Chapter 11

Urothelial Cell Carcinoma of the Upper Urinary Tract: Introduction

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Introduction

Urothelium is the specialized epithelium that covers the urinary collecting system from the tips of the renal papillae to the prostatic urethra. Tumors of the urothelium can be benign but the vast majority are malignant carcinomas. Carcinomas of the urothelium are common and the upper urinary tract is the affected site in roughly 5% of cases. Similarly, 5–10% of tumors that involve the kidney actually arise from the renal collecting system. It is unusual to find an upper urinary tract tumor as a result of screening imaging. Rather, most patients present with symptoms of flank pain or hematuria and are evaluated specifically to rule out tumoral involvement of the collecting system. Nonetheless, a thorough evaluation of the collecting systems should be routinely sought in most renal imaging procedures, even if typical symptoms are not present.

This chapter discusses widely available imaging modalities used to diagnose upper urinary tract tumors: ultrasonography, intravenous pyelography, retrograde pyelography, and antegrade pyelography. For each of these imaging techniques we have attempted to present a discussion of special indications for usage, practical strengths and weaknesses, interpretation pointers and pitfalls, evidence of efficacy for diagnosing upper urinary tract tumors, and potential complications resulting from usage. References are used liberally and are meant to provide a comprehensive reading list for the reader interested in further exploring the published evidence for the imaging modalities and ideas presented herein.

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Ultrasonography

The Normal Upper Urinary Tract

Kidney

Ultrasound examination of the kidney is typically performed with a 2.5–5 MHz transducer with the patient in any one of a number of positions. The kidneys are usually best viewed on deep inspiration and transverse and longitudinal images are obtained. Characteristics that should be routinely examined are the size and shape of the kidney, the echogenicity of the cortex relative to the spleen and liver, the thickