding of hydronephrosis is the gross manifestation of a heterogeneous group of pathologies including the previously mentioned congenital and structural abnormalities or a wide range of primary or secondary pathological entities. Obstruction can be partial or complete, unilateral or bilateral, acute or chronic.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No dilatation, calyceal walls are opposed to each other</td>
</tr>
<tr>
<td>1</td>
<td>Normal parenchymal thickness and only renal pelvis splitting. No parenchymal atrophy</td>
</tr>
<tr>
<td>2</td>
<td>Mild dilatation of the intrarenal pelvis. Urine fills extrarenal pelvis and major calyces dilated. No parenchymal atrophy</td>
</tr>
<tr>
<td>3</td>
<td>Grade 2 and uniform dilatation of minor calyces (moderate dilatation of the renal pelvis and calyces with blunting of fornices and flattening of papillary impression). No parenchymal atrophy</td>
</tr>
<tr>
<td>4</td>
<td>Grade 3 and thin parenchyma (usually severe ballooning of the renal pelvis and calyces with loss of their borders associated with parenchymal atrophy)</td>
</tr>
</tbody>
</table>

### 2.4 DISEASES OF THE URINARY TRACT IN ADULTS

#### 2.4.1 Urinary tract infections (UTI)

Infections of the UT are among the most prevailing infectious diseases imposing an enormous resource burden on health care (240). The vast majority of infections are ascending, i.e. through the urethra and upwards with an increased risk of infection following catheterization and instrumentation (241). Most of the UTI are caused by enteric microorganisms. Infection to the UT can also spread secondarily via the haematogenous route, which is usually “restricted to a few relatively uncommon microorganisms, such as Staphylococcus aureus, Candida, Salmonella and Mycobacterium tuberculosis” (240, 242).

The diagnosis of UTI that requires treatment might occasionally be challenging. If one collects a suprapubic bladder puncture urine specimen, then any count of bacteria is relevant. The European Association of Urology (EAU) guideline list the following quantitative mid-stream sample of urine (MSU) bacterial counts (colony-forming unit, CFU) as being clinically relevant (243):
- ≥103 cfu/mL of uropathogens in a MSU in acute uncomplicated cystitis in women
- ≥104 cfu/mL of uropathogens in a MSU in acute uncomplicated pyelonephritis in women
- ≥105 cfu/mL of uropathogens in an MSU in women, or > 104 cfu/mL uropathogens in an MSU in men, or in straight catheter urine in women, in a complicated UTI

The classification of the level of infection according to the anatomical level does not include specific UUT parts. While lower tract infections can cause urethritis and/or cystitis, the ascending infection through the UUT can lead to pyelonephritis where both the renal pelvis and kidney’s parenchyma become inflamed, and subsequently this can progress to sepsis at the level of the bloodstream. UTI is typically diagnosed on the basis of clinical symptoms and laboratory findings (240). While most of the uncomplicated UTIs do not need any further radiological evaluation, more severe clinical symptoms or sepsis do need to be carefully evaluated to rule out the presence of obstruction, predisposing factors for infection or possible complications. Imaging is also reserved for patients who are poor responders to therapy and for those with an atypical presentation or with potentially life threatening symptoms (240, 243).
2.4.1.1 Imaging in UTI
In the modern era, there is no role for KUB or IVU in the primary evaluation of patients with UTI due to the low detection rate of abnormalities (244, 245). Ultrasound is usually the primary investigation of choice for the prompt evaluation of the presence of obstruction (246), and should be performed in the early stages of the disease or in cases where there have been prolonged symptoms or a failure of treatment (247, 248). Ultrasound is not always sufficient to make a diagnosis of pyelonephritis at gray scale due to the lack of possible detectable abnormalities (249). The signs of obstruction detected by US include the detection of congenital anomalies or hydronephrosis, renal enlargement and changes in the renal parenchyma such as “loss of renal sinus fat due to edema, changes in echogenicity due to both edema (hypoechoic) or hemorrhage (hyperechoic), loss of corticomedullary differentiation, abscess formation, and areas of hypoperfusion” (243). False negative findings and misinterpretations can occur, especially when the pelvis is filled with pus or hematoma since the identification of the dilated cavities can be very difficult in these situations. Furthermore, microabcesses and subtle inflammatory changes around the pelvicalyceal system or kidneys might be invisible. In selected cases when US is equivocal, MRI can aid in the diagnosis as it has been shown to be a highly sensitive and safe investigational procedure for confirming uncomplicated pyelonephritis. Furthermore the role of diffusion weighted imaging is promising (250-252).

Complicated UTI is reported to have serious implications including a crude mortality of 6.5%; certain factors such as age >75 years, immunosuppression and septic shock independently were associated with mortality (253). Complications of the UTI are uncommon but they tend to occur more frequently in diabetics or in patients after instrumentations, warranting prompt diagnosis and therapy in these populations (254, 255). Emphysematous pyelonephritis and emphysematous pyelitis and acute papillary necrosis are all serious complication, usually difficult to detect with US and require the application of more accurate cross-sectional imaging modalities.

CT and CTU are the primary investigations of choice in the rapid evaluation of UTI and its complications due to their widespread availability, but it should be recognized that MRI is a suitable alternative for young adults or in patients with contraindications to iodinated contrast agents (256, 257). In cross-sectional imaging, alternating bands of hypo- and hyper-attenuation corresponding to infected and non-infected parenchyma are visualized and reflect the presence of bacterial nephritis which might occasionally have a mass effect. The presence and cause of obstruction including ureteral stones are also rapidly depicted, as are the presence or absence of perirenal or retroperitoneal complications e.g. abscesses are documented as well as any focal or global enlargement of the kidney, perinephric stranding and thickening of Gerota fascia, all of which are signs of inflammation (243, 258).

2.4.1.2 Special forms of UTI
Xanthogranulomatous pyelonephritis is a rare “chronic destructive granulomatous process that is believed to result from an atypical, incomplete immune response to subacute bacterial infection” in association with pelvicalyceal urolithiasis, commonly staghorn (243, 259, 260). The combination of a nonfunctioning enlarged kidney with inflammatory changes also extending outside of the renal and pelvicalyceal system with central calculus at CT are diagnostic.

The UT is the most common extrapulmonary site of tuberculosis (243) with subtle and non-specific clinical symptoms or any distinctive laboratory findings. Imaging findings result from identifying evidence of a combination of papillary necrosis and parenchymal destruction (243). There is an increased risk of tuberculosis in patients with chronic renal failure and on dialysis as compared to the general population (243, 261). The collecting system is thickened and distorted with an irregular stricture and cavity formation. Scarring produces irregular abnormalities in the renal contour commonly with calcifications.
Malacoplakia is a rare, inflammatory process related to an abnormal host response to chronic infection; it might be encountered more frequently in patients with acquired immunodeficiency syndromes or diseases, or in transplant recipients but usually the reports describe only individual cases (262, 263). Malacoplakia is preceded by urosepsis usually caused by E coli and it results in a deterioration in kidney function which can even lead to acute kidney failure. The classic appearance is an enlarged kidney with multiple hypovascular masses and commonly there is a bilateral involvement (264). The MRI findings include multiple small nodules 1-2 cm in diameter low in signal on both T1 and T2 with intervening fibrous stroma (265). Biopsy is required to confirm this rare condition.

2.4.2 Trauma to the upper urinary tract

Trauma to the UUT “is defined as a physical injury or a wound caused by an extrinsic agent. Death from injury is twice as common in males as in females, especially from motor vehicle accidents and interpersonal violence” (240, 266). The kidney is the most commonly injured organ in the genitourinary system while ureteral trauma is relatively rare and mainly is due to iatrogenic injuries or penetrating gunshot wounds (267, 268). Iatrogenic injuries to the ureters are most frequently due to gynecologic, colorectal, and vascular pelvic surgery. There is also some potential for considerable ureteral injury to occur during endoscopic procedures to clarify some ureteric pathology such as a tumor or lithiasis (269).

The classification system of the UT trauma commonly follows the recommendations of the American Association for the Surgery of Trauma. Trauma to the pelvicalyceal system is evaluated together with the kidney injury (Table 4) while trauma of the ureter is classified separately (Table 5) (270, 271)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of injury</th>
<th>Description of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Contusion</td>
<td>Microscopic or gross hematuria, urologic studies normal</td>
</tr>
<tr>
<td></td>
<td>Hematoma</td>
<td>Subcapsular, nonexpanding without parenchymal laceration.</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma</td>
<td>Non-expanding perirenal haematoma</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&lt;1.0 cm parenchymal depth of renal cortex without urinary extravasation</td>
</tr>
<tr>
<td>III</td>
<td>Laceration</td>
<td>&gt;1.0 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Parenchymal laceration extending through renal cortex, medulla, and collecting system</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Completely shattered kidney</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Main renal artery or vein injury with contained hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Avulsion of renal hilum which devascularizes kidney</td>
</tr>
</tbody>
</table>
Table 5. Ureter injury scale.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of injury</th>
<th>Description of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>Contusion or hematoma without devascularization</td>
</tr>
<tr>
<td>II</td>
<td>Laceration</td>
<td>&lt;50% transection</td>
</tr>
<tr>
<td>III</td>
<td>Laceration</td>
<td>≥50% transection</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Complete transection with &lt;2cm devascularization</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Avulsion with &gt;2cm of devascularization</td>
</tr>
</tbody>
</table>

2.4.2.1 Imaging in trauma

CT is the primary investigation of choice in the evaluation of UUT injuries and is incorporated in the trauma protocol for evaluating possible significant injuries. If CT of the abdomen is not indicated in less severe abdominal trauma and the patient has non-visible hematuria and no shock after blunt trauma, then there is a low likelihood that there is some concealed significant injury of the UUT (0.1%–0.5%) (272, 273). On the other hand, patients with penetrating trauma to the torso have a high incidence of significant renal injuries (266). If there is such a suspicion on the basis of an entry or exit wound, imaging should be performed, regardless of the degree of hematuria (266). On the other hand, “hematuria may be absent when ureteral tear, vascular pedicle injury, or ureteropelvic junction avulsion occurs” (272). In these cases, the extent of renal injury and the degree of hematuria exhibit no direct relationship. Other clinical signs, symptoms and CT findings should be used to guide further imaging and management (272).

Although US can detect lacerations, it cannot accurately assess the extent of damage nor provide functional information about excretion or urine leakage (266). Furthermore US is operator dependent and has low reported sensitivities, in the range 44%–95% for the detection of retroperitoneal blood and retroperitoneal injury (272, 273). Nevertheless, US is useful for the routine follow-up of parenchymal lesions or hematomas and for serial evaluation of stable injuries, as well as for the assessment of the resolution of urinomas (240, 274). Preliminary results pointed to a promising role for contrast-enhanced US in the initial evaluation and staging of pediatric and low-energy trauma patients or for the follow-up of the conservatively managed solid organs trauma patients (275).

CT promptly provides “anatomic and functional information necessary to determine the type and extent of parenchymal, vascular, or collecting system injuries and other possible associated abdominal injuries” (272). Simultaneously, patients have to be continuously monitored. Whenever a serious UUT injury is suspected, it has been postulated that an unenhanced CT scan might be useful in the primary evaluation of possible hematomas (276). The abdomen is usually scanned during the portal venous phase to evaluate other organs and this corresponds approximately to the early nephrographic phase, which allows identification of parenchymal injuries. Whenever vascular examination is necessary, bolus-tracking multiphase CT can be performed during the arterial phase (272) although many trauma protocols include double bolus techniques to routinely obtain combined arterial and nephrographic images in all trauma patients. It should be emphasized that in cases where “significant perinephric or periureteral fluid is found, or whenever confusing findings requiring further characterization are depicted during the portal phase” (272) it is obligatory to undertake a delayed 5 minutes scan to evaluate the possibility of urine extravasation (272). Delayed images are also useful to differentiate between pseudoaneurysm and free bleeding (273, 277). A high dose CT is not usually necessary for unenhanced and delayed phases, thus reducing the radiation dose of the examination.
Early complications develop within the first month of UUT trauma and include urine “extravasation with urinoma formation, infected urinoma, perinephric abscess, sepsis, and delayed bleeding secondary to arteriovenous fistula or pseudoaneurysm” (272). Late complications are manifested as hypertension, hydronephrosis, calculus formation and chronic pyelonephritis (278, 279).

Follow-up CT scans should be performed on patients with fever, unexplained decreased hematocrit or significant flank pain. Repeat imaging can be safely omitted for patients with grade 1-4 injuries as long as they remain clinically stable (240, 266, 280). Nevertheless, it has been emphasized that high-grade penetrating injuries undergoing operative intervention should carry the lowest threshold for repeat imaging (281).

2.4.3 Urolithiasis

Nephrolithiasis is a common chronic kidney condition with a lifetime prevalence of 10% in men and 5% in women (282, 283). The incidence of stone formation depends on geographical, climatic, ethnic, dietary and genetic factors (284). Nephrolithiasis is also a recurrent disease and although the recurrence risk is determined by the underlying etiology, the recurrence rate has been estimated to be as high as 50% within the first 5 years after the initial stone episode (285). Prevalence and recurrence rates are also increasing presumably due to changes in environmental factors including lifestyle and dietary habits as well as climate changes (286).

The EAU classifies stones into those caused by infection (calcium oxalate, calcium phosphate, uric acid) or non-infectious (magnesium ammonium phosphate, carbonate apatite, ammonium urate) causes; genetic defects (cystine, xanthine, 2,8-dihydroxyadenine) or adverse drug effects (284). Urinary stones can be classified according to size, location, X-ray characteristics, etiology of formation, composition, and risk of recurrence (282). Stone composition is important in clinical and medical management decisions, with the most frequent stone types being calcium oxalate (76%), calcium phosphate (12%), uric acid (7%), cystine (2%) and struvite (2%) (282).

2.4.3.1 Risk patients

Patients with higher risk for stone formation or recurrence are defined by the EAU as those with an early onset of urolithiasis (especially children and teenagers), patients with a familial history stone formation and those subjects with uric acid and urate-containing or with infection stones. Diseases associated with higher risk stone formation are hyperparathyroidism, metabolic syndrome, gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn’s disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion), bariatric surgery and sarcoidosis. Some anatomical abnormalities are associated with stone formation e.g. medullary sponge kidney (tubular ectasia), UPJ obstruction, calyceal diverticulum, calyceal cyst, ureteral stricture, vesico-uretero-renal reflux, horseshoe kidney and ureterocele (284).

2.4.3.2 Pathogenesis: plaques and plugs

No single theory of pathogenesis can totally account for human kidney stones (287). It is clear that retention of crystals within the kidney is necessary for stone formation. Studies conducted during the last decade have highlighted the role of calcium phosphate deposits in the papilla tip, as a starting point of calcium oxalate stone formation. These are called the Randall’s plaque in tribute to Alexander Randall who first reported these findings eight decades ago (288); he postulated that kidney stones were formed and attached to two types of pre-calculus lesions. A pre-calculus lesion type 1 is when sub-epithelial deposits of calcium phosphate and calcium carbonate, arising from pathologic conditions of the renal papilla, break through the papillary surface exposing themselves to the calyceal urine and establishing the Randall’s plaque from
which most idiopathic calcium oxalate stones develop. On the other hand, a pre-calculus lesion type 2 is formed when there is excessive urinary supersaturation and necrosis of tubular epithelial cells causing crystallization of stone salts and plugging of the terminal collecting ducts, creating Randall’s plug (289-291). Some stones develop on crystalline plugs protruding out of the ducts of Bellini, while others are more likely to be formed free in urine both within the lumens of dilated inner medullary collecting ducts behind the plugged ducts of Bellini, or inside the calyces and renal pelvis. Multiple physicochemical factors are also needed in stone formation including urinary solute supersaturation, disorders in urinary pH and/or inhibitors of crystallization.

2.4.3.3 Diagnostic imaging

Patients with ureteral stones usually present with symptoms of acute pain. Other signs include nausea, vomiting, and occasionally fever. However, ureteral stones may also be asymptomatic. The evaluation includes both a detailed medical history and a physical examination.

