Urothelial Cell Carcinoma

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chapter 5

History, development, and the current role of retrograde ureteropyelography in diagnosing upper urinary tract tumors

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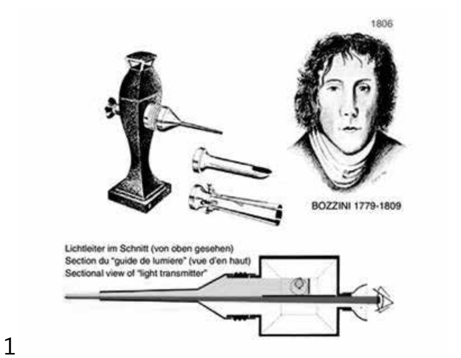
5 History, development, and the current role of retrograde ureteropyelography in diagnosing upper urinary tract tumors

Today it is possible to examine the whole urothelium, starting from the calyces of the kidney and running towards the urethral meatus, in a harmless way with respect to the integrity of the body. There is a long history behind this that involves not only many experiments with animals but also involving humans.

The interest the physicians have in being able to diagnose pathology in body cavities hidden from the naked eye has existed since ancient times. The bladder was the first cavity to be sounded. By catheterization of the urethra, using rolled-up palm leaves or metal sounds, for example, it became possible to relieve painful retention of urine. The first reference to endoscopy was from Hippocrates (460-377 BC), who described the use of a rectal speculum. Over two thousand years later, the evolution of imaging of the urinary tract continued with the concept of internal visualization of the human cavities through natural orifices, which was introduced in 1806 by Philipp Bozzini (1773-1809), an army surgeon living in Frankfurt, Germany.[1] He invented an instrument that was the forerunner of the modern endoscope. His "Lichtleiter" consisted of a candle holder in a box and a hollow tube (like a speculum) for viewing, which could be used for making the pharynx, nasal cavities, or female urethra visible [1,2] (Figure 1). The instrument failed when applied to the bladder, because it was too large for the urethra and the view obtained from reflected candlelight was too weak. Moreover, his instrument caused burns in patients and investigators; the Faculty of Medicine in Vienna stated its disapproval of the instrument



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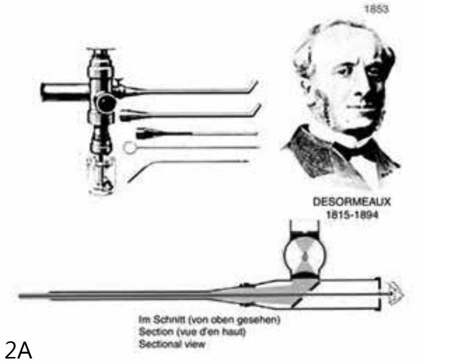

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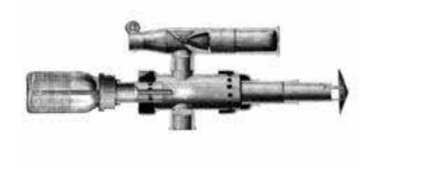
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Figure 1
Bozzini and his "Lichtleiter".
Adapted from Sports Injuries, 1st ed. Berlin Heidelberg: Springer-Verlag; 2012:5–13. Doral MN, Tandogan RN, Mann G, Verdonk R et al. Chapter "The Past and the Future of Arthroscopy", Hans H. Pässler, Yuping Yang.

Figure 2
A. Desormeaux and his urethroscope. B. Desormeaux's urethroscope with a lamp burning alcohol and turpentine held in a reservoir in the handle.

A Adapted from Sports Injuries, 1st ed. Berlin Heidelberg: Springer-Verlag; 2012:5–13. Doral MN, Tandogan RN, Mann G, Verdonk R et al. Chapter "The Past and the Future of Arthroscopy", Hans H. Pässler, Yuping Yang.
B Adapted from De l'endoscope by A.J. Desormeaux, 1865, (Courtesy of Wellcome Library, London, UK).

when it came to examining such "private regions" of the human body. This led to a delay in any further development. Nevertheless, almost five decades later Antonin-Jean Desormeaux (1815-1894), a surgeon working in L'Hôpital Necker in Paris, and under the aegis of the person considered the father of urology, Professor Jean Casémir Felix Guyon (1831-1920), constructed an instrument with a lamp burning alcohol and turpentine held in a reservoir in the handle, along with a concave mirror with a central hole to reflect light into the organ by means of the instrument [2] (Figure 2). In 1853, Desormeaux's urethroscope was the first to be introduced into the urethra and bladder of a patient. It was Maximillian Nitze (1848-1906) who constructed an operating cystoscope between 1891 and 1894. He optimized visibility by means of two essential ideas. First, he used lenses in the form of a miniature telescope to magnify the image at the end of the endoscope. Second, he illuminated the bladder through the endoscope's tip, using a water-cooled electric platinum-filament lamp.[3] In collaboration with Joseph Leiter (1830-1892), an optician from Vienna, he constructed an angled metal 21 French catheter containing lenses and a water-cooled platinum wire (Figure 3). Then Nitze constructed cold and hot wire loops for galvanocautery, and was the first to succeed in coagulating a bladder papilloma. With the invention of the incandescent light bulb, the visibility of the endoscopic instrument was optimized. It was Thomas Alva Edison (1847-1931), an American inventor and businessman, who made practical improvements to and patented the incandescent light bulb in 1879, which led to widespread commercial use.[4] Subsequently, several others developed a special tube that allowed for catheterization of the ureters and the exchange of fluid during examination. Today we still use the moveable lever, integral to the cystoscope, to guide the ureter catheter designed by Joaqim Albarran (1860-1912), a professor of urology working together with Desormeaux in L'Hôpital Necker in Paris (Figure 4: Albarran lever). At the same time it was the Czech gynecologist Karl Pawlik (1849-1914) of Prague, who was the first to conduct a radical cystectomy for treatment of bladder cancer in 1889; he had already probed the female ureter by means of finger control of an air-filled bladder in 1886.[1,5]

Retrograde ureteropyelography (RUP)

With the discovery of the X-ray by Wilhelm Conrad Roentgen (1845-1923) in 1895, the development of real urography began. There are many reports of the first visualization of renal and ureteral calculi in 1898 on the plain abdominal film.[6,7] In 1897, the surgeon Théodore Tuffier(1857-1929), also working at L'Hôpital Necker in Paris, was the first to pass a radiolucent catheter, guided by a metallic wire that was facilitated by the Albarran's lever integrated in the cystoscope, through the ureteral orifice in the bladder and into the ureter (Figure 4). But the first imaging technique of the bladder was reported by Adam Wittek in 1903.[8] He filled the bladder with air to exhibit a stone in it. All sorts of gas (air, oxygen, and carbon dioxide), injected in the peritoneum and the retroperitoneal space, were used in radiology for many years until better imaging techniques such as IVU and CT-scanning became available to obtain a better view of the renal outlines. A year later, P. von Wulff showed a bladder anomaly by filling the bladder with a mixture of bismuth, starch, and water. It was Maurice-Auguste Chevassu (1877-1957), a French urologist and surgeon, who in 1904 invented a bulb-ended sound (so-called sonde-bouchon) with an open tip, which facilitated entering (and also designed to prevent reflux of injected contrast from) the ureteral orifice in order to administer contrast retrogradely into the upper urinary tract (figure 5). But the technique of how to visualize the upper urinary tract using the technique of retrograde pyelography was described by Friedrich Voelcker (1872-1955) from Germany and Alexander von Lichtenberg (1880-1949) from Hungary, both working as surgeons at the university center in Heidelberg, Germany.[9,10] Initially they performed a cystogram by instilling a colloidal silver media – formerly used for antiseptic wound treatment, called Kollargol (German brand name) in a 2% to 5% solution – into their own bladders without major adverse events. This rapidly led to the retrograde injection of the ureteral orifices through catheters in order to perform the first retrograde pyelography in 1906. This Kollargol salt solution, comprised of the cation silver and the anion iodide, which together formed silver iodide, was very radiopaque. William Frederick Braasch (1878-1973), a prominent urologist and head of the urology department of the Mayo Clinic in the US, amassed a great deal of practical experience using this new technique, resulting in a book titled Pyelography (1915), which described most of the structural lesions, including malignant diseases, recognized today.[11] Furthermore, he used other contrast agents such as sodium iodide (12%) and sodium bromide (25%), and also noted their eventual negative consequences.

Technique of RUP

Since RUP is a minimally invasive method of imaging the upper urinary tract that requires cystoscopic visualization in order to introduce a catheter into the ureteral orifice, sterility is important. Potential introduction of bacteria

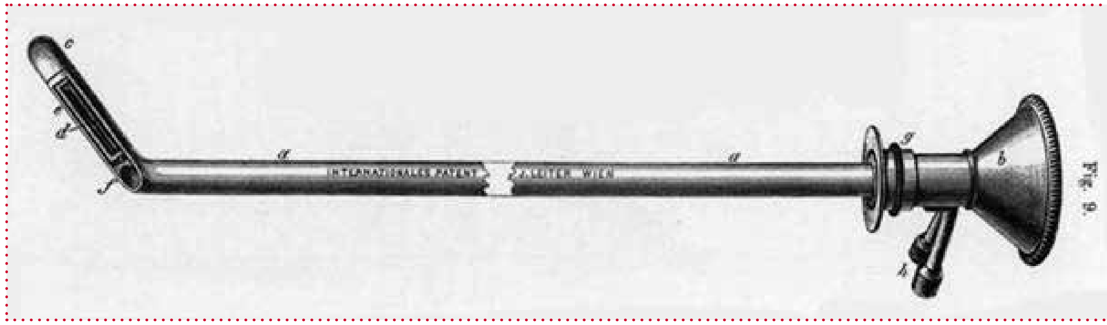

Figure 3
The Nitze-Leiter instrument.
Adapted from the web page of the Medical University of Vienna, Vienna, Austria, Department of History of Medicine.

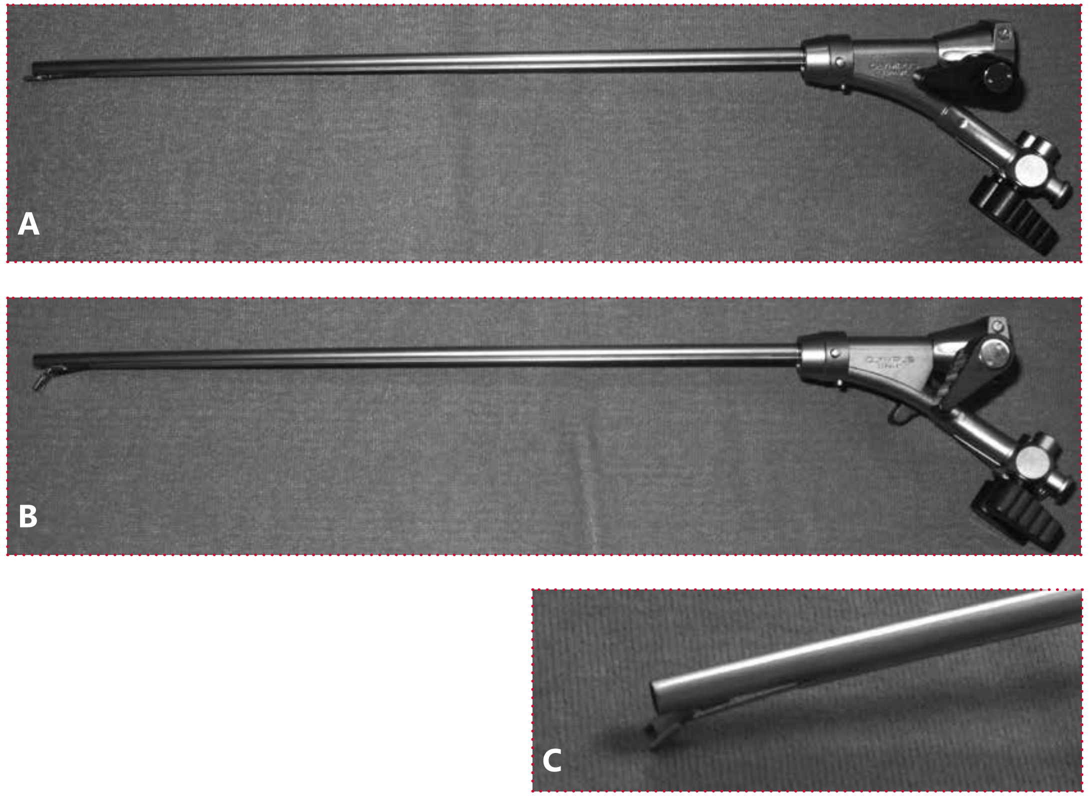

Figure 4
Albarran's lever, as we still use it today, which allows ureteric catheters to be deflected in order to assist cannulation of ureteric orifices.
A In horizontal position.
B In deflected position.
C Close up.

directly into the renal collecting system and bloodstream can lead to serious sepsis. Before injecting contrast into the catheter, it allows urine to be collected from both upper tracts separately for cytologic analyses. Prior to inserting the catheter into the urine, air bubbles need to be eliminated by rinsing the catheter, because these can act as false filling defects. After a plain film, 5 to 10 ml of diluted contrast agent is slowly injected to avoid high pressure. Under fluoroscopic guidance the ureter and the renal collecting system are assessed in turn (Figure 6). The imaging features of upper urinary tract tumor, visualized with RUP, appear as filling defects, irregularities of the contour, stenosis of the ureter, nonvisualized calyces, and hydronephrosis. The cup-shaped collection of contrast, distal to the filling defect, is called the Goblet or Champagne glass sign, and suggests a ureteral tumor.[12,13] Viewed independently from comparison with other imaging techniques, the RUP as it is performed today has its advantages and disadvantages. One of its greatest advantages is fluoroscopic monitoring, performed by the urologist him/herself, which allows the region of interest to be optimized in order to correctly diagnose any pathology. In this way, contrast instillation in the ureter can be repeated in the same setting so as to reach optimal intracavitary filling (opacification) throughout the whole tract for evaluation of any pathology. As for the exposure to contrast media involved in RUP, severe adverse events are only seen infrequently. Allergic reactions to the contrast agents used in retrograde studies are very rare (0.26%). And only a few case reports have documented anaphylactic reactions during RUP.[14,15] Contrast-induced nephropathy has been described, but seems to be associated with bilateral obstruction. Moreover, in patients with renal impairment, who cannot excrete intravenous contrast or are at risk of developing deterioration of their renal failure upon exposure to intravenous contrast, RUP can offer complete urography without the previously mentioned dangers. Finally, ancillary diagnostic procedures and therapeutic interventions, which can be performed at the same time as the RUP, should be mentioned. In addition to collecting selective ureteral cytology, a ureteral stent can be placed directly into the ureter to relieve symptoms caused by any eventual obstruction caused by a tumor. The major disadvantage of the RUP technique is the difficulty or even the impossibility of cannulating the ureter as a result of an enlarged prostate, a tumor at the ureteral orifice, the presence of a bladder diverticulum, cloudy or hematuric urine, or a reimplanted ureter. More experienced urologists will deal with these problems better as a result of their superior skills and acquired techniques. The main inconvenience of RUP in terms of the patient is the requirement of cystoscopy and ureteral catheterization. However, this negative aspect will not be relevant when performed during the transurethral resection of the tumor, a procedure performed under spinal or general anesthesia. Although the technique is minimally invasive, several serious complications from cystoscopy and ureteral catheterization have been described, including perforation of several locations of the urinary tract, stricture with secondary obstruction, and infection and sepsis. When the injection pressure due to the ureteral contrast is too excessive, or there is trauma in the urothelium of the renal pelvis and calyces, contrast media can leak into lymphovascular spaces.[16] The very rare negative consequences from this backflow can be air embolism, renal tubular toxicity, renal ischemia, renal transplant rejection, prolonged obstruction, urinoma, or retroperitoneal abscess. Backflow should be prevented by keeping the intrapelvic pressure low (< 30 mmHg), although some individuals with normal anatomy will suffer from backflow despite perfect low-pressure technique. The final drawback of RUP is that this technique cannot establish extrauretral extension or distant spread of a detected tumor. For staging of a diagnosed upper urinary tract tumor, additional imaging is required.