Unenhanced CT is the golden standard in the evaluation of urolithiasis and is frequently the primary investigation in the evaluation of patients with acute flank pain. Nevertheless, concerns have been raised about the radiation exposure and the delivered dose. Recently a retrograde shift has been noted towards reinstating a combined US and KUB approach in the primary evaluation of stone disease (292, 293). Westphalen et al reported that there had been a 10 fold increase in the use of CT for patients with suspected kidney stone without any associated change in the proportion of diagnosis of kidney stone, significant alternate diagnoses, or admission to the hospital (294).

2.4.3.4 Imaging guidelines


Unenhanced CT is recognized as being the most accurate standard investigation and in acute disease, it is the method of choice. Nevertheless, the guidelines state that US is safe, reproducible and inexpensive, and should be used as the primary diagnostic imaging tool for routine evaluation. The sensitivity and specificity are consequently reported to be 45% and 94% for ureteric stones and 45% and 88% for renal stones. Furthermore, whenever unenhanced CT is used, it is recommended to reduce the radiation risk by using a low-dose CT protocol in patients with body mass index < 30. Enhanced CTU is preferable over IVU in “complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance” (284). According to these guidelines, MRU cannot be used to detect urinary stones, but this is an inaccurate statement (Figure 9), since it does not take into account the many positive results from the relevant literature (114, 173, 180, 184, 185, 178).
Figure 9. Four different patients with left sided flank pain and an etiology of urinary tract stone at different levels and visible in the excretory T1-weighted images. A stone lodging in the minor lower-pole calyx is visible as a filling defect in Image A. A stone at the level of the lower-pole’s major calyx is visible as a filling defect in image B. A stone seen as a signal-void area in the proximal part of the left ureter has caused a total obstruction in image C. A very small (<3 mm) stone is visible as a filling defect in the distal ureter close to the urinary bladder.

b. ACR Appropriateness Criteria® Acute Onset Flank Pain — Suspicion of Stone Disease (2011)
Unenhanced CT is reported to be the most rapid and accurate technique for evaluating flank pain with reduced-dose techniques preferred and is given an appropriateness score of 8. US and KUB may be appropriate (score 6) and are “preferred examination in pregnancy, in patients who are allergic to iodinated contrast, and if unenhanced CT is not available” (295). MRU and IVU may be appropriate even although both are given a score of 4. In the summary of the literature review, MRU was stated to display lower sensitivities, but with referenced studies focusing mostly on only static fluid techniques (295).

The guideline adopts a novel approach for evaluating the most accurate achievable information in clinically different scenarios. In those cases where the information may be obtained by two equally sensitive or nearly equally sensitive imaging modalities, it is often possible to make rational medical decisions without additional imaging studies or with a lower-cost option and thus the lower cost option should be favored. Unenhanced CT is recommended to establish the diagnosis in most cases, with a low energy protocol advocated if body habitus is favorable. Conventional radiography and ultrasound are endorsed for monitoring the passage of most radiopaque stones as well as for most patients undergoing stone removal (205).

2.4.4 Tumors of the upper urinary tract

2.4.4.1 Background and incidence
Urothelial carcinomas (UC) are a common disease worldwide (29, 296); these refer to tumors of the whole UT from the pyelocalyceal cavities down to the urethra. Bladder tumors account for 90-95% of all UCs and are the most common malignancy of the urinary tract (297). UUT carcinomas are a disease of older age (mean age at diagnosis is 64 yr.) and are relatively uncommon. In 17 screening studies of healthy patients who were found to have asymptomatic microscopic hematuria and underwent subsequent workup, the overall malignancy rate was only 2.6%. In patients found to have asymptomatic microscopic hematuria during an unrelated medical evaluation, the overall malignancy rate was 4%. In these populations, the vast majority of patients were >35 years (298).
Pyelocalyceal tumors are about twice as common as ureteral tumors, but both account for only 5-10% of all UCs. The estimated annual incidence of UUT cancers in Western countries is approximately 2 cases per 100,000 inhabitants and 60% of these are invasive at diagnosis (compared with 15–25% of bladder tumors) (299, 300). The age-standardized incidence and mortality rates of renal pelvis and ureter cancer are significantly higher in males than females. Figures from the Finnish cancer registry show that the incidence of all UCs has increased with time. In 2013, a total of 928 UCs were reported in men and 259 in women; these values represent 3.5 and 3.1 fold increases in incidence since 1967 (301). UCs are the third most frequent cancers in men in Finland after prostate and lung cancers. In women, the incidence is lower and UCs are 16th place in the rank order of cancer cases. Incidences of UCs in the ureter and renal pelvis are not usually reported separately in the Finnish registry, nevertheless it was reported that in 2008, a total of 56 renal pelvis cancers were detected (301).

Carcinomas of the UUT and bladder share many similarities yet some investigators have proposed that they should be considered as distinct urothelial entities with anatomical, biological and molecular differences (302, 303). Nevertheless, a recent study showed comparable prognosis at identical stages between these entities (304). On the other hand, there is a prognostic impact of tumor location when adjusted for tumor stage: Ureteral and multifocal tumors have a worse prognosis than renal pelvic tumors (305, 306).

Synchronous bilateral UUT carcinoma has been reported to occur in 1%–2% of cases of renal lesions and 2%–9% of cases of ureteric lesions (307). In 17% of cases, synchronous bladder cancer is present. Metachronous tumors in the bladder have been reported in 15-50% of patients initially presenting with UUT carcinoma. In contrast, patients with a primary bladder tumor have a low risk (2-6%) of synchronous UUT carcinoma (308, 309).

2.4.4.2 Risk factors
There are certain factors associated with a greater risk of developing UUT cancers i.e. genetic predispositions such as hereditary nonpolyposis colon cancer and environmental exposures including a history of bladder cancer, cigarette smoking, chronic UTIs and overuse of analgesics (28, 31). Historically, UUT carcinoma “amino tumors” were related to occupational exposure to carcinogenic aromatic amines (29). “Several studies have revealed the carcinogenic potential of aristolochic acid contained in Aristolochia fangchi and Aristolochia clematis which causes a specific mutation in the p53 gene, which occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy” (29). Recent molecular toxicological studies have claimed that the Balkan, Taiwanese, and Chinese herbal nephropathies are probably the same environmental disease (310, 311).

2.4.4.3 Histology
The vast majority of UUT carcinomas are low stage, slowly growing, tumors. On the other hand pedunculated or diffusely infiltrating tumors are less common, accounting for approximately 15% of UUT carcinomas but these types tend to behave more aggressively. Cancers with micro-papillary, clear cell, neuroendocrine or lymphoepithelial morphological variants correspond to high-grade tumors (312).

Squamous cell carcinoma of the UUT is rare and represents < 10% of pyelocalyceal tumors and usually is associated with chronic inflammatory and infectious diseases arising from urolithiasis (29). Other histological subtypes are adenocarcinoma (< 1%), small cell carcinoma, and sarcoma (29, 313).

The TNM classification for upper urinary tract urothelial carcinoma is presented in Table 6 (314).
### Table 6. TNM classification for upper urinary tract urothelial carcinoma.

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscle</td>
</tr>
<tr>
<td>T3 (Renal pelvis)</td>
<td>Tumor invades beyond muscularis into peripelvic fat or renal parenchyma</td>
</tr>
<tr>
<td>T3 (Ureter)</td>
<td>Tumor invades beyond muscularis into periureteric fat</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent organs or through the kidney into perinephric fat</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single lymph node 2 cm or less in the greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### 2.4.4.4 Presentation

Hematuria is the most common symptom found in the diagnosis of UUT carcinoma (75–82 % of cases) (315). Hematuria may be microscopic or gross (macroscopic). The established definitions of microscopic hematuria nowadays use threshold values of ≥3 RBCs per high-power field (316, 317).

Pain is non-specific and is usually related to ureteral obstruction or locoregional tumor extension. Irritative or infectious symptoms are additional non-specific symptoms. A palpable mass is a sign of advanced disease. An asymptomatic presentation is also possible when hematuria or obstruction are detected incidentally or during follow-up of high risk patients. In many patients with microscopic hematuria, no specific pathological etiology is found. Usually the most common causes behind microscopic hematuria are UTI, benign prostatic hyperplasia and urolithiasis. Nevertheless, UT malignancy is found in up to 5% of patients with asymptomatic microscopic hematuria compared to 30-40% malignancy rates in patients presenting with macroscopic hematuria (317, 318). In addition, it has also been stated that asymptomatic microscopic hematuria in patients who are taking anticoagulant drugs requires urologic and nephrologic evaluation, regardless of the type or level of the anticoagulant therapy (298).
2.4.4.5 Initial evaluation
According to the AUA guideline, a dipstick reading suggestive of hematuria is too nonspecific and should not lead to imaging or further investigation without the confirmation of three or more red blood cells per high power field (298).

Basic laboratory tests, e.g. white blood cell count and the evaluation of renal function by assessing glomerular filtration rate, serum creatinine, and blood urea nitrogen, are recommended in the initial evaluation along with the assessment of the medical history and clinical status. After benign causes of asymptomatic microscopic hematuria have been excluded, e.g. infection or contamination, a urologic evaluation is undertaken. Cystoscopy remains a cornerstone of the urologic evaluation of patients with hematuria because of its efficacy and safety profile and is recommended by the AUA for all asymptomatic microscopic hematuria patients older than 35 years (298).

2.4.4.6 Guidelines for imaging patients with hematuria
Patients with macroscopic and symptomatic microhematuria should undergo a prompt and full evaluation. There are however controversies related to the algorithms in the evaluation of asymptomatic hematuria between different guidelines.

It is widely accepted that US, IVU and KUB all have lower sensitivities than multidetector CTU, which has the highest sensitivity and specificity in the evaluation of patients with hematuria. The role of MRU is still unclear because of the limited amount of data, nevertheless MRU is accepted as a substitute when CTU is contraindicated or undesirable in all guidelines.

Guidelines and available practice patterns for the evaluation of hematuria vary by location, specialty, and organization. Most of the guidelines were generally developed after a systematic review of the literature, evaluation of evidence-based data when available, and consensus of expert opinions when evidence-based data were insufficient (298). The National Institute for Health and Clinical Excellence performed a meta-analysis on hematuria in 2006 yet failed to draft solid recommendations due to the lack of evidence. Economic evaluations may favor ultrasound followed by CT for patients with a negative test, but found to have persistent hematuria during follow-up screening; this may be a cost-effective approach, yet decisions should be made on the basis of each individual patient (316). This outdated guideline will not be further discussed.

a. The American College of Radiology (ACR) Appropriateness Criteria® (revised 2014)
In the ACR guideline, it is stated that more than three red blood cells per high-power field on two of three properly collected urinalysis specimens warrant some type of imaging to evaluate the upper tracts (319). According to the ACR, imaging is not usually needed in young women with simple cystitis and whose hematuria resolves after successful therapy. Patients who have clear-cut evidence of glomerulopathy should undergo a chest X-ray and kidney US before biopsy (for patients with disease of renal parenchyma as the cause of hematuria, the rating is 8 on a scale of 1-9) (320) and also to screen for renal morphologic abnormalities. Although ACR states that there is no universal agreement about the optimal imaging work-up of hematuria, ACR has given its highest rating to CTU (rating 9), followed in descending rank order by, retrograde pyelography is rated 6, US and MRI both 5 and finally IVU 1.

In the summary of the recommendations, ACR states: “Although MRI is an excellent technique to evaluate the renal parenchyma for masses and other abnormalities, it is inferior to CTU and IVU in detection of small stones and urothelial lesions” (320). Also as the ACR summarizes that although the sensitivity of MRU in detecting urothelial lesions remains under investigation, it claims that “at present MRU is not believed to be the equivalent of either IVU or CTU” but this view is based on a reference to only two old review articles (167, 321).
In patients with impaired renal function, or contraindications to CTU or MRU, or suboptimal CTU or MRU, the ACR states that retrograde pyelography may be a reasonable adjunct to cystoscopy. It is also worthwhile mentioning that the ACR does not limit imaging according to the patient’s age.

b. American Urological Association (AUA; revised 2012)
The AUA recommends that asymptomatic microhematuria should prompt a urologic evaluation when benign causes have been ruled out. Cystoscopy is indicated routinely only in patients >35 yrs. old and if younger than that, only at the discretion of the physician. The initial evaluation should include a radiologic evaluation regardless of age, specifically multi-phasic CT scan because of its consistently high sensitivity and specificity. The panel acknowledges that the use of US alone, or in combination with IVU, is an alternative imaging strategy but note that it is a less optimal option for imaging because these techniques do not reliably produce diagnostic certainty. According to the expert opinion, whenever the visualization of the collecting system detail is deemed imperative, a combination of MRI with retrograde pyelograms provides alternative evaluation of the entire upper tract, e.g. in patients with compromised renal function. When both CTU and MRU are contraindicated, a combination of unenhanced CT and retrograde pyelography might be helpful. Otherwise and in general, the panel does not advocate the routine use of retrograde pyelography (322).

c. Canadian Urological Association (CUA; 2008)
In contrast to the previous guideline, the CUA states that US, IVU and CT are all imaging modalities acceptable for the evaluation of the patient with microscopic hematuria. “However, taking into consideration patient safety (ionizing radiation and exposure to contrast), availability, and cost, it is recommended that US be used as the imaging test of first choice. CT and IVU are justified when additional tests are believed to be indicated” (323). All patients with microscopic hematuria should be investigated by urine cytology and imaging of the UUT (323). Cystoscopy is reserved for patients > 40 years of age, or for those with positive or atypical cytology, or any patient with the presence of any of the following risk factors: smoking history, occupational exposure to chemicals or dyes, history of irritative voiding symptoms, analgesic abuse with phe-nacetin, history of pelvic irradiation, or cyclophosphamide exposure.

On the other hand, in the most recent guideline for postoperative surveillance of UUT urothelial carcinoma (2013), the primary surveillance method of choice is stated to be CTU. In contrast, the ipsilateral UUT should be assessed by ureteroscopy and selective cytology or biopsy in all patients following nephron-sparing procedures and not by CTU because it lacks high sensitivity according to one study referred to in the guideline (324).

d. European Society of Urogenital Radiology (ESUR CTU Working Group; 2008)
Similarly to the CUA, US is recommended as the first-line imaging modality for hematuria in patients who have a low to medium pretest probability of UUT carcinoma regardless of age, with CTU reserved as a problem solving test if the traditional work-up remains negative and significant undiagnosed symptoms persist (152). The patients with the highest risk are defined as patients with macrohematuria and age > 40 yrs. It is also stated that CTU can be justified as a first line test for the upper and lower urinary tract in hematuria patients with a high pre-test probability for UC. Important risk factors include age >40 years, macroscopic hematuria, smoking, history of GU malignancy, and occupational exposure. The risk from the use of radiation is relatively less important in such high-risk groups and any comprehensive two- or three-phase CTU protocol can be performed (152).
Furthermore, the ESUR guideline suggests differentiated approaches to CTU protocols: if the clinical situation is supposedly benign in nature e.g. “depiction of anatomical variants of the urinary system, iatrogenic ureter trauma, CTU as add-on to evaluation of acute flank pain”, a limited one split-bolus combined nephrographic-excretory phase is recommended. For “more comprehensive patient evaluation when CTU is used as a problem-solving test e.g. chronic symptomatic stone disease, intervention planning, complex infections, urinary diversions, and clinical settings with low pre-test probability of malignant disease, such as the evaluation of hematuria in younger patients or assessment of the urinary tract in patients with other abdominal tumors or tumor-like conditions”: In these situations, a low-dose, split-bolus, two-phase CTU examination can be performed by adding an unenhanced phase (152).

The triphasic protocol is reserved for patients with a high risk or high test probability of UUT tumors. These situations include macroscopic hematuria, hydronephrosis (malignant cause), medullary and papillary necrosis.

e. European Association of Urology (EAU; 2015)
The guideline states that CTU has the highest diagnostic accuracy for high-risk patients but does not take any standpoint on different possible imaging protocols. On the other hand, the EAU guideline states that CTU is generally preferred over MRU for diagnosing UUT carcinomas and that the sensitivity of MRU is 75% for tumors < 2 cm based on a biased study results (186) as previously discussed.

The recommended diagnostic pathway summary is as follows: “urinary cytology should be performed as part of a standard diagnostic work-up; cystoscopy should be done to rule out concomitant bladder tumor; CTU must be part of the diagnostic work-up; diagnostic ureteroscopy and biopsy should be performed, certainly in cases where additional information will impact treatment decisions and retrograde ureteropyelography is an optional tool for the detection of UUT carcinoma” (29).

The guidelines take into consideration not only the difference in cost and radiation burden of the various radiologic modalities, but also the disease prevalence and the risk profile of the individual patient (325). In this model which in this respect is similar to ESUR guideline, CTU is assessed as the primary investigational method of choice for high-risk patients, i.e. patients aged >50 yrs. with macrohematuria. CTU is also recommended but only as a second line investigation in medium risk patients >50 yrs. with microscopic hematuria or ≤50 yrs. with macrohematuria If first line US is negative and there is a risk or persisting hematuria. Patients with low risk and microhematuria and ≤50 yrs. are recommended only to be screened by US as the first line investigation and if normal, no further evaluation is needed. A step further into the justification of the use of CTU is suggested through the introduction of a scoring system of known risk factors for urologic malignancies but this quantification system still needs to be validated.

MRU is stated to have a high contrast resolution and has the possibility for better tissue characterization. However, MRU is costly, technically demanding, and not widely practiced. Therefore, MRU expertise is available only in specific dedicated centers (325). It is recognized in these guidelines that there are hardly any comparative data on the role of MRU in hematuria. Radiologists involved in the diagnosis of UUT carcinoma are required to have wide knowledge of tumor behavior, prognosis and follow-up protocols.
2.4.4.7 Findings at imaging

The majority of UUT tumors are papillary with a broad base morphologic structure. Pedunculated or diffusely infiltrating tumors are less common. Infiltrating tumors are characterized by thickening and induration of the ureteral or renal pelvic wall and further infiltrating adjacent structures (326). Loss of renal sinus fat and abnormal enhancement of the adjacent parenchyma are signs of a T3 tumor while T4 tumors show a perinephric extension. In the MRI images, small size, peripheral location, low intratumoral signal intensity on T2-weighted images as well as low-level enhancement were found to be associated with low-grade papillary carcinomas (327). Nevertheless, the appearance does not correlate with tumor histology or grade (161). Early UUT carcinoma might be seen as a small defect in the excretory phase or as only a wall thickening (161, 328). UC will often show early enhancement in the arterial phase images, making the inclusion of an arterial phase into protocols extremely useful (16). Fat stranding around the ureter has traditionally been associated with infectious ureteritis or urinary tract infections. However, it might also represent an extramural spread of tumor (30). Hydronephrosis and hydroureter in the presence of an enhancing mass are highly suggestive of tumor. Tumors that present as a stricture will usually be associated with soft-tissue thickening (17). In the MRI images, tumors are well demonstrated in the dilated UT due to the higher signal intensity of the urine in the T2-weighted images and the lower signal intensity of tumors (Figure 10). However, UC is nearly isointense to renal parenchyma in both T1- and T2-weighted images, emphasizing the importance of using gadolinium contrast material if one wishes to assess properly the tumor extent (30, 329).

![Figure 10](image-url)

*Figure 10.* Patient with microhematuria and hydronephrosis in the ultrasound assessment. T2-weighted MR image shows isointense tumor filling the distal ureter with no stranding in the surrounding fat (right sided image, arrow). Left sided image shows hydronephrosis and atrophied kidney with synchronous small tumor (arrow).

2.4.4.8 Follow-up

Surveillance regimens for patients with diagnosed UUT malignancy are based on cystorenoscopy and urinary cytology for > 5 years. “Stringent follow-up is mandatory to detect metachronous bladder tumors, local recurrence, and distant metastases” (29). Intravesical recurrence after radical nephroureterectomy to treat UUT carcinoma has a median time of 22 mo. (range 6.7-56.5) (330). A meta-analysis of the available data identified the following significant predictors of recurrence: patient-specific predictors i.e. male gender, previous bladder cancer and preoperative chronic kidney disease; tumor-specific predictors i.e. positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage and necrosis; treatment-specific predictors were laparoscopic approach, extravesical bladder cuff removal and positive surgical margins (330). Oncologic follow-up of high risk patients with UUT carcinomas is conducted according
to tumor stage and grade, location and treatment modality thus reflecting the risk of recurrence over time (331). The EAU recommends CT monitoring yearly after radical nephroureterectomy in non-invasive disease and half yearly in invasive cases for at least 5 yrs. A more intensive follow-up program is recommended after conservative endoscopic treatment with the addition of cystoureteronephroscopy.

In one study, those patients with macrohematuria, whose initial evaluation was negative, approximately 80% of cases remained symptom free at approximately 7 yrs. follow-up whereas <10 % had recurrence of symptoms and were diagnosed with a urological malignancy (332). In another study, men who had complete and negative evaluations for asymptomatic microhema-
turia displayed little risk (<1%) of subsequently developing a UT malignancy (333).

2.4.5 Miscellaneous

2.4.5.1 Amyloidosis
Amyloidosis is a rare, usually systemic disease although some 10%-20% of cases can be localized. Amyloidosis is caused by extracellular deposition of fibrillar protein amyloid of beta-structure in organs or tissues. It is a condition affecting men more often than women. Secondary amyloidosis can be associated with a range of diseases including rheumatoid arthritis, multiple myeloma, chronic infections or inflammations, Waldenstrom’s macroglobulinemia or familial Mediterranean fever (334, 335). Imaging findings tend to be nonspecific. Amyloidosis of the UT, although rare, is more often reported in the urinary bladder and very rarely in the UUT with radiographic and endoscopic appearances mimicking those of carcinoma (336, 337). Amyloid lesions may be associated with diffuse soft-tissue thickening, low attenuation and slowly pro-
gressive calcifications. A biopsy is needed before it is possible to make a diagnosis (338).

2.4.5.2 Ureteritis cystica
Ureteritis cystica manifests as cystic areas of glandular metaplasia associated with chronic urothelial inflammation (339). Numerous 2-3 mm defects of a near uniform size can be present in the ureter and up to 2 cm in the renal pelvis. Radiographically, a differential diagnosis of multiple transitional cell tumors, ureteral pseudodiverticula, nonopaque calculi, polyps, papill-
ary tumors, vascular impressions, tuberculosis, iatrogenic gas bubbles, gas-forming microor-
ganisms, and submucosal hemorrhage can be considered with an appropriate clinical correla-
tion (339, 340).

2.4.5.3 Retroperitoneal fibrosis
Aberrant “fibro-inflammatory tissue develops usually around the infra-renal portion of the ab-
dominal aorta and the iliac arteries and leading to entrapment of the neighboring structures such as the ureters causing hydronephrosis” (341, 342). Idiopathic retroperitoneal fibrosis ac-
counts for more than two out of every three cases. It is an immune-mediated disease, which can either be isolated, associated with other autoimmune diseases, or arises in the context of a mult-
focal fibro-inflammatory disorder, recently renamed as IgG4-related disease. The remaining one out of every three subjects will have a secondary cause such as neoplasm, infection, trauma, radiotherapy, surgery, or exposure to certain drugs (342). The diagnosis of retroperitoneal fibrosis can be readily made by either CT or MRI, although neither technique can reliably differenti-
ate between idiopathic or secondary fibrosis, therefore biopsy is recommended (342).
2.4.5.4 Other urinary and extraurinary causes
Tumors in close vicinity to the UUT can compress or infiltrate this tissue i.e. cancers of the kidney, bladder, prostate, gastrointestinal tract and gynecological cancers. Infections from the gastrointestinal tract e.g. diverticulitis or Crohn’s disease can rarely fistulate also into the UUT or the inflammation can extend transmurally, leading to obstruction and hydronephrosis.
3 Aims of the study

The general aim of this thesis was to compare the performance of modern UUT cross-sectional imaging modalities (i.e. CT and MRI) and to assess the feasibility and clinical role of MRU in the evaluation of the UUT in adults.

The specific aims were:

1. to compare the usefulness of T2-weighted sequences with T1-weighted excretory MRU in the evaluation of patients with acute flank pain.

2. to compare MRU with unenhanced helical CT in patients with acute flank pain

3. to evaluate the visualization of the UUT with 3.0T MRU compared to CTU in patients with obstruction and in high risk patients for developing a UUT malignancy.
4 MR Urography in Evaluation of Acute Flank Pain: T2-Weighted Sequences and Gadolinium-enhanced Three-dimensional FLASH Compared with Urography

4.1 ABSTRACT

4.1.1 Objective
The aim of this study was to compare the usefulness of breath-hold heavily T2-weighted sequences with gadolinium-enhanced three-dimensional fast low-angle shot (3D FLASH) MR urography in the evaluation of patients with acute flank pain.

4.1.2 Subjects and methods
Forty consecutive patients with symptoms of acute flank pain underwent MR urography followed immediately by excretory urography. Heavily T2-weighted (combined thin-slice half-Fourier acquisition single-shot turbo spin-echo [HASTE] and thick-slab single-shot turbo spin-echo) and 3D FLASH sequences were evaluated separately and independently by two experienced radiologists for the presence, cause, level, and degree of obstruction. Interobserver agreement was calculated using the kappa statistic. Excretory urography and the final clinical diagnosis were used as reference.

4.1.3 Results
Twenty-six patients were found to have unilateral obstruction caused by ureteral stones. Both MR urography methods were excellent for detecting obstruction. In the detection of stones 3D FLASH was superior, with a sensitivity of 96.2% and 100% and specificity of 100% and 100% for observers A and B, respectively, compared with a sensitivity of 57.7% and 53.8% and a specificity of 100% and 100%, respectively, for T2-weighted sequences. The best degree of obstruction was seen with 3D FLASH, and the interobserver agreement was excellent for stone detection (κ = 0.97).

4.1.4 Conclusion
T2-weighted sequences alone are not sufficient for examining patients with acute flank pain. However, the combined use of both T2-weighted and 3D FLASH sequences will ensure better confidence in the evaluation of acute suspected renal colic. MR urography can replace conventional excretory urography when the latter is contraindicated or undesirable.

4.2 INTRODUCTION
For many years excretory urography was the technique used to examine patients with acute flank pain. Functional and anatomic details are provided by this imaging technique. The use of ionizing radiation and contrast material are the major drawbacks of excretory urography. Limitations also include the inability to visualize radiolucent stones and the possible obscuring of small stones by superimposed bowel and bony structures.

Recently, the use of MR urography using heavily T2-weighted turbo spin-echo sequences such as rapid acquisition with relaxation enhancement (RARE) and half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences has been described in patients with urinary tract
High-resolution images can be achieved with breath-hold and rapid acquisition sequences. HASTE and RARE can show acute urinary obstruction and perirenal high-intensity signals. However, information about renal function is not provided, small stones are difficult to detect, and a nondilated urinary tract is not fully visualized. The use of a paramagnetic contrast agent permits the evaluation of renal excretory function and better visualization of the nondilated urinary tract. However, to our knowledge, there are no prospective clinical studies comparing T2-weighted and rapid gadolinium-enhanced sequences to evaluate patients with suspected acute renal colic.

The aims of this study were to define the clinical value of MR urography in the evaluation of patients with acute flank pain with reference to conventional excretory urography and to compare the diagnostic accuracy and interobserver agreement of heavily T2-weighted (thin-slice HASTE and thick-slab turbo spin-echo) sequences with gadolinium-enhanced three-dimensional fast low-angle shot (3D FLASH) imaging.

4.3 SUBJECTS AND METHODS

4.3.1 Study Design
During the study period from April 1999 through December 1999, all patients who presented to the emergency department of our hospital with symptoms of acute flank pain, and for whom excretory urography was planned as an emergency examination, underwent MR urography followed immediately by excretory urography. Patients with intermittent symptoms of flank pain were included only if they had experienced an attack of acute flank pain less than 72 hr before seeking medical attention. Patients who presented to the emergency department during the night underwent imaging the next morning. Children, pregnant women, and patients with pacemakers, metallic implants, or severely impaired renal function were excluded. The study was approved by the ethics committee at our hospital, and informed consent was obtained from all patients.

Patients
A total of 40 patients were prospectively evaluated. During the study period, three patients were excluded. In one patient, the obstruction resolved during MR urography examination, and a small distal ureteral stone passed into the urinary bladder (confirmed on sonography). In another patient, 3D FLASH sequence was not performed because of equipment-related technical difficulties. In the last patient, MR urography could not be performed because of the patient’s extreme obesity. In addition, three patients refused to participate in the study. A total of 80 kidneys were examined. Before presentation to our hospital, the duration of symptoms was less than 72 hr in 34 patients (85%), and six patients (15%) had experienced intermittent symptoms during a period ranging from 4 to 14 days. Nevertheless, all patients had acute flank pain symptoms during the 24 hr before presentation to the emergency department. Data regarding patient characteristics, relevant laboratory test results, duration of symptoms, and timing and duration of imaging are presented in Table 7.
4.3.2 Imaging Methods

MR imaging was performed using a 1.5-T scanner (Magnetom Vision; Siemens, Erlangen, Germany) with a phased array body coil. Patients were asked to void before MR urography examination. Otherwise, no specific preparation was required, and no external compression was applied. Breath-hold sequences were used. Both two-dimensional T2-weighted MR urography and 3D T1-weighted MR urography were performed in coronal orientation.

T2-weighted MR urography was performed with thin-slice (fat-suppressed HASTE; TR/TE, 11.90/95; flip angle, 150°; slice thickness, 3-6 mm; matrix, 240 × 256; acquisition time, 15 sec) and thick-slab (fat-suppressed single-shot turbo spin-echo; 2800/1100; flip angle, 150°; slab thickness, 40 mm; matrix, 240 × 256; acquisition time, 7 sec) acquisitions. Field of view was adjusted individually to accommodate different patient sizes. HASTE was also performed in axial orientation (7- to 9-mm slice thickness) to cover the entire abdomen and retroperitoneal space.

T1-weighted MR urography was performed with gadolinium-enhanced 3D FLASH acquisition (4.6/1.8 msec; flip angle, 30°; effective slice thickness, 1.75 mm; field of view, 400 mm; matrix, 200 × 512; acquisition time, 23 sec). Three-dimensional FLASH was also performed in sagittal orientation on the affected side when considered necessary.

A low-dose diuretic injection of 0.1 mg/kg of body weight (total individual dose not exceeding 10 mg) of furosemide (Furesis; Orion, Espoo, Finland) was used to enhance excretion 30-60 sec before the administration of contrast material. Three-dimensional FLASH sequences were routinely repeated 5 and 15 min after the administration of 0.1 mmol/kg of body weight of gadopentatate dimeglumine (Magnevist; Schering, Berlin, Germany), and delayed follow-up was performed when necessary. The total MR urography examination time was calculated starting with the beginning of the first localizing sequence and ending at the acquisition of the last 3D FLASH sequence. The total imaging time of T2-weighted sequences was approximately 6 min, and the total imaging time of all MR urography sequences, if excretion was not delayed, was approximately 25 min.

Maximum-intensity-projection (MIP) images, and occasionally multiplanar reconstruction and original source images, were available on films for evaluation, and both observers had access to source images from the workstation, to review if needed.
Excretory urography was performed with an IV bolus injection of 1.5 mL/kg of body weight (total dose not exceeding 100 mL) of iohexol (300 mg I/mL Omnipaque; Nycomed, Cork, Ireland). No abdominal compression was used. An unenhanced radiograph of the abdomen was initially obtained followed by full-size radiographs at 5 and 15 min after the administration of contrast material. Oblique images of the ureterovesical junction were obtained, if needed, to better visualize the distal ureters. The examination was completed if no obstruction was detected. If obstruction was noted, follow-up radiographs on the side of obstruction were obtained at 30 and 60 min, and additional radiographs were obtained as needed until the cause or level of obstruction was identified. The duration of excretory urography examination was calculated starting with the injection of contrast material and ending at the retrieval of the last diagnostic image.

Image Interpretation

The excretory urography examinations were interpreted in consensus by a radiologist and a urologist for the presence, cause, degree, and level of obstruction and for the extravasation of contrast material. If the interpretation of the excretory urography was questionable, or the cause of obstruction could not be definitely determined, the presence of a ureteral stone or obstruction was confirmed on helical CT or by passage of the stone. The largest diameter of a stone, if present, was measured directly from hard-copy images and was reported in millimeters after subtraction of a magnification factor of 1.09. After reviewing all patient charts, the final conclusive diagnosis was made on the basis of a combination of clinical and imaging results and the findings of interventional examinations or procedures.