Contrast agents

Improvements in contrast agents made over the last 100 years have made RUP much safer for the patient. In the era when silver media were used, in the urinary tract of dogs the silver could be seen to act as foreign bodies and cause focal necrosis. Another cause of adverse effects from this earlier technique was the exaggerated distension of the renal pelvis. This not only might cause tearing lesions but also could facilitate contrast into the body's circulatory system, which might lead to major adverse reactions.[11] Although the silver-containing media even resulted in fatalities, several urologists continued to use various silver preparations (silver oxide and silver iodide) for over a decade. For a while, a minor improvement was made with the introduction of a crystalloid.[10] But in 1918 the silver decade definitively came to an end, and surgeon Donald F. Cameron from the University of Minnesota proposed sodium iodide for the retrograde study of the upper tract.[17]
The advantage of iodine is its greater molecular weight and its quality of selective absorption of X-rays. Moreover, it is not that hypertonic. Oily contrast compounds have also been used, for example Lipiodol, also known as ethiodized oil, which we know today from markers used for positioning techniques in radiotherapy. Lipiodol will not form a nice homogeneous solution with water or urine and, therefore, is not suitable for pyelography.[18]

It was not until 1929 that Uroselectan, the precursor of later iodinated, intravenously used contrast agents, was first reported by an American urologist Moses Swick (1900-1985), at the time working at the St Hedwig's Krankenhaus in Berlin.[19] Initially on a research fellowship, he was studying antibacterial drugs as internist in Leopold Lichtwitz's Clinic in Hamburg, Germany. Lichtwitz was experimenting with the compound Selectan neutral, formerly used as a treatment for coccus infections in cows and synthesized by Arthur Binz (1868-1943), professor of chemistry at the Agricultural College in Berlin, for the treatment of urinary tract infections in man.[20] While Swick was evaluating the compound in rabbits, the studies revealed that it was promptly excreted in the urine, and, since this compound was iodine-containing, he obtained radiographs, which showed urograms. Thereafter, he gave several injections of Selectan neutral to patients, and intravenous ureteropyelography (IVU) was born. Swick attributed the toxic manifestations, such as nausea, vomiting, and double vision (actually a hangover), to the methylgroup – better known as alcohol – based on empirical findings. As a result, he contacted Binz, who was synthesizing a new compound containing iodine atoms with the methyl radical substituted. Further modification took place together with Kurt Räth, a colleague of Binz and professor of chemistry of the Agricultural College of Berlin, by increasing the solubility and lowering toxicity. The new preparation, named Uroselectan (Iopax), yielded good X-ray visualization. Eventually, Uroselectan was replaced by ionic monomers, then by tri-iodinated nonionic agents (Omnipaque), and finally by iso-osmolar nonionic compounds (Visipaque).[20] These newer and safer agents are commonly used in different cross-sectional imaging techniques today. However, there are still some drawbacks to IV contrast-enhanced imaging. In addition to allergic reactions (0.6%), contrast-induced nephropathy is a feared complication of intravenous iodinated contrast media.[21] In a recent meta-analysis, the pooled incidence of contrast-induced nephropathy was 6.4%. The risk of the need for renal replacement therapy after contrast-induced nephropathy was low, at 0.06%. The decline in renal function persisted in 1.1% of patients.[22] The toxic effects caused by iodinated contrast media are considered multifactorial. Numerous studies on toxicity of contrast media on various cell types in cell culture models have shown evident signs of apoptosis and impairment of several cell functions.[23] This has led to direct cell-membrane damage and increased oxidative stress to cultured cells, endothelium, and tubules. As a result, hypoperfusion, hypoxia, high osmolarity, and high viscosity may aggravate the cytotoxic effects. In light of these potential nephropathy-inducing conditions, several adaptations of contrast protocols have been made to minimize the risks for the patient.