The MR urography investigation and reconstructions were performed by a radiologist who was not involved in analyzing MR urograms. T2-weighted and 3D FLASH sequences were evaluated separately and independently by two experienced radiologists for the presence and cause of obstruction. A stone was defined as a complete or partial filling defect in the urinary tract. Other causes of obstruction, if present, were defined as extrinsic, intrinsic, or indeterminate. The degree of obstruction was assessed subjectively as not present, mild, moderate, or severe. The following criteria were used to assess the degree of obstruction on both excretory and MR urography: no obstruction (no distension of the intrarenal collecting system or ureter; no delay in excretion; absence of columnization [subsequently described]), mild obstruction (the ureter visualized as a persistent column of signal intensity or contrast material, proximal to the level or cause of obstruction on the symptomatic side; mild prominence of the renal pelvis; the whole urinary tract is visualized on 15-min urogram), moderate obstruction (enlargement of the calyces with blunting of the calyceal fornices, but the intruding shadows of the papillae, although flattened, are still easily seen; delayed urogram), severe obstruction (increasingly dense nephrogram with markedly delayed excretion; obvious dilatation of the ureter; dilatation and rounding of the calyces with obliteration of the papillae).

Also, the presence of extravasation and perirenal high-intensity signal and the level of obstruction were noted. High-intensity signal was subjectively evaluated to be absent, mild, or substantial. The level of obstruction was classified as ureteropelvic junction; proximal, middle, or distal third of the ureter; or ureterovesical junction. The technical quality of MR urograms was judged as good, suboptimal, or inadequate on the basis of the completeness of visualization of the urinary tract and the presence of disturbing artifacts. Observers were aware of the side of the symptoms. No other clinical data or information from other studies were provided, and the observers were not aware of the clinical outcome.
4.3.3 Statistical Analysis
The sensitivity, specificity, and overall accuracy of both T2-weighted and 3D FLASH were calculated for the two observers separately. The kappa statistic was used to measure interobserver and intertechnique agreement. Strength of agreement was classified as slight (≤0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), or excellent (0.81-1.0) (351).

The correlation of high-intensity signal with the degree of obstruction seen in excretory urography was calculated using Spearman's correlation coefficient, which was considered to be significant if the p value was less than 0.05.

Statistical analysis was performed with a PC statistical software package (SPSS version 9.0 for Windows; Statistical Package for the Social Sciences, Chicago, IL).

4.4 RESULTS
At final diagnosis, 26 patients (65%) were found to have ureteral stones causing unilateral obstruction. Other final diagnoses were acute appendicitis (n = 1), acute ulcerative colitis (n = 1), urinary tract infection (n = 1), and biliary colic (n = 1). In the other patients (n = 10), the cause of flank pain remained undetermined, and the symptoms resolved on clinical follow-up. Excretory urography revealed a definite stone in 22 patients. In four patients, excretory urography was interpreted as indeterminate, and the presence of a stone was later confirmed on CT in three patients. In the fourth patient, the cause of obstruction could not be visualized on CT. A week later the patient passed a stone, after which the clinical symptoms resolved, and the final clinical diagnosis was ureterolithiasis.

In 12 patients the stone passed spontaneously. In three patients the stones were treated with extracorporeal shock wave lithotripsy. Five patients underwent ureteroscopy and stone extraction. In another five patients the stone could no longer be visualized on unenhanced abdominal radiographs or excretory urograms. One patient was asymptomatic on follow-up and refused further evaluation; the passage of stone was not confirmed but the clinical and radiologic diagnosis were of a definite small ureteral stone.

All of the MR urograms were judged to be of good technical quality. Gadolinium-enhanced 3D FLASH MR urography was highly accurate in showing stones as intraluminal filling defects. Observer B correctly diagnosed all cases, but observer A did not detect a ureteral stone in one case. Observer A did not see evidence of a definite stone in 11 patients (42%) on heavily T2-weighted sequences, and observer B did not see such evidence in 12 patients (46%) on heavily T2-weighted sequences. All of the missed stones except one were less than 5 mm in diameter as determined by excretory urography, and the grade of obstruction was mild in most of these cases (in 6 cases for observer A and 7 for observer B). The sensitivity, specificity, overall accuracy, and interobserver agreement values for the detection of ureteral stones and obstruction are shown in Table 8.
Table 8. Diagnostic accuracy of MR urography and interobserver Kappa values in the detection of ureteral Stones and assessment of obstruction.

<table>
<thead>
<tr>
<th>Compared Data</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Overall Accuracy</th>
<th>Interobserver κ (±95% CI)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
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<tr>
<td>Detection of stone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-weighted sequences</td>
<td>57.7</td>
<td>53.8</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3D FLASH</td>
<td>96.2</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Assessment of obstruction</td>
<td></td>
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<td>T2-weighted sequences</td>
<td>100</td>
<td>100</td>
<td>98.1</td>
<td>100</td>
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<tr>
<td>3D FLASH</td>
<td>100</td>
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</table>

T2-weighted sequences include half-Fourier acquisition single-shot turbo spin-echo and thick-slab turbo spin-echo sequences. Comparison is based on excretory urography and clinical data. Eighty kidneys were evaluated. CI = confidence interval, 3D FLASH = three-dimensional fast low-angle shot.

The mean size of detected stones on excretory urography was 4.5 mm, ranging from 2 to 15 mm. When measured from 3D FLASH sequence images, the mean size was 4.1 mm (range, 3-7 mm) for observer A and 3.8 mm (range, 2-10 mm) for observer B. The Spearman’s correlation coefficient for stone size compared with excretory urography was 0.48 for observer A (p = 0.02) and 0.37 for observer B (p = 0.06).

The presence of obstruction was correctly diagnosed by both observers with 3D FLASH MR urography in all cases. For T2-weighted sequences, observer A had one false-positive result, and observer B correctly interpreted all cases.

As determined by excretory urography, the degree of obstruction was graded as mild in 10 patients, moderate in 12 patients, and severe in four patients. The degree of intertechnique agreement with gadolinium-enhanced 3D FLASH MR urography was substantial for observer A (κ = 0.78) and excellent for observer B (κ = 0.88). Interobserver agreement was excellent (κ = 0.85). The degree of intertechnique agreement between excretory urography and T2-weighted sequences was only moderate for both observers (observer A, κ = 0.54; observer B, κ = 0.48). Interobserver agreement for T2-weighted sequences was substantial (κ = 0.64).

The level of obstruction was at the ureteropelvic junction in one, the proximal ureter in six, the distal ureter in four, and the ureterovesical junction in 15 patients, as determined by excretory urography. Both the gadolinium-enhanced 3D FLASH MR urography (observer A, κ = 0.87; observer B, κ = 0.90) and T2-weighted sequences (observer A, κ = 0.80; observer B, κ = 0.90) agreed well with the results of excretory urography in the assessment of the level of obstruction.
Extravasation of contrast media was seen on excretory urography in two patients (7.7% of patients with a proven ureteral stone). Extravasation was clearly seen on 3D FLASH MR urography in these patients, and a third patient was found to have minimal extravasation not visualized on excretory urography.

Both observers found perirenal high-intensity signal to be present in 24 patients (92%) with ureteral stones on T2-weighted images. In two patients with intermittent symptoms, high-intensity signal was judged to be absent by both observers. High-intensity signal was also interpreted by observer A to be positive in two patients and by observer B in three patients, in the absence of a stone or obstruction. The sensitivity and specificity of perirenal high-intensity signal in predicting the presence of acute ureteral obstruction was 96% and 92% and 96% and 89% for observers A and B, respectively. Interobserver agreement in the assessment of high-intensity signal was substantial (κ = 0.80). The Spearman’s correlation coefficient between the degree of obstruction on excretory urography correlated significantly with the degree of perirenal high-intensity signal (r = 0.86, p < 0.001 for observer A; r = 0.84, p < 0.001 for observer B).

4.5 DISCUSSION

The usefulness of MR urography using T2-weighted turbo spin-echo sequences has been discussed in several reports (343, 345, 348, 352-357). T2-weighted sequences have been shown to be a rapid, safe, and noninvasive imaging technique that can reliably reveal hydronephrosis (358). The results of our T2-weighted sequences were comparable with those of previously reported studies. O’Malley et al. (359) reported similar results in the detection of obstruction and in evaluating the degree of urinary tract dilatation. For the level of obstruction, we obtained slightly better agreement: 0.80 for observer A and 0.90 for observer B, compared with 0.74 and 0.60 in the study of O’Malley et al. This could be attributed to the different T2-weighted techniques used in these studies. The fact that we used a combination of thin-slice HASTE and thick-slab turbo spin-echo sequences in the same imaging session might have also increased confidence in showing the level of obstruction.

The difficulty in detection of small ureteral stones with T2-weighted sequences is a known limitation of this technique (114, 344, 346). Although the exact level of obstruction was readily recognized, in this study the cause of obstruction could not be seen with confidence in many cases. The other limitations of heavily T2-weighted sequences include insufficient spatial resolution and the inability to obtain functional information. Calyceal, fornical, and infundibular anatomy could not be seen with the same detail as in excretory urography (360). In this context, the use of a paramagnetic contrast agent clearly improves the diagnostic value of MR urography because T1-weighted sequences are capable of revealing even small amounts of gadolinium.

Contrast-enhanced MR urography is a new concept in imaging patients with urinary tract abnormalities. In his initial experimental study, Nolte-Ernsting et al. (14) presented the advantages of this imaging technique in retrieving high-spatial-resolution images in nonobstructed urinary tracts. Also, in contrast to heavily T2-weighted turbo spin-echo sequences, image quality was not influenced by superimposed abdominal fluid collections. Furthermore, the excretory function of the kidneys could be evaluated. The need for a diuretic to optimize the endoluminal concentration of gadolinium and to produce accelerated distension was addressed. The usefulness of this technique has been evaluated in a clinical study of 71 patients using a respiratory-gated T1-weighted spoiled 3D gradient-echo sequence (15). The acquisition time, however, was relatively long, ranging from 6 min 39 sec to 8 min 41 sec. T1-weighted sequences with long acquisition times have also been reported in pediatric urogenital imaging (361).

In our study we used a commercially available ultrafast breath-hold 3D FLASH sequence with an imaging time of only 23 sec to generate high-resolution images in the evaluation of patients with acute flank pain. Gadolinium-enhanced MR urography proved to be highly accurate
in detecting obstruction and determining its cause and level. The results of our study were in concordance with those of Nolte-Ernsting et al. (15), except for higher accuracy in detecting the cause of obstruction. For the detection of ureterohydronephrosis, the sensitivity and specificity were reported to be 90% and 100% (15) with reference to excretory urography. Excellent agreement was also seen in our study for both observers. In the study of Nolte-Ernsting et al., the sensitivity and specificity for the detection of a specific filling defect such as a calculus were 80% and 98%, 64% and 91%, and 84% and 91% for three observers. In the present study both observers identified almost all filling defects correctly. This can be attributed, in part, to our use of a different, ultrafast imaging technique with considerably shorter imaging time, which minimized movement artifacts. Also, we had the advantage of gaining experience with this imaging method on a limited number of volunteers and patients with acute flank pain before this study.

The present study shows the superiority of gadolinium-enhanced MR urography over static-fluid imaging. Functional information was obtained in the same way as with excretory urography, enabling more accurate evaluation of the degree and cause of obstruction. Three-dimensional FLASH sequence, with its short acquisition time, permits repeated series of breath-hold images in optimal orientations, thus providing obvious improvement to the methods previously described by other investigators. The whole urinary tract, including nondilated ureters, can be visualized. The high-resolution images allow good reconstructed image quality. High-quality MIP images and multiplanar reconstructions are of use especially in evaluating the distal ureters. MIP images resemble those of excretory urography, with better spatial resolution than HASTE or thick-slab turbo spin-echo sequences. Also, extravasation can be clearly seen. During this study we were able to visualize the fine anatomic details of the pelvicalyceal system with 3D FLASH sequences (Figure 11), and in some patients we saw calyceal diverticula and papillary blush. We did not, however, conduct systematic side-by-side comparison with excretory urography for these details.

Several issues, however, are to be considered with this new imaging technique. Gadolinium-enhanced MR urography cannot be recommended for the evaluation of pregnant women and is of no use in the evaluation of the urinary tract on the side of the nonexcreting kidney. Furthermore, in cases of severe obstruction and delayed excretion, the long duration of excretory MR urography for revealing the underlying abnormality increases patient and personnel inconvenience. On the other hand, the imaging time is not significantly longer than that of excretory urography. In the present study, if excretion was delayed, the patient was removed from the magnetic tube and the examination was repeated at different intervals, as needed, until the level and cause of obstruction were visible. In this study, 3D FLASH MR urography seemed to slightly underestimate the size of stones, a fact that should be taken into consideration when planning for conservative treatment. Breath-hold techniques also require cooperative patients; therefore, severely ill patients, infants, small children, and possibly the elderly may fail to comply, which results in somewhat poorer image quality.

Unfortunately, our patient population did not include obstructive disease entities other than ureteral stones; this exclusion can be considered a limitation of this study. However, in our prospective study the patient material was consecutive and represents clinical reality at our institution.

The false-positive interpretation of perirenal high-intensity signal, in a minority of cases, was suggestively attributed to chemical-shift misregistration artifacts. Otherwise, misregistration and pulsation artifacts, occasionally noted in all sequences, were not found to interfere with the interpretation of source images. Occasionally, we noted turbulence-induced artifacts in the pelvicalyceal system, probably caused by diuretic-induced diuresis, especially in the first excretory acquisitions. These artifacts were not visible on subsequent sequences. In some cases, we were also able to see signal void lines in the urinary bladder originating from the ureteral orifices and caused by a ureteral jet, which we found to be an additional useful sign in excluding obstruction.
The amount of diuretic used was relatively small but was considered sufficient to optimize image quality. However, one patient with severe obstruction caused by a large stone had sudden exacerbation of acute flank pain symptoms requiring analgesic medication immediately after diuretic injection, which we considered to be a complication. The pain rapidly subsided, and the patient continued with the MR urography examination.

T2-weighted sequences revealed renal, ovarian, or hepatic cysts in 12 patients. A large gallbladder stone was also visualized in one patient. These findings were believed to be of no acute clinical value. In one patient, the cause of acute pain was attributed to gallbladder stones clearly visualized on T2-weighted images. The nondilated common bile duct with no filling defects was also visible. These findings were later confirmed using sonography and surgery. In another patient, mild right-sided colonic and pericolic edema with a small amount of ascites were noted by both observers. A possible colitis was suggested. The final diagnosis was ulcerative colitis proved by biopsy.

The economic aspects of MR urography have been discussed in detail in the editorial comments by Hattery and King (360). We agree that emphasis must be first on the patient and the quality of care, and second on economics. Nevertheless, the high cost of MR urography and its limited availability play major roles in restricting its wide use. We believe that the selection of patients with clinically atypical symptoms, and the simultaneous use of other sequences immediately after gadolinium injection to examine the whole abdomen, thus providing a complete one-step diagnostic workup, could justify the use of MR urography. At our hospital, the calculated cost of contrast-enhanced MR urography is approximately $500, compared with $97 for excretory urography and $185 for unenhanced CT. In our practice, we now recommend the use of contrast-enhanced MR urography for cooperative children and young adults. By reducing the field of view to a minimum, we are able to reduce the imaging time of 3D FLASH to 15 sec, which seems to be tolerable to some older children.

Unenhanced CT is becoming increasingly accepted as the first imaging “test of choice” in the evaluation of patients with acute flank pain. CT is shown to be a safe, rapid, and highly accurate technique in the detection of ureteral stones, allows precise determination of stone size and location, and also shows secondary signs of obstruction (362). CT also enables the diagnosis of a wide range of disease entities that can result in flank pain and can confidently exclude many serious diseases. A well-known limitation of this technique is the difficulty in differentiating distal calculi from pelvic phleboliths (148). Also, the exposure to ionized radiation is higher than with urography (119). In this context, children and young adults will benefit most from the MR urography advances. In obstetric patients, T2-weighted sequences might provide sufficient information and thus eliminate the need for the use of contrast material and ionized radiation. Other future roles of MR urography could include use in showing the anatomic details of the pelvicalyceal systems and ureters and use in the functional evaluation of kidneys, especially in patients with kidney failure or contrast allergy. Another advantage of MR urography might be the evaluation of abdominal organs in cases of atypical symptoms with suspicion of an inflammatory process, due to the superiority of T2-weighted sequences in revealing edema and even small amounts of ascites.