Excretory urography or intravenous urography (IVU)

The existence of infections in the pre-antibiotic era resulted in a growing resistance to the invasiveness of this retrograde procedure. A contrast medium that would be safely excreted by the kidneys was needed. The first excretory ureteropyelography with intravenous sodium iodide was produced in 1918 and reported in 1923 by internist Leonard George Rowntree (1883-1959), and dermatologist Earl Osborne (1895-1960) and coworkers at the Mayo Clinic, US.[16] Further development of excretory urography (1929-1931), with both oral and intravenous contrast, was carried out with contrast that produced poor visualization and frequent toxicity. As excretory urography techniques were refined and newer agents were developed, it became one of the most useful and accurate examinations in clinical urology for the four decades after 1930[20,24] (Figure 7). Using IVU as an alternative to these retrograde studies has meant a shift from the urologist to the radiologist, when performing the imaging of and diagnosis of upper urinary tract pathology. Although the urologist could still carry out this procedure, most urology practices have lost their own X-ray facility. And this might also have contributed to the decrease in enthusiasm for practicing RUP on a wide scale.

Modern imaging of the upper urinary tract

In 2001, there seemed to be no question that IVU would remain the primary modality for evaluation of the urinary tract. Still, the introduction of sectional imaging and its rapid development did end up completely replacing the IVU.[10] IVU was inexpensive and could assess renal function, estimate the degree of obstruction, and depict surgical anatomy. However, IVU had poor sensitivity with regard to the detection of small (≥ 3cm) masses. Its other drawbacks were the dependency of sufficient renal function, potential contrast-induced nephropathy, and the necessity of obtaining delayed films in cases of severe obstruction.[25] In 1974, radiologist Morton Arthur Bosniak showed that nephrotomography increased the detection of renal masses compared to standard IVU alone[26] (Figure 8). In the late 1970s, ultrasound was also added as an important modality, primarily in the differentiation between solid and cystic masses of the kidney (Figure 9). After 1980, computer tomography (CT) quickly emerged as a powerful "all-in-one" sectional imaging tool for diagnosing many diseases of the urinary tract, such as renal infection, calculi, (malignant) masses, and trauma. However, at the time IVU was still needed to image the urothelium.

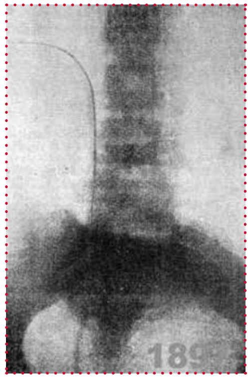

Figure 5
First radiopaque catheterism of the ureter by Tuffier.
Adapted from a manuscript submitted to the International Society for the History of Radiology (ISHRAD) for eventual publication on the website of the society. Discussion intended to be held on November 11, 2011, at the ISHRAD meeting of the BIR.

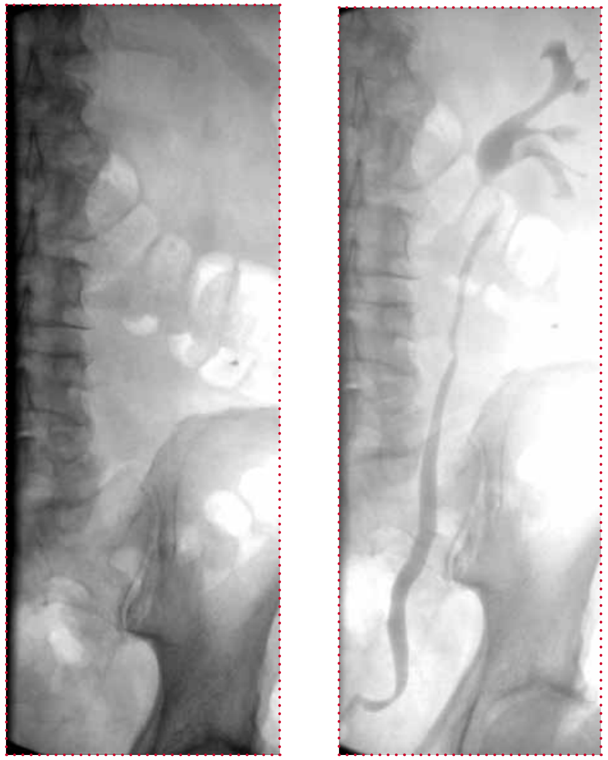

Figure 6
Normal RUP.
From the collection of the urology department of the University Medical Center Groningen. No signs of UUTT.

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8A

8B

Figure 7
IVU without signs of UUTT.
Adapted from Wikipedia on ureteral cancer. (Wikimedia Commons, the free media repository)

Figure 8
Nephrotomography
A. IVU revealing calcified (L) psoas abscess (black arrow), impinging on the ureter.
B. Nephrotomography with calcified caseous renal mass (arrowheads) more apparent.

Adapted from Merchant S, Barati A, Merchant N, Tuberculosis of the genitourinary system-Urinary tract tuberculosis: Renal tuberculosis-Part I. Genitourinary and Obstetric Radiology (2013) 23, 1; 46-63.

Later on, with the introduction of the multi-row detector CT in the 1990s, it was possible to produce a large number of thin section images in a short period of time. The spatial, temporal, and contrast resolution became sufficient for appropriate images of the urothelium. Subsequently, contrast administration and scanning protocols were developed to produce IVU-like images of the urinary tract, referred to as CT-urography (CTU) (Figure 10).[27] As in IVU, normal renal function is a prerequisite in CTU in order to produce evaluable (opacified) images in a safe way with respect to potential development of renal failure. Meanwhile, magnetic resonance imaging (MRI) has become an important imaging technique as well, especially in patients with renal insufficiency and in patients with an allergy to iodine contrast media. Comparatively speaking, the MRI technique was evolved to produce urographic images, which are referred to as MRU. Currently, CTU is the modality of choice for evaluation of macroscopic hematuria. It allows stones, parenchymal renal masses, and, to a high degree, urothelial abnormalities to be identified.[27] Regarding the diagnosis of these urothelial growths, rates from the recent literature in terms of sensitivity and specificity for detection of upper urinary tract tumor are 96% and 99%, respectively.[28] American and European guidelines recommend the use of CTU in such cases.[29,30] The scientific evidence is primarily based on several studies aimed solely at the performance of the CTU but without any comparison to the performance of other imaging modalities. The sensitivity / specificity figures mentioned for the detection of upper urinary tract tumor for CTU, MRU, IVU, and RUP in literature are 96% / 99%, 69% / 97%, 80% / 81%, and 96% / 96%, respectively.[31] Hence, in addition to CTU, the performances of MRU and RUP seem to be, at the very least, comparable. Considered independently from the influence of guidelines as to the choice of certain imaging modalities in daily practice, the availability of the different techniques plays an important role in their actual use. For example, since the majority of all urology practices no longer have their own X-ray facilities, performing an RUP has become a time-consuming procedure. First, the urologist needs to canalize the orifice of the ureter with a catheter. Then a mobile X-ray device has to be organized or the patient has to be transported to the X-ray department in order to perform the retrograde urography.

Each single modality, CTU, RUP, or MRU, has advantages and disadvantages, which might alter the choice of the one recommended for specific patients.

The benefits and drawbacks of the RUP have already been discussed. It is clear that CTU and MRU have major advantages, not only with regard to accuracy but also in terms of a low level of inconvenience for patients. As a result, it saves the urologist in question time and expense. On the other hand, the increased use of CTU is associated with a higher radiation exposure for the growing population using the healthcare system. Though there is clear evidence that larger radiation doses are carcinogenic, the true risk of radiation-induced carcinogenesis has never been directly studied and therefore remains uncertain.[32] Furthermore, the large increase in the use of IV contrast, which accompanies CTU, is one of the new hazards to be dealt with, in particularly among the population who need to be imaged on a regular basis, such as those at high risk for non-muscle-invasive bladder cancer. In an attempt to diminish radiation and intravenous contrast exposure, many protocols have been developed, but consensus regarding the optimal protocol has yet to be reached.[27] The challenge remains to use the most sensitive and specific imaging technique with the lowest exposure to IV contrast and to potentially damaging radiation.