In conclusion, MR urography is a valuable imaging technique for examining patients with acute flank pain. T2-weighted sequences can rapidly reveal the presence of perirenal high-intensity signal, obstruction, and level of obstruction, and thus rapidly provide information for diagnosing the urinary tract abnormality. The addition of gadolinium-enhanced sequences significantly increases the diagnostic efficacy of MR urography. Further investigations are needed to evaluate the usefulness of MR urography in comparison with the diagnostic value of helical CT in the examination of patients with acute flank pain.
Figure 11. 52-year-old man with right-sided flank pain. Half-Fourier acquisition single-shot turbo spin-echo maximum-intensity-projection (MIP) image (a) shows obstruction and substantial perirenal high-intensity signal (solid arrow). Proximal ureteral duplication is also visualized (open arrows). Peripelvic cysts are visible on opposite side (arrowheads). Excretory urogram (b) shows obstruction and duplication (arrows). Three-dimensional fast low-angle shot (FLASH) MIP image (c) shows obstruction and duplication (arrows), and fine anatomic details are better visualized than on a and b. Three-dimensional FLASH MIP source image (d) shows stone (arrow) as partial filling defect in distal ureter. Reprinted with permission from the American Journal of Roentgenology.
5 Patients with Acute Flank Pain: Comparison of MR Urography with Unenhanced Helical CT

5.1 ABSTRACT

5.1.1 Purpose
To compare unenhanced helical computed tomography (CT) and magnetic resonance (MR) urography, by using T2-weighted and contrast material–enhanced T1-weighted imaging to examine patients with acute flank pain, with reference to excretory urography and final clinical diagnosis.

5.1.2 Materials and methods
Forty-nine patients underwent CT, MR urography (with T2-weighted and gadopentetate dimeglumine–enhanced T1-weighted sequences), and excretory urography. CT and MR urographic findings were evaluated separately and independently by two radiologists each (CT, observers A and B; MR urography, observers C and D) for the presence, cause, level, and degree of obstruction. The final conclusive diagnosis was based on the combination of excretory urographic, clinical, and interventional results.

5.1.3 Results
At final diagnosis, 32 (65%) patients were found to have ureteral stones causing unilateral obstruction. In ureteral stone detection, the sensitivity and specificity of CT were 90.6% (29 of 32 patients) and 100.0% (17 of 17 patients), respectively (observer A) and 90.6% (29 of 32 patients) and 94.1% (16 of 17 patients), respectively (observer B), while those of MR urography were 93.8% (30 of 32 patients) and 100.0% (17 of 17 patients), respectively (observer C) and 100.0% (32 of 32 patients) and 100.0% (17 of 17 patients), respectively (observer D). Spearman correlation coefficients for stone size at CT were 0.76 (P < .001) and 0.75 (P < .001) and at MR urography, 0.49 (P = .005) and 0.51 (P = .004).

5.1.4 Conclusion
In routine clinical practice, CT is the modality of choice in the evaluation of patients with acute flank pain. MR urography is an accurate and suitable alternative imaging technique in selected patients.

5.2 INTRODUCTION

For many decades, conventional excretory intravenous urography was the examination of choice in patients with acute flank pain. Smith et al (115) described the use of helical computed tomography (CT) without contrast material enhancement in patients suspected of having acute ureteric colic. In further studies (53, 116, 119, 363), CT has proved to be superior to excretory urography in demonstrating the cause, level, and size of ureteral stones, and also in providing a differential diagnosis or excluding other serious diseases. CT is now considered the imaging study of choice in evaluating patients with acute flank pain (2, 364, 365).

Magnetic resonance (MR) urography is a more recent imaging concept in evaluating the urinary tract. Investigators in several studies (114, 344, 345, 356, 358, 359, 366) have described the
use of T2-weighted sequences in patients with various urologic abnormalities. T2-weighted sequences have been shown to be rapid, safe, and noninvasive for reliable depiction of urinary tract dilatation and level of obstruction. Nevertheless, the nondilated urinary tract is not visualized, and a tiny calculus may be hidden by the surrounding bright signal from urine (367). Nolte-Ernsting et al (14, 15) described contrast material–enhanced excretory MR urography after low-dose diuretic injection and concluded that this technique is a promising and accurate alternative to excretory urography for imaging the morphology of the urinary tract. Since then, the authors of a few articles (349, 350, 368, 369) have discussed the application of this technique.

The purpose of this study was to compare unenhanced helical CT and MR urography, by using T2-weighted and contrast-enhanced T1-weighted sequences, in examining patients with acute flank pain, with reference to excretory urography and the final clinical diagnosis.

5.3 MATERIALS AND METHODS

5.3.1 Study Design
During the study period of April 1999 to January 2000, all patients who presented to the emergency department of our hospital with symptoms of acute flank pain and for whom excretory urography was planned as an emergency examination underwent unenhanced helical CT followed immediately with MR urography and excretory urography, in that order. Patients with intermittent symptoms of flank pain were included only if they had experienced an attack of acute flank pain less than 72 hours before seeking medical attention. Patients who presented to the emergency department during the night underwent imaging the next morning. Children, pregnant women, patients with claustrophobia, and patients with pacemakers, metallic implants incompatible with MR imagers, or severely impaired renal function were excluded. After reviewing all patient charts, the final conclusive diagnosis was made on the basis of a combination of excretory urographic findings, clinical findings, interventional examination or procedure findings, and clinical outcome. The ethics committee at our hospital approved the study, and informed consent was obtained from all patients.

5.3.2 Patients
During the study period, 55 patients with acute flank pain were referred for excretory urography. Three of these patients were excluded from the study. In the first patient, the obstruction resolved during MR urography, and a small distal ureteral stone passed into the urinary bladder and was confirmed with ultrasonography (US). In the second patient, MR urographic sequences were not performed in full because of equipment-related technical difficulties; and in the third patient, MR urography could not be performed because of the patient’s extreme obesity. In addition, three patients refused to participate in the study. Hence, 49 patients (10 women and 39 men; mean age, 52 years) underwent evaluation according to the study protocol, and 98 kidneys were examined. The mean serum creatinine level was 103 μmol/L (range, 71–158 μmol/L; normal range, 62–105 μmol/L). Before arrival at our hospital, the duration of symptoms was less than 72 hours in 41 (84%) patients, and eight patients had experienced intermittent symptoms during a period of 4–14 days. Nevertheless, all patients had acute flank pain symptoms during the 24 hours before presentation to the emergency department.
5.3.3 Imaging Methods

5.3.3.1 Helical CT
Unenhanced helical CT was performed with a Somaton Plus-S scanner (Siemens, Erlangen, Germany). Two breath-hold clusters of approximately 25 seconds each were obtained, from the top of the kidneys to the bottom of the bladder. Collimation of 5 mm, pitch of 1.4, increment of 3 mm, 120 kV, 160 mA (in 40 patients), and 210 mA (nine patients with body mass index > 27) were used. No specific preparation was required. The total CT examination time was calculated starting with the beginning of acquisition of the first reference scan and ending at the acquisition of helical data.

5.3.3.2 MR urography
MR imaging was performed with a delay of 15–30 minutes after CT, by using a 1.5-T scanner (Magnetom Vision; Siemens) with a phased-array body coil. Patients were asked to void before the MR urographic examination. Otherwise, no specific preparation was required, and no external compression was applied. Breath-hold sequences were used.

T2-weighted MR urography was performed with thin-section (fat-suppressed half-Fourier rapid acquisition with relaxation enhancement [RARE] imaging, with a repetition time msec/echo time msec of 11.90/95, 150° flip angle, 3–6-mm section thickness in coronal orientation, 240 × 256 matrix, and 15-second acquisition time) and thick-slab (fat-suppressed single-shot turbo spin-echo; 2,800/1,100, 150° flip angle, 40-mm slab thickness in coronal and sagittal orientations, 240 × 256 matrix, and 7-second acquisition time) acquisitions. Field of view was adjusted individually to accommodate different patient sizes. RARE imaging was also performed in transverse orientation (7–9-mm section thickness) to cover the entire abdomen and retroperitoneal space.

A low-dose intravenous diuretic injection of 0.1 mg per kilogram of body weight (total individual dose not exceeding 10 mg) furosemide (Furesis; Orion, Espoo, Finland) was used to enhance excretion 30–60 seconds before the administration of contrast material. A T1-weighted gradient-echo sequence (fat-saturated fast low-angle shot [FLASH]; 117/4.1, 80° flip angle, 7–9 mm section thickness, and 16-second acquisition time) was performed in transverse orientation to cover the whole abdomen and retroperitoneal space 20–30 seconds after administration of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany).

T1-weighted MR urography was performed with gadolinium-enhanced three-dimensional (3D) FLASH imaging in coronal orientation (4.6/1.8, 30° flip angle, 1.75-mm effective section thickness, 400-mm field of view, 200 × 512 matrix, and 23-second acquisition time). Three-dimensional FLASH imaging was also performed in sagittal orientation on the affected side of the body, when necessary. Three-dimensional FLASH sequences were routinely repeated 5 and 15 minutes after the administration of contrast material, and delayed follow-up was performed when necessary, as determined by the performing radiologist (M.S.). The total MR urographic examination time was calculated by starting at the beginning of the first localizing sequence and ending at acquisition of the last 3D FLASH sequence. Maximum intensity projection images and, occasionally, multiplanar reconstructions and original source images were available as hard copies for evaluation. Observers had access to the workstation (Vision; Siemens, Erlangen, Germany) to review source images.

5.3.3.3 Excretory urography
Excretory urography was performed after a delay of 15–30 minutes and with an intravenous bolus injection of 1.5 mL/kg (total dose not exceeding 100 mL) iohexol (300 mg iodine per milliliter Omnipaque; Nycomed, Cork, Ireland). No abdominal compression was performed. A radiograph of the abdomen was initially obtained, followed by full-sized radiographs obtained 5
and 15 minutes after administration of contrast material. Oblique images of the ureterovesical junction were obtained, if needed, to better visualize the distal ureters. The examination was completed if no obstruction was detected. If an obstruction was noted, follow-up radiographs were obtained at 30 and 60 minutes on the side of the body on which the obstruction occurred, and further radiographs were obtained as needed until the cause and/or level of obstruction were demonstrated, as determined by the performing radiologist. The duration of the excretory urographic examination was calculated by starting from the injection of contrast material and ending at acquisition of the last diagnostic image.

CT and MR imaging examinations were saved on optical disks, and images were retrieved as needed for further evaluation at dedicated workstations. To evaluate the preference for CT or MR urography from the patients’ point of view, patients were interviewed by the radiologist at the end of each study and were asked to state the preferred investigation and the reason for their choice.

Image Interpretation

Excretory urographic images were interpreted by means of consensus by a radiologist (M.S.) and a urologist (A.H.) for the presence, cause, degree and level of obstruction, and extravasation of contrast material. If a patient had more than one ureteral stone, detection of the stone causing the obstruction was noted. A stone was diagnosed if the contrast material–filled ureter terminated at the level of a high-attenuating structure or a calcification seen on precontrast radiographs. The largest diameter of a stone, if present, was measured directly from hard copies and was reported in millimeters after correction of a magnification factor of 1.09 (magnification = [focus-to-film distance/focus-to-object distance]). Exact correction was problematic because of patients’ different body geometries but has been found to result in improved accuracy (24). For simplicity, in the current study, the longest calculated focus-to-object distance was considered constant for all patients. In cases in which a stone was not visualized on excretory urographic images, the size of stones was based on the actual size of retrieved stones, if available, or on US measurements.

MR urographic and CT investigations and reconstructions were all performed by the same radiologist, who was not involved in analyzing images. CT images were evaluated by two experienced radiologists (S.K., A.M.) (observers A and B) independently. T2-weighted and 3D FLASH MR images were first evaluated separately and independently by two other experienced radiologists (K.P., R.L.V.) (observers C and D). The results of these separate readings have been discussed previously. The whole MR urographic examination was later evaluated independently by the same two observers (C and D). There was a period of approximately 2 months between the first readings (T2- and T1-weighted sequences) and of at least 6 months for the last reading. Each examination was given a different code not known to the observers to preserve patient anonymity. The observers were aware of the side of the body on which the symptoms occurred. No other clinical data or information from other studies was provided, and the observers were blinded to clinical outcome. CT and MR urographic observers were not involved in analyzing excretory urographic images or in obtaining clinical or radiologic data.

Images were evaluated for the presence and cause of obstruction. At CT, a stone was defined as a calcification within the ureteral lumen. At MR urography, a stone was defined as a complete or partial filling defect within the urinary tract. The largest diameter of the stone, if present, was measured at dedicated workstations and reported in millimeters. Other calyceal stones also were noted. Other causes of obstruction, if present, were defined as extrinsic, intrinsic, or indeterminate. The degree of obstruction was assessed subjectively as not present, low grade, or high grade. The following criteria were used to assess the degree of obstruction at MR urography and excretory urography:

1. No obstruction: no distension of the intrarenal collecting system or ureter, with no delay in excretion.
2. Low-grade obstruction: visualization of the ureter as a persistent column of signal intensity or contrast material proximal to the level or cause of obstruction on the symptomatic side, with mild prominence of the renal pelvis and visualization of the entire urinary tract at 15-minute urography.

3. High-grade obstruction: enlargement of the calyces, with blunting of the calyceal fornices, dilatation of the ureter, delayed urography, and increasingly intense nephrogram.

At CT the degree of obstruction was classified as:
1. No obstruction: no distension of the intrarenal collecting system or ureter.
2. Low grade: mild prominence or minimal dilatation of the renal pelvis, with or without mild ureteral prominence.
3. High grade: obvious dilatation of the renal pelvis and intrarenal cavities, with dilatation of the ureter.

In addition, extravasation and perirenal high signal intensity or stranding and level of obstruction were noted. Other secondary signs of obstruction, such as nephromegaly, periureteral and ureterovesical junction edema, and the “tissue rim” sign, were noted. The level of obstruction was classified as the ureteropelvic junction; the proximal, middle, or distal third of the ureter; or the ureterovesical junction. Other possible causes of acute flank pain were also noted. The technical quality of MR imaging and CT examinations was judged as good, suboptimal, or inadequate on the basis of the completeness of visualization of the urinary tract and the presence of artifacts influencing image interpretation and evaluation.

5.3.3.4 Statistical Analysis
The sensitivity, specificity, and overall accuracy of MR urography and CT were calculated for all observers separately. The $\kappa$ statistic was used to measure interobserver and intertechnique agreement. Strength of agreement was classified as slight ($\leq 0.20$), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or excellent (0.81–1.00) (351).

The size of obstructing ureteral stones measured at CT and MR urography was correlated to the final size of the stones by using the Spearman correlation coefficient and was considered significant if $P$ was less than .05. Furthermore, the Spearman correlation coefficient was used to determine whether there was statistical correlation between the findings of stone and obstruction between the paired kidneys of the same patient and with random choice of pairs. Analyses were performed separately for observers A, B, C, and D.

Statistical analysis was performed by using a personal computer statistical software package (SPSS version 9.0 for Windows; SPSS, Chicago, Ill).

5.4 RESULTS
All CT and MR urographic images were judged to be of good technical quality. The actual imaging time for CT was less than 1 minute in all patients. For MR urography, the mean actual imaging time was 56 minutes (range, 25–350 minutes) and for excretory urography was 48 minutes (range, 20–240 minutes).

At final diagnosis, 32 (65%) patients were found to have ureteral stones causing unilateral obstruction. Three of these patients had two ureteral stones each. Other final diagnoses were acute appendicitis (one patient), acute ulcerative colitis (one patient), urinary tract infection (one patient), sactosalpinx and tubal torsion (one patient), and biliary colic (one patient). In all other cases ($n = 12$), the cause of flank pain remained undetermined, and symptoms had resolved at clinical follow-up.