Current role of RUP in diagnosing upper urinary tract tumor

At the same time as IVU fully emerged as the urological imaging tool, urologists ceded a part of their knowledge and concern in terms of specific urological pathology, in particular that involving the upper urinary tract. From that point on, retrograde studies have no longer formed the basis for urological imaging, resulting in the loss of availability of X-ray facilities in urological practices. From an economical standpoint, this alteration has saved time and expense for those practices. In the meantime, CTU and MRU continue to be recommended as first-choice imaging tools in the detection of upper urinary tract tumor. The advantages of RUP, however, are now apt to be forgotten, and, with that, the detailed knowledge and thorough experience involved in it will gradually disappear from daily practice. Both in primary investigation of a ureteral carcinoma, as well as in follow-up of the upper urinary tract in patients with NMIBC or those formerly treated for upper urinary tract tumor, not every patient will be a suitable candidate for CTU or MRU because of the reasons already discussed. In those patients, and in patients with suboptimal CTU, who warrant additional imaging, RUP has always been a valuable technique. And, likewise in the future, it is to be expected that RUP will not disappear from upper urinary tract imaging with respect to diagnosing abnormalities of the urothelium.

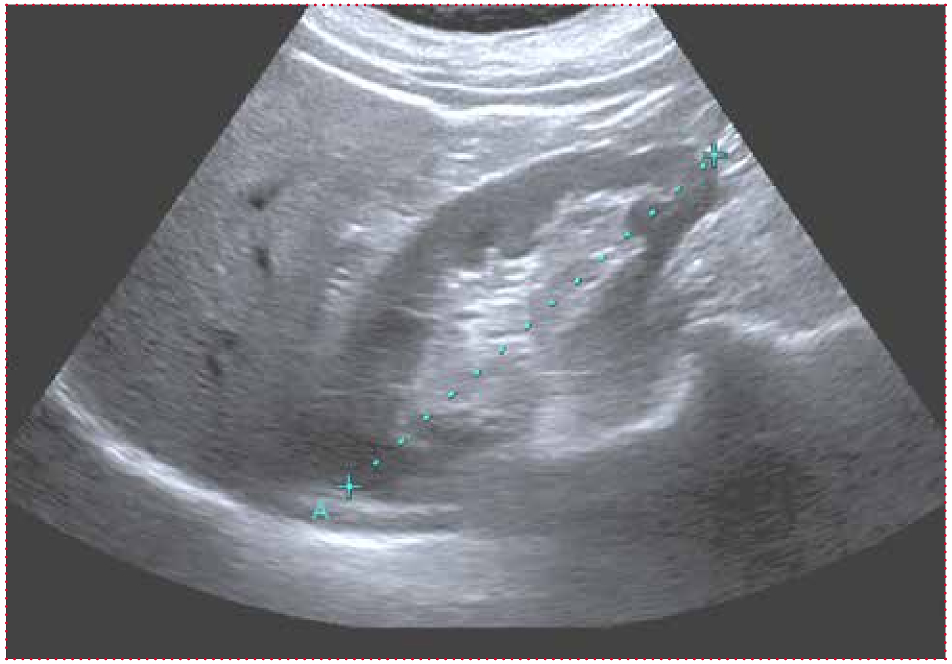

Figure 9
Ultrasound of the right kidney.
From the collection of the urology department of the University Medical Center Groningen.

A

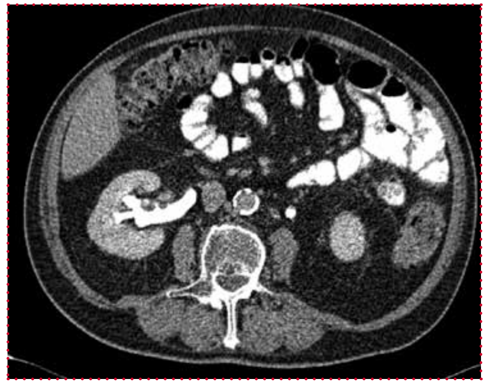

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Figure 10
CTU
A Coronal section.
B Transversal section. In the right renal pelvis a tumor is to be expected.

From the collection of the urology department of the University Medical Center Groningen.

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