In 21 patients, the stone passed spontaneously (stones were retrieved in 13 patients; in the other eight, the stone could no longer be visualized when controlled by plain abdominal radio-
graphs or excretory urography). In five patients, ureteral stones were treated with extracorporeal shock-wave lithotripsy. Five patients underwent ureteroscopy and stone extraction. The last patient was asymptomatic at follow-up and refused further investigation. The passage of a stone was not confirmed in this patient, but the clinical and radiologic diagnoses were of a definite small ureteral stone.

Because a statistically significant negative correlation was detected between the paired kidneys, which proved to be clearly higher than when the kidneys were randomly paired, in this study, statistical analyses were performed on a per-patient-unit (on the basis of the side of the body on which symptoms of acute flank pain occurred) basis rather than on a per-kidney-unit (two kidneys per patient) basis.

At CT, observers A and B correctly detected the cause of obstruction in 29 patients. Observers had three false-negative findings each, and observer B had one false-positive finding. At MR urography, observer C correctly detected 30 ureteral stones, with two false-negative findings. Observer D correctly interpreted all cases. At CT, a unilateral ureteral obstruction was detected in 30 patients and missed in two patients by observer A. Observer B detected obstruction in 32 patients (including one false-positive finding) and missed an obstruction in one patient. At MR urography, both observers correctly interpreted all cases. The sensitivity, specificity, overall accuracy, and interobserver agreement values for the detection of ureteral stones and obstruction, as compared with the final diagnosis, are shown in Table 9. Other calyceal stones were found at CT in 24 kidneys by both observers and at MR urography in two and eight kidneys by observers C and D, respectively.
Table 9. Diagnostic accuracy of CT and MR urography in detecting ureteral stones and obstruction in 49 patients with acute flank pain.

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<tr>
<th>Compared Data</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Overall Accuracy</th>
<th>Interobserver K Statistics</th>
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<td><strong>CT</strong></td>
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<td>Observer</td>
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<td><strong>MR Urography</strong></td>
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<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Stone</td>
<td>93.8</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(30/32)</td>
<td>(32/32)</td>
<td>(17/17)</td>
<td>(17/17)</td>
</tr>
<tr>
<td>Obstruction</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(32/32)</td>
<td>(32/32)</td>
<td>(17/17)</td>
<td>(17/17)</td>
</tr>
</tbody>
</table>

Data are percentages, unless otherwise indicated. Raw data are numbers of patients. MR urography included T2-weighted and contrast-enhanced T1-weighted sequences. CT scans were interpreted by observers A and B, and MR urographic images, by observers C and D.

The diagnostic performance of the observers in the assessment of the level and degree of obstruction is shown in Table 10.
Table 10. Diagnostic Performance of Observers in Assessment of Level and Degree of Obstruction in 49 Patients.

<table>
<thead>
<tr>
<th>Level of Obstruction</th>
<th>CT Observer A</th>
<th>CT Observer B</th>
<th>MR Urography Observer C</th>
<th>MR Urography Observer D</th>
<th>Excretory Urography</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Obstruction</td>
<td>19</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Location of Obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteropelvic Junction</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Upper third of ureter</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Lower third of ureter</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Ureterovesical junction</td>
<td>14</td>
<td>14</td>
<td>19</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Degree of obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>10</td>
<td>16</td>
<td>17</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>High grade</td>
<td>20</td>
<td>16</td>
<td>15</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>

Data are numbers of patients. CT findings were interpreted by observers A and B; MR urographic findings, by observers C and D.

The degree of intertechnique agreement in assessment of the degree and level of obstruction (CT and MR urography vs excretory urography) is shown in Table 11. The interobserver agreement (κ statistic) for the degree of obstruction was 0.51 for observers at CT and 0.88 at MR urography. For the level of obstruction, interobserver agreement was 0.81 and 0.83 for CT and MR urography, respectively.

Table 11. Degree and level of obstruction: Degree of intertechnique agreement of CT and MR urography with excretory urography in 49 patients.

<table>
<thead>
<tr>
<th>Obstruction</th>
<th>CT Observer A</th>
<th>CT Observer B</th>
<th>MR Urography Observer C</th>
<th>MR Urography Observer D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree</td>
<td>0.58</td>
<td>0.60</td>
<td>0.70</td>
<td>0.81</td>
</tr>
<tr>
<td>Level</td>
<td>0.83</td>
<td>0.72</td>
<td>0.83</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data are κ values.

The mean size of detected stones at final diagnosis was 5.3 mm (range, 2.0–18.0 mm). When measured from CT images, the mean size was 6.2 mm (range, 3.0–18.0 mm) and 5.4 mm (range,
2.0–17.0 mm) for observers A and B, respectively. At MR urography, mean sizes were 3.5 (range, 2.0–7.0 mm) and 5.2 mm (range, 3.0–12.0 mm) for observers C and D, respectively. Spearman correlation coefficients for stone size, as compared with final stone size, were 0.76 (P < .001) and 0.75 (P < .001) at CT and were poorer at MR urography, 0.49 (P = .005) and 0.51 (P = .004). In this study, there were six ureteral stones greater than 6 mm in diameter. At MR urography, observer C underestimated the size of five stones. Observer D underestimated the size of three stones but also overestimated the size of four other smaller stones.

Extravasation of contrast medium was demonstrated at excretory urography in three patients. Extravasation was clearly demonstrated at MR urography in these patients, and a corresponding area of fluid collection was seen at CT and T2-weighted imaging performed prior to furosemide administration. A fourth patient was found to have minimal extravasation not visualized at excretory urography.

Stranding or perirenal high signal intensity was interpreted as present in 27, 26, 28, and 30 kidneys for observers A, B, C, and D, respectively, including two false-positive interpretations each by observers A and B. The diagnostic accuracy of perirenal high signal intensity or stranding in predicting acute ureteral obstruction on the side of the body on which symptoms occurred is shown in Table 12.

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observer A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>84.4 (27/32)</td>
<td>81.3 (26/32)</td>
</tr>
<tr>
<td>Specificity</td>
<td>88.2 (15/17)</td>
<td>88.2 (15/17)</td>
</tr>
<tr>
<td>PPV</td>
<td>93.1 (27/29)</td>
<td>92.9 (26/28)</td>
</tr>
<tr>
<td>NPV</td>
<td>75.0 (15/20)</td>
<td>71.4 (15/21)</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>85.7 (42/49)</td>
<td>83.7 (41/49)</td>
</tr>
<tr>
<td><strong>Observer B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81.3 (26/32)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Observer C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87.5 (28/32)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>100.0 (17/17)</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>100.0 (28/28)</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>81.0 (17/21)</td>
<td></td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>91.8 (45/49)</td>
<td></td>
</tr>
<tr>
<td><strong>Observer D</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>93.8 (30/32)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>100.0 (17/17)</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>100.0 (30/30)</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>89.5 (17/19)</td>
<td></td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>95.9 (47/49)</td>
<td></td>
</tr>
<tr>
<td>Interobserver $\kappa$ statistic</td>
<td>0.79 (0.62, 0.96)</td>
<td>0.92 (0.80, 1.00)</td>
</tr>
</tbody>
</table>

Data are percentages, unless otherwise indicated. Raw data in parentheses are numbers of patients.

NPV = negative predictive value, PPV = positive predictive value.

* Numbers in parentheses are 95% CI.

Both CT and MR urography enabled diagnosis of appendicitis. In one patient with ulcerative colitis, both observers missed minimal pericolic inflammatory changes at CT, whereas both observers correctly detected high signal intensity and small amounts of ascites at MR urography. In one patient with biliary colic, only observer D noticed small gallbladder stones not detected on CT images. The normal common bile duct was also seen on RARE images. All observers missed tubal torsion; in this case, observer C identified a trace of high signal intensity around the ovary, but no diagnosis was suggested.

Finally, 40 patients stated that CT was their preferred examination because of its short duration. Only five patients mentioned MR urography as the preferred examination, because of “the
relaxed atmosphere” in the magnetic tube and “efficient air conditioning.” Four patients believed that the imaging modalities were equivalent.

5.5 DISCUSSION

Use of contrast material and inability to provide a differential diagnosis are considered the major limitations of excretory urography. CT can usually depict calculi regardless of their chemical composition, because of the higher attenuation of stones as compared with surrounding soft tissues (2, 117, 365). Data from the current study showed that CT was highly accurate in depicting ureteral stones, without any contrast material administration. In the current study, three stones were missed at CT by both observers: One small stone (2 mm in diameter) was clearly visualized retrospectively, but the remaining two stones (3 mm each) were not detected, even retrospectively, with confidence, and both stones proved to be of uric acid composition at chemical analysis. Nevertheless, obstruction was detected, with obvious secondary signs of obstruction, thus potentially providing sufficient evidence of a ureteral stone. After taking these facts into consideration, it can be concluded that CT depicted ureteral stones in most patients and enabled confirmation of the presumed diagnosis of urinary tract calculi in the rest of the patients.

A ureteral stone is traditionally diagnosed when a calcific opacity is detected in the ureteral lumen. This presents a challenge at MR urography, at which calcifications are not directly visualized, and detection of a ureteral stone is based on a filling defect inside the ureteral lumen, a sign that is nonspecific and may also represent a blood clot or tumor (346, 352). When obstruction is due to another cause, such as an intraluminal neoplasm, it can usually be identified with conventional MR sequences (346). Although acute obstruction is most frequently secondary to ureteric calculus, a signal-void intraluminal filling defect with smooth margins seen with both T1- and T2-weighted sequences and a lack of enhancement after contrast material administration are usually sufficient for diagnosing a ureteral stone. Nevertheless, this is not always straightforward, and severe surrounding soft-tissue edema can mimic or obscure a tumorous process. In this study, although a filling defect was visualized in two cases, observer C could not rule out the possibility of a tumor as the underlying abnormality, because of severe ureterovesical junction edema. In such unclear cases, it is advisable to obtain a radiograph of the abdomen to confirm a calcification at the site of obstruction. Unfortunately, our consecutive patient population did not include individuals with urologic abnormalities other than ureteral stones.

T2-weighted sequences are not always sufficient in detecting small ureteral stones, and T1- and T2-weighted sequences complement each other. Although there are no prospective MR studies, to our knowledge, of the evaluation of patients with acute flank pain, a recent study by Verswijvel et al (369) showed the high diagnostic accuracy of contrast-enhanced T1-weighted imaging in demonstrating the underlying urologic abnormality, including tumors and ureteral stones.

Occasional difficulty in differentiating a ureteral stone from a phlebolith is a known limitation of CT that is discussed in several previous articles (2, 134, 365). However, with experience and use of secondary signs of obstruction, this difficulty can usually be overcome (370). The “comet sign”, lower attenuation, and absence of a soft-tissue rim sign might help in differentiating a pelvic phlebolith from a ureteral stone (134). In our study, observer B had one false-positive result. Phleboliths are not visualized at MR urography, and thus there were no misinterpreted cases.

A major advantage of helical CT over excretory IVU is that the exact stone burden is revealed because of markedly improved soft-tissue contrast (364). In our study, CT clearly depicted even tiny calyceal stones, whereas at MR urography, both observers failed to visualize nearly all small calyceal stones. Increasing the spatial resolution might be a solution to this problem, by reducing both the field of view and the effective section thickness to cover only the kidneys (decreased
matrix size); however, further improvement in the spatial resolution of MR imagers is obviously still needed.

Both CT and MR urography were highly accurate in demonstrating obstruction. Although administration of a diuretic before the performance of 3D FLASH sequences might, presumably, increase the frequency of detected obstruction through rapidly increased diuresis, heavily T2-weighted sequences alone without any diuretic are also highly accurate in demonstrating minimal obstruction, as has been reported by other investigators (355, 357, 359). Central fluid collection was detected with CT and T2-weighted MR sequences in patients with extravasation; hence, there is no conclusive data to assume possible fornicial rupture due to the use of such a small amount of diuretic. Both CT and MR urography were equally effective in demonstrating the level of obstruction.

Another limitation of CT is the inability to directly evaluate the excretory function of kidneys. Nevertheless, for evaluation of degree of obstruction, agreement of CT findings with excretory urographic findings was moderate for both observers, based only on estimation of the degree of urinary tract dilation. Excretory MR urography enables evaluation of the excretory function of the kidney in the same way as excretory urography, thus explaining the higher agreement. However, degree of obstruction is not a crucial piece of information that can influence patient treatment. Stone size and location, patient symptoms, and absence of infection are the most important parameters used to determine need for urologic intervention (2). CT already can be used to provide the needed radiologic information and to measure the size of ureteral stones more accurately than can excretory urography or nephrotomography (371). In our study, the correlation of stone size was clearly better when measured from CT images rather than from MR urographic images, which we consider an important strength of CT over MR urography. In our study and clinical practice, we have noted slight underestimation of stone size, possibly because of partial volume effect obscuring the stone margins from the surrounding high urine signal.

Perirenal edema seen as soft-tissue stranding at CT and as high signal intensity at MR urography is another useful and highly accurate sign in predicting acute ureteric obstruction. Stranding is less prominent at CT than at MR urography (168), as was also noted in our study. Minimal perirenal edema or fluid collection was easily detected with heavily T2-weighted sequences. However, this is a nonspecific sign, and any insult to the kidney may result in perirenal stranding.

Another advantage of helical CT is short imaging time. The examination time necessary to reveal the cause of obstruction might be markedly prolonged at excretory urography and excretory MR urography. Occasionallly, in cases of severe obstruction, T2-weighted MR sequences may prove sufficient in determining the cause of obstruction and thus eliminating the need for prolonged follow-up sequences. Nevertheless, imaging time will still be longer than for CT.

CT and MR urography were equally accurate in excluding other causes of acute flank pain. MR urography did well in detecting inflammatory changes in the three patients with extrarenal diseases causing acute flank pain symptoms and showed a gall bladder stone in a fourth patient.

MR urographic investigation demands the presence of highly qualified radiologists with thorough knowledge of and experience in MR imaging, as well as other qualified personnel. Because most of our patients with acute flank pain present to the emergency department at times other than during duty hours, MR urography is likely to be performed the next day, thus resulting in delayed diagnosis and management. It might also be speculated that the good performance of MR urography was due in part to the retrospective image analysis performed by the observers in the current study, which is different from that performed by the physician on call, who has to make a rapid conclusive decision on whether or not a patient has ureteral stones or other underlying disease. In addition to the higher cost of MR urography and limited availability, two other important factors should be considered in choosing the imaging technique to evaluate acute
flank pain: clinician acceptance of the new imaging modalities, and patient satisfaction. The urologic surgeons at our hospital have readily accepted both CT and MR urography, and our limited interview showed that a majority of patients prefer CT over MR urography. Furthermore, helical CT is widely available and easy to perform, and all radiologists and technicians are well acquainted with this imaging modality.

In this study, we have shown the high diagnostic accuracy of MR urography in examining patients with acute flank pain. It should, however, be reserved for selected patients, in our opinion, when the use of contrast medium or ionized radiation is undesirable (e.g. in pregnant women, cooperative children, and young adults), in spite of the fact that pregnant women and children were excluded from this study, since it would be more difficult to perform a controlled study of these populations. At our hospital, we now also recommend MR urography in patients with nephropathy when information about anatomic details of the pelvicalyceal systems, ureters, and excretory function of the kidney is needed. Another possible application of MR urography is in patients with human immunodeficiency virus who are undergoing crixivan (Indivar; Merck, Rahway, NJ) therapy, since they can present with nonopaque stones (140), and in patients with atypical symptoms, especially if there is suspicion of an extraurinary inflammatory process or biliary disease.

In conclusion, in routine clinical practice, unenhanced helical CT is meritoriously the investigation of choice in the examination of patients with acute flank pain. MR urography is an acceptable substitute when other clinical advantages favoring MR urography are present.
6 Comprehensive MR Urography Protocol: Equally Good Diagnostic Performance and Enhanced Visibility of the Upper Urinary Tract Compared To Triple-Phase CT Urography

6.1 ABSTRACT

6.1.1 Objective
To prospectively compare the diagnostic performance and the visualization of the upper urinary tract (UUT) using a comprehensive 3.0T- magnetic resonance urography (MRU) protocol versus triple-phase computed tomography urography (CTU).

6.1.2 Methods
During the study period (January-2014 through December-2015), all consecutive patients in our tertiary university hospital scheduled by an urologist for CTU to exclude UUT malignancy were invited to participate. Diagnostic performance and visualization scores of 3.0T-MRU were compared to CTU using Wilcoxon matched-pairs test.

6.1.3 Results
Twenty patients (39 UUT excreting units) were evaluated. 3.0T-MRU and CTU achieved equal diagnostic performances. The benign etiology of seven UUT obstructions was clarified equally with both methods. Another two urinary tract malignant tumors and one benign extraurinary tumor were detected and confirmed. Diagnostic visualization was slightly better in the intrarenal cavity areas with CTU but worsened towards distal ureter. In the comparison, full 100% visualizations were detected in all areas in 93.6% (with 3.0T-MRU) and 87.2% (with CTU) and >75% visualization in 100% (3.0T-MRU) and 93.6% (CTU). Mean CTU effective radiation dose was 9.2 mSv.

6.1.4 Conclusions
Comprehensive 3.0T-MRU is an accurate imaging modality achieving comparable performance with CTU; since it does not entail exposure to radiation, it has the potential to become the primary investigation technique in selected patients.

6.2 INTRODUCTION

Recent advances in multidetector computed tomography (MDCT) technology have made possible rapid high resolution imaging in multiple phases. Research into MDCT applications has resulted in imaging protocols that produce optimal opacification, visualization and distension of the upper urinary tract (UUT) (152), and CT urography (CTU) has become the primary investigation of choice for the evaluation of hematuria and high risk patients for UUT malignancy. While CTU achieves excellent pooled 96% sensitivity and 99% specificity (153), it is necessary to expose the patient to radiation which is a cause of concern and a major drawback with this technique (152).
Magnetic resonance urography (MRU) is a costly, time-consuming and expertise-demanding imaging modality. Additionally, it has also been reported to suffer from other limitations i.e. lower spatial resolution, an inability to directly visualize calcifications and a susceptibility to a wide range of artefacts (173, 372). Nevertheless, MRU has many established advantages including its high contrast resolution, good sensitivity for contrast media and most importantly, its safety. There are no fundamental limitations to utilizing MRU (178), and it is recommended in many guidelines as a suitable alternative to CTU whenever the latter is contraindicated or undesirable (29, 81, 325). In infants and children, MRU is already a well-established imaging modality in the evaluation of the UUT (373), yet research is lacking for wider applications in adults. Previously, MRU has been shown to be highly sensitive at detecting the presence and level of an obstruction (185, 374) and highly accurate in the evaluation of patients with acute flank pain (375).

The majority of MRU reports have been retrospective and based on devices with a field strength of 1.5T. In comparison to 1.5T-MRI, 3.0T imaging achieves higher signal-to-noise ratios, improved spatial resolution and faster scanning, all of which contribute to better visualization of anatomical details. The use of a higher field could theoretically mitigate some of the current limitations of MRU and help to obtain higher image resolution (372). The 3.0T-MRU literature however is scanty e.g. there are no comparative studies of comprehensive CTU and 3.0T-MRU protocols.

The European Society of Urogenital Radiology (ESUR) CTU Working Group defines a CTU examination as one that involves the use of MDCT with thin-slice imaging, intravenous administration of contrast medium, and imaging in the excretory phase. The ESUR guidelines list several alternative approaches to minimize the radiation dose in different clinical situations (152). Nonetheless, a comprehensive MRU protocol must be adopted to fully evaluate the kidneys and UUT; it consists of both T2-weighted and a combination of T1-weighted sequences in different orientations and at different time intervals after the administration of contrast material to maximize the clinical value (173). Nevertheless, there is no consensus about what represents the optimal MRU protocol.

The aim of this prospective study was to evaluate the excretory phase urothelium-surface visualization of the UUT and to compare the diagnostic performance of a comprehensive 3.0T-MRU protocol with triple-phase CTU in the evaluation of consecutive patients with obstruction and in high-risk patients for UUT malignancy.

### 6.3 MATERIALS AND METHODS

#### 6.3.1 Study design

This prospective study was approved by the ethics committee of Kuopio University Hospital, and written informed consent was obtained from all patients. During the study period from January-2014 through December-2015, all high-risk patients and patients with UUT obstruction of unknown etiology, detected by ultrasound, and who were scheduled for CTU to rule out UUT malignancy were invited to participate. The exclusion criteria were: glomerular filtration rate (GFR) <45; allergy to iodinated or gadolinium contrast agents; known hypersensitivity to furosemide or sulfa; contraindications to MRU (including claustrophobia).

A total of 20 patients (12 men and 8 women, mean age 65.7 years, range 40-82 years) underwent both examinations (figure 12). During the study period, a total of 14 other patients fulfilled inclusion criteria yet did not participate.
Figure 12. Flow chart of study patients, indications for imaging and results as determined by clinical evaluation, the results of imaging studies and the final histopathological diagnosis.

(UC= Urothelial carcinoma; RCC= Renal Cell Carcinoma)

6.3.2 Imaging Studies

6.3.2.1 MRU
3.0T-MRU protocol and sequence characteristics are described in Table 13. After T2- weighted sequences, axial-T1-sequence was obtained before the intravenous administration of a low-dose furosemide 0.1 mg/kg of body weight (Furesis; Orion, Espoo, Finland) to enhance diuresis with the total individual dose not exceeding 10 mg delivered 1-2 minutes before the intravenous injection of 0.05 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Roissy CdG, France) via power injector (3ml/sec) followed by 20 ml of saline flush. T1-weighted sequences were obtained at different timing intervals: during the corticomedullary (30 sec; axial), nephrographic (90 sec; coronal) and excretory phases (5, 10 and 15 min; coronal and at 15 min axial).
Table 13. Magnetic Resonance (MR) and Computed Tomography (CT) Urography Imaging protocols.

**MR Urography Protocol**
- Patients were asked to void immediately before the examination
- Supine position
- 3.0-T (Philips Achieva TX, Philips N.V., Eindhoven, The Netherlands)
- 16-element phased-array body coil (Sense-XL-Torso) centered over the abdomen and pelvis
- Parallel imaging (acceleration factor of 2)
- Commercially available breath hold sequences

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE (ms)</th>
<th>Flip angle</th>
<th>Acquisition matrix</th>
<th>Orientation</th>
<th>Slice thickness (mm)</th>
<th>FOV (mm)</th>
<th>Scanning time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-TSE1</td>
<td>1058/80</td>
<td>90</td>
<td>224x224</td>
<td>axial</td>
<td>3.6</td>
<td>290x362x160</td>
<td>16</td>
</tr>
<tr>
<td>T2-TSE</td>
<td>1058/80</td>
<td>90</td>
<td>224x224</td>
<td>coronal</td>
<td>3.6</td>
<td>400x343x120</td>
<td>16</td>
</tr>
<tr>
<td>T2-TSE FS2</td>
<td>1058/80</td>
<td>90</td>
<td>224x224</td>
<td>axial</td>
<td>3.6</td>
<td>290x362x160</td>
<td>16</td>
</tr>
<tr>
<td>T2-TSE FS</td>
<td>1058/80</td>
<td>90</td>
<td>224x224</td>
<td>coronal</td>
<td>3.6</td>
<td>400x343x120</td>
<td>16</td>
</tr>
<tr>
<td>DWI3</td>
<td>shortest/95</td>
<td>90</td>
<td>240x240</td>
<td>axial</td>
<td>6</td>
<td>403x261x349</td>
<td>215</td>
</tr>
<tr>
<td>T1-TFE4</td>
<td>shortest</td>
<td>10</td>
<td>232x233</td>
<td>axial</td>
<td>4/2*</td>
<td>320x369x350</td>
<td>24</td>
</tr>
<tr>
<td>T1-TFE</td>
<td>shortest</td>
<td>10</td>
<td>232x233</td>
<td>coronal</td>
<td>2/1*</td>
<td>320x350x100</td>
<td>16</td>
</tr>
</tbody>
</table>

**CT Urography protocol**
- 128-slice MDCT scanner (SOMATOM definition Edge, Siemens, Erlangen, Germany) with automatic tube-current modulation
- Preparation: hydration with 1000 ml water orally 30-60 min prior to CT; voiding immediately before mounting CT table
- Unenhanced CT: from the top of kidneys to the base of the bladder
- 90s after contrast: combined corticomedullary-nephrographic phase scan through the whole abdomen
- 10 min after contrast: a test image at the level of mid ureter and repeated twice, if needed, at 2 min intervals if no contrast was detected in ureters
- 10-14 min after contrast: Excretory-phase scan from the top of kidneys to the bladder base

1 TSE= Turbo Spin Echo sequence
2 FS= Fat Saturation
3 Diffusion weighted echo planar imaging with automatically calculated ADC maps, FS and with five respective b factors (0, 200, 400, 600, and 800 s/mm².
4 TFE= Ultra-fast fat saturated unenhanced three-dimensional Turbo Field Echo (THRIVE)
* Overcontiguous acquisition slice thickness/ Reconstructed slice thickness
6.3.2.2 CTU
A triple-phase CTU protocol scheduled three hours after the MRU was conducted in accordance with the ESUR recommendations (Table 13). Furosemide was injected in a similar dose as in the MRU i.e. at 1-2 min before the injection of iodinated contrast (1.5 ml/kg, maximum dose of 100 ml) (Omnipaque 350 mgI/mL, Cork, Ireland) delivered via power injector at 4 ml/sec followed by 30 ml saline flush. Split contrast-boluses of 70 and 30 ml were used with the latter bolus ending 25 seconds before scanning. Axial reconstructions of 1mm and 3mm axial, coronal and sagittal images of all phases were saved into the digital archiving system which undertakes full option interactive multiplanar and volume reconstructions (Sectra PACS, version 15.1.20.2, Sectra Workstations IDS7, Linköping, Sweden).

6.3.3 Image Interpretation
The CTU scans were interpreted independently and blindly by two radiologists (MP,SK) and those obtained from the MRU by two other radiologists (RV,MS). Each radiologist had over 20 years of experience in multimodality abdominal imaging. Investigations were evaluated for the presence of obstruction, tumors and additional findings. A tumor was defined as a solid lesion with contrast enhancement, a benign stricture as a smooth walled fixed narrowing without a distinguishable mass and urothelial thickening as an enhancing thickened segment with no definite discrete mass. Furthermore, the UUT was divided into six anatomical areas: upper pole cavities, middle and lower pole cavities, renal pelvis, and upper-, middle-, and lower ureter. For each anatomical area in each UUT, opacification at CTU and diagnostic visualization at MRU (for simplicity, both outcomes will be subsequently referred to as visualization) were scored into 6 categories: 1) 0%; 2) 1-25%; 3) 26-50%; 4) 51-75%; 5) 76-99% and 6) 100%. Furthermore, the distension of the UUT was reported in millimeters and measured with both CTU and MRU at three levels: a) the anteroposterior diameter of the renal pelvis, b) mid-ureter and c) distal ureter. The volume of the bladder was further assessed from CTU and the last MRU images by multiplying the longest 3-axis diameter measurements with a constant factor of 0.52 (376). Two observers (MS,RV) evaluated side-by-side both CTU and MRU for UUT visualization. Furthermore, one observer (MS) assessed the visibility of UUT by additionally examining only the 5-10 min excretory sequences and these readings were compared to those obtained from the full examination.

Finally, the patients were asked to fill in a questionnaire rating each examination on a scale of 1-10 based on their own subjective impressions and to name their examination of choice. Patients were also asked if they would accept MRU as a possible sole follow-up examination.

6.3.4 Radiation Dose
The effective dose of each patient was computed on the basis of scanned areas and individual scan protocol details using the CT-EXPO software (v.2.3.1., copyright Georg Stamm and Hans Dieter Nagel, Hannover/Buchholz, Germany). The consistency of the simulation dose parameters (CTDI, DLP) with the scanner patient dose report was verified.

6.3.5 Statistics
The statistical analysis was performed with SPSS-software for Windows (version 19; SPSS, Chicago, Ill). Differences between groups were considered significant if the p-value was <0.05. Non-parametric Wilcoxon matched-pairs test was performed to compare CTU and MRU mean visualization scores as well as the mean differences between diameter measurements. A parametric paired t-test was used to compare differences between the mean volumes estimated by MRI and CT.
6.4 RESULTS

A total of 40 UUT units were evaluated. One obstructed nonfunctioning kidney was excluded from the visualization score and distension analysis. The mean GFR was 77.7 (range 49-100). One excretory phase CTU was repeated 4 minutes after the first session which exhibited non-diagnostic opacification. The mean radiation dose was 9.2 mSv (range 5.8-18.0 mSv).

Both CTU and MRU achieved equivalent diagnostic performance (Figure 12) and both techniques detected two malignant tumors and one suspected ureteral tumor. The two confirmed malignant tumors showed restricted diffusion (Figure 3). Furthermore, an extraperitoneal tumor was diagnosed by both methods and a neurinoma was suggested by both MRU observers based on the tumor’s signal and DWI findings; this was confirmed at final histology. The benign etiologies of other obstructions (benign strictures and vascular compressions) were equally well visualized by both techniques.

Visualization scores are presented in Table 14, and percentage visualizations in Table 15. Briefly, CTU showed slightly better intrarenal cavity visualization but consistently poorer visualization towards the distal ureters. In the side-by-side analysis, MRU achieved better overall excretory phase visualization than CTU in 8/20 (40%) and equal performance in 10/20 (50%). One short segment of one distal ureter was not visualized at MRU due to the presence of a susceptibility artefact.

Figure 13. Volume rendering shaded reconstruction of CT (left sided image) and MR (right sided) urography examination in the same patient showing the same anatomical structures with somehow better opacification of the distal ureters at MR urography.
Table 14. Mean visualization scores of the upper urinary tract as evaluated by four observers and their significance values at computed tomography (CT) urography compared to magnetic resonance (MR) urography (whole examination at different time intervals jointly analyzed).

<table>
<thead>
<tr>
<th>Area</th>
<th>Difference between methods</th>
<th>Difference between readers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT1</td>
<td>MR3</td>
</tr>
<tr>
<td>A</td>
<td>5.48</td>
<td>5.78</td>
</tr>
<tr>
<td>B</td>
<td>5.55</td>
<td>5.68</td>
</tr>
<tr>
<td>C</td>
<td>5.63</td>
<td>5.82</td>
</tr>
<tr>
<td>D</td>
<td>5.08</td>
<td>5.88</td>
</tr>
<tr>
<td>E</td>
<td>5.05</td>
<td>5.88</td>
</tr>
<tr>
<td>F</td>
<td>4.48</td>
<td>5.85</td>
</tr>
</tbody>
</table>

Areas: A=upper cavities; B= middle and Lower cavities; C=Renal pelvis; D=Ureter, proximal third; E= Ureter, middle third; F= Ureter, lower third. CT1= CT first observer; CT2: CT second observer; MR3: MR third observer; MR4: MR fourth observer.
Table 15. Percentage visualization (total=100% and subtotal >75%) of different areas of the upper urinary tract (UUT) as visually evaluated by four independent observers at excretory phase CT and MR urography (whole examination with three time points jointly analyzed).

<table>
<thead>
<tr>
<th>Area</th>
<th>CTU observer 1</th>
<th>CTU observer 2</th>
<th>MRU Observer 3</th>
<th>MRU observer 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*V=100% N (%)</td>
<td>V&gt;75% N (%)</td>
<td>*V=100% N (%)</td>
<td>V&gt;75% N (%)</td>
</tr>
<tr>
<td>A</td>
<td>25 (64.1)</td>
<td>37 (94.9)</td>
<td>39 (100)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>B</td>
<td>27 (69.2)</td>
<td>38 (97.4)</td>
<td>39 (100)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>C</td>
<td>31 (79.5)</td>
<td>38 (97.4)</td>
<td>35 (89.7)</td>
<td>38 (97.4)</td>
</tr>
<tr>
<td>D</td>
<td>21 (53.8)</td>
<td>34 (87.2)</td>
<td>35 (89.7)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>E</td>
<td>19 (48.7)</td>
<td>34 (87.2)</td>
<td>31 (79.8)</td>
<td>33 (84.6)</td>
</tr>
<tr>
<td>F</td>
<td>14 (35.9)</td>
<td>23 (59)</td>
<td>25 (64.1)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>Total</td>
<td>137 (58.5)</td>
<td>204 (87.2)</td>
<td>204 (87.2)</td>
<td>219 (93.6)</td>
</tr>
</tbody>
</table>

*Excretory phase visualization of the urothelium. 20 patients with 39 UUT-units were evaluated. Areas (Diagrams below): A=upper cavities; B= middle and Lower cavities; C=Renal pelvis; D=Ureter, proximal third; E= Ureter, middle third; F= Ureter, lower third.
CTU rated the bladders as being more distended (mean 435.3 ml) than observed with MRU (mean 341.3 ml, p=0.035). The renal pelvis was more distended at CTU (19.3 mm vs. 17.9 mm; p=0.002), but no major differences were detected in ureteral distension (Table 16). Four UUT-units (10.3%) showed layering effect at CTU. MRU visualization scores for the first 10 min showed consistently lower scores at all levels compared to the full examination, but this reached statistical significance only at the level of middle and lower intrarenal cavities and mid-ureter (p<0.05).

<table>
<thead>
<tr>
<th>Localization</th>
<th>MRU 5 min</th>
<th>MRU 10 min</th>
<th>MRU 15 min</th>
<th>CTU</th>
<th>P</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis (mm)</td>
<td>17.3</td>
<td>17.7</td>
<td>17.9</td>
<td>19.3</td>
<td>0.180</td>
<td>0.224</td>
<td>0.085</td>
<td>0.002</td>
</tr>
<tr>
<td>Proximal Ureter (mm)</td>
<td>5.5</td>
<td>5.8</td>
<td>6.1</td>
<td>6.3</td>
<td>0.120</td>
<td>0.091</td>
<td>0.001</td>
<td>0.299</td>
</tr>
<tr>
<td>Distal Ureter (mm)</td>
<td>5.2</td>
<td>5.4</td>
<td>5.4</td>
<td>5.0</td>
<td>0.237</td>
<td>0.854</td>
<td>0.106</td>
<td>0.060</td>
</tr>
</tbody>
</table>

P-value of significance between MRU at 5 and 10 minutes; P1- value of significance between MRU at 10 and 15 minutes; P2- value of significance between MRU at 5 and 15 minutes; P3- value of significance between MRU at 15 minutes and CTU.

Finally 16 patients (80%) chose CTU as their preferred examination (score CTU=9.4 vs. MRU=8.9), nevertheless all patients were willing to undergo MRU if it was deemed necessary as the only follow-up examination in the future due to its radiation-free profile.

**6.5 DISCUSSION**

Our results show that the diagnostic performance of a comprehensive 3.0T-MRU protocol was equivalent to that obtained with CTU, generally considered as the gold standard. Furthermore, the visualization of the UUT, especially in the ureters, was more complete with MRU. This indicates that the 3.0T-MRU has the potential to achieve high accuracy in the evaluation of the UUT in high risk patients.

The distension of the intrarenal cavities was better with CTU due to the hydration and diuresis protocol used. Increased diuresis and consequently more filled bladder secondarily results in better distension and opacification of the calyces and pelvis (157). Nevertheless this occasionally comes at the expense of a contrast layering effect which decreases opacification. Furthermore, full opacification of the slender and contractile ureters is still incomplete with one excretory phase CTU acquisition, whereas the possibility to conduct repeated excretory sequences at MRU proved useful in achieving full (i.e.100%) diagnostic visualization in up to 93.6% of all areas and >75% visualization in all patients.

Our results are in agreement with a previous report by Childs et al. (173), which showed that 3.0T-MRU is feasible and highly accurate, regardless of the frequent artifacts since these rarely interfere with the interpretations. We achieved >75% visualization of the UUT in all patients with multiple excretory sequences opposed to a corresponding value of 90.8% (173). We also confirm that signal loss due to metallic susceptibility artefact impairs the visibility of UUT structures in close vicinity to these implants. Therefore this limitation of MRU should be acknowledged e.g. in the follow-up of patients after reconstructive urological surgery.
Until the present study, there has been no comparison in the same patient population of the actual performance of a comprehensive 3.0T MRU protocol with the triple-phase CTU approach. We found that the two procedures performed equally well which is in contrast to a previous retrospective study that applied a limited 1.5T-MRU protocol with only one T1-excretory sequence at 10 min as compared to split-bolus CTU (188). Our study highlights that MRU should not try to duplicate CTU protocols, but since it is a safe modality, multiple excretory acquisitions are recommended since this can achieve better contrast visualization. Furthermore, we stress the importance of utilizing a comprehensive protocol that includes also post-contrast enhancement phases e.g. the corticomedullary and/or nephrographic phase sequences in the complete evaluation of the UUT. There is recent evidence demonstrating the high accuracy of contrast enhanced CT compared to excretory phases (166), but it seems most likely that both phases complement each other (377). Furthermore, based on previous CTU and MRU reports, it is apparent that single excretory phase imaging at 5 or 10 minutes results in incomplete UUT visualization, e.g. Dillman et al. (378) reported >75% opacifications of intrarenal cavities to be as low as 41%. Interestingly, in this study, the ureter was only slightly more distended at different MRU-time intervals and although this did not always reach statistical significance due to the small patient population, consistently better visualization was present at 15 min emphasizing the importance of repetition acquisitions at longer intervals after the induction of enhanced diuresis. Our excretory protocol was devised and refined years ago and it reflects the local expertise. We also emphasize that it is important to obtain images not only in the coronal plane but also in the axial orientation as this will facilitate the evaluation of possible small lesions or wall thickenings.

The accuracy of MRU in the evaluation of hematuria or high risk patients has yet to be determined. Nevertheless, an approximate sensitivity of 75% for UUT has been reported based on studies where most of the recruited patients have had relative contraindications to CTU, therefore rendering their results incomparable to normal CTU patient populations (29, 186, 379). Furthermore, it might be also speculated that the thicker 3-4 mm slice thicknesses used in those studies decreased the sensitivity.

MRU is not without its shortcomings; it is a rather lengthy examination which requires patient cooperation. Patient preferences are not usually reported in radiological comparative studies, but we believe that it is important to include the viewpoints of our patients in the evaluation process of new imaging modalities or protocols. Even though MRU was deemed to be slightly less patient friendly, all patients stated that they would be willing to undergo MRU again as the sole examination due to its safety profile.

The radiation dose of 9.2 mSv administered in our triple-phase MDCT protocol is within reported limits [1], yet it is substantial and, for comparison, exceeds 8 years of natural background radiation exposure in our country (on average 1.1 mSv/yr.). A crude estimation for the excess relative risk of death due to cancer from receiving a 9.2 mSv dose is one excess radiation induced death per 2000 exposed individuals if one applies the radiation-induced mortality rate of 5% per Sievert of radiation exposure (380). MRU is therefore a reasonable alternative in patients who would be predicted to require repeated radiation examinations or in those with long life expectancies.

The small patient population is the major limitation of this study. Not all findings were operatively verified and additionally there were only a small number of tumors which is a further limitation.

Although the role of diffusion weighted imaging (DWI) was not separately evaluated in this study, it is worth mentioning that DWI was most helpful in evaluating tumors in the present study and is a promising imaging modality for improving accuracy of staging and follow-up of urothelial cancers and adding further strength to MRU imaging (381).
To conclude, a comprehensive 3.0T-MRU protocol involving multiple excretory sequences has the potential to display as high accuracy as can be achieved with CTU while eliminating the risk of exposing the patient to ionizing radiation.
7 General Discussion

Advances in cross-sectional imaging continue to revolutionize diagnostic possibilities. Nonetheless, non-dilated slender and contractile UUT has been and continues to be a challenge to imaging, requiring rapid and highly accurate diagnostic tools.

The introduction of helical CT was a turning point in the evaluation of urolithiasis. Unenhanced CT is a fast and highly accurate imaging modality and it rapidly supplanted IVU and became the primary investigation of choice and the golden standard in the evaluation of acute flank pain. The advent of MDCT has further intensified research into its applications and MDCT became the golden standard in the evaluation of all aspects of the UUT and can be considered to constitute a landmark of modern imaging of the UUT.

Hematuria is one of the major indications for CTU. Macrohematuria and symptomatic microhematuria need to be evaluated promptly, but there is still no consensus about which strategy is best in the different guidelines for the evaluation of asymptomatic microhematuria. There are genuine concerns raised about the risk of radiation exposure as many patients undergo high radiation dose investigations simply to rule out the rather rare possibility of UUT malignancy. US is recommended by some guidelines in certain situations e.g. in the initial evaluation of asymptomatic microhematuria in low risk patients. US is also recommended in the primary evaluation of the UT in infants, children and young adults as well as pregnant women.

The escalated utilization of MDCT imaging techniques with expanded clinical indications has been associated with both increased radiation dose and the accompanying increased cancer risk as a consequence of the associated exposure to radiation. A reduction in radiation dose can be achieved by adopting low-dose MDCT applications both through the automatic dose reduction modulations with specific low dose protocols, and the improved iterative reconstruction techniques, without compromising the diagnostic sensitivity.

T2-weighted MR sequences can be applied in UUT imaging and provide high sensitivity in the detection of obstruction and edema but they are not helpful in the detection of their causes. A major breakthrough in MR 3D imaging came with the introduction of diuretic-assisted contrast enhanced MRU followed by the more accurate rapid breath-hold 3D sequences. Although promising and safe, relatively little research has been conducted into MRU applications in clinical practice. Furthermore, several criticisms have been directed against MRU: it is less widely available, is susceptible to a wide range of artifacts, is more expensive, involves a lengthy examination, and is unable to provide direct visualization of calcifications.

However MR scanners are nowadays becoming more widely available and radiologists have increasingly gained experience in abdominal imaging. Furthermore, artifacts seldom degrade the diagnostic quality of images, except for the susceptibility artefact which are more prominent at higher fields but these can be avoided by appropriate patient selection. The inability to directly visualize calcification is not of concern when a comprehensive protocol is used, which although lengthy, provides full differential diagnostic information. It is true that the higher cost associated with the use of MRU is an issue of administrative concern in an era of cost containment. Equally important, quality of provided care should be assessed individually and whenever exposure to radiation or iodine-containing contrast material is considered an issue of concern, it is the responsibility of the treating physician and the radiologist to offer a suitable substitute without compromising quality. One could argue that the published studies and guidelines on MRU are biased, at least to some extent, against MRU. The quality of studies differs substantially and the literature is still scanty on this issue. There is still no consensus on the use,
protocol and indications for MRU, these issues can only be resolved by conducting more high quality research.

There is also a lack of consensus about the optimal imaging protocol in the different guidelines and in the incorporation of risk factors into the imaging algorithm of UUT. The level of evidence is still limited and there is also a need for a high quality research, especially in the evaluation of patients with hematuria. Costs and radiation exposure issues should be assessed on an individual basis, hand in hand with the probability of UUT malignancy.

7.1 STUDY I AND II

These results revealed that MRU is a suitable alternative to CT and both procedures have comparable accuracies in the evaluation of patients with acute flank pain. After the publication of these results, several reports and reviews have further examined the role of MRU, yet the present studies remain the only ones evaluating MRU and CT in comparison to IVU in the setting of acute flank pain (178, 182, 185, 382-391). Furthermore, although the importance of T1-weighted sequences is recognized in the acute setting of abdominal pain (387), the published MRU studies have rarely used both T1 and T2 techniques (392). Some studies have described promising alternatives to the use of T1 sequences or full comprehensive protocol by using the combination of stone or perinephric fluid and ureteral dilation. Consequently, 3.0T HASTE MRU achieved a sensitivity of 84% and a specificity of 100% (393). In another study, Regan et al achieved a similar accuracy to that of spiral CT by using a combination of HASTE MRU and KUB to diagnose the presence of acute calculus ureteric obstruction (184). Nevertheless, in our opinion, T2- and T1-weighted sequences complement each other and MRU should include a comprehensive protocol structured to each clinical situation.

7.2 STUDY III

This study adopted a novel approach in the evaluation of the UUT by introducing multiple contrast enhanced and excretory sequences in an organized temporal sequence, mainly in the coronal orientation but also adding an axial excretory sequence. The comprehensive MRU protocol proved not only to maximize visualization of the UUT but also was found to be suitable for the evaluation of pathologies both inside and outside the UUT. It is proposed that this protocol represents a viable alternative for clinicians and radiologists since it has the potential to provide equally good results as attainable with CTU, without exposing the patient to ionizing radiation. Further research will be needed to confirm the usefulness of this protocol in a larger patient population.

7.3 PAST EXPERIENCE AND FUTURE DIRECTIONS

The first MR studies were conducted approximately two decades ago. Although the basic core principles of MR imaging remain constant, there have been marked technical developments in the coil elements as well as parallel imaging acceleration capabilities during these twenty years. Now, when supplemented with the improved image reconstruction algorithms which have reduced imaging time without sacrificing image quality, it is possible to acquire thinner slice sections at higher image resolutions. These results show that both T2- and T1-weighted imaging complement each other and together constitute a comprehensive protocol with the potential to diagnose all aspects of UUT pathologies. In the acute setting, fat suppressed T2-weighted sequences are superior in the evaluation of possible edema and even small amounts of ascites; consequently MRU can be used primarily to evaluate patients with atypical symptoms or with clinical signs of possible inflammatory disease. Gadolinium enhanced T1-weighted sequences
are superior in the resolution of the etiology of the obstruction, although multiple sequences are needed at different time intervals to achieve the maximum benefit. This ensures not only a full evaluation of the UUT but also of the abdominal cavity providing differential diagnostic or staging information in applicable situations.

The availability of MRI scanners is continuously improving but there is still limited access to 3T scanners compared to the more widely available 1.5T scanners. There have been no relevant comparison of performance of MRU at different field strengths but we believe that MRU can be equally diagnostic with both field strengths. Theoretically, 3.0T imaging achieves higher signal-to-noise ratios, improved spatial resolution and faster scanning resulting in improved anatomical details.

Based on our experience, the following MRU protocol can be recommended using breath hold sequences: T2-weighted TSE sequences in both coronal and axial orientations (in the acute setting, fat suppressed); unenhanced 3D T1-weighted TFE sequence in either the axial or coronal orientations followed by furosemide-diuretic injection (0.1 mg/kg of body weight with the total individual dose not exceeding 10 mg) 1-2 min before the administration of 0.1 mmol/kg gadolinium with 1.5T and half of this dose with 3T. The axial T1-weighted corticomedullary phase-scan is followed by another nephrographic phase-scan in the coronal orientation. It is usually sufficient to collect excretory sequences at 5, 10 and 15 minutes in the coronal orientation followed by a final sequence in the axial orientation. DWI sequences can be added to further evaluate possible mass-lesion findings.

These present studies have introduced new insights into UUT imaging, but they do have some limitations. The major limitation in all of these studies was the relatively small patient population evaluated, also further complicated by the small numbers of malignant events in the third study. Nevertheless this represented the local reality in our institution. Although it is not possible to draw too far-reaching conclusions on the actual diagnostic accuracy of MRU in the evaluation of high risk patients for UUT malignancy, we were able to show that the proposed comprehensive MRU protocol has the potential to evaluate the UUT as completely as CTU, with an added safety benefit. It is predicted that improvements and refinements in MRI applications will result in improvements in image quality, functional evaluation and anatomical structure delineation. Further studies will be needed to confirm these conclusions.
8 Conclusions

1. T2-weighted sequences can rapidly reveal the presence of perirenal high-intensity signal, obstruction, and the level of obstruction. Nevertheless, T2-weighted sequences alone are not sufficient for examining patients with acute flank pain. The combined use of both T2- and contrast enhanced T1 weighted sequences can achieve excellent accuracy in the evaluation of acute suspected renal colic.

2. MRU and CT show comparable accuracies in the evaluation of patients with acute flank pain. MRU is a suitable substitute when other clinical advantages favoring MRU are present.

3. A comprehensive 3.0T-MRU protocol with multiple excretory sequences has the potential to achieve as high accuracy as can be attained with triple-phase CTU while simultaneously eliminating the risk of administering ionizing radiation to the patient.
9 References


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The development of computed tomography (CT) technology represented a milestone in the evaluation of the upper urinary tract (UUT) and at present, it constitutes the most up-to-date way of imaging the UUT. This thesis investigated the role of magnetic resonance urography (MRU) in the evaluation of patients with acute flank pain, with obstruction and with high risk of UUT malignancy. It is concluded that MRU achieves comparable results as CT, without exposing the patient to ionizing radiation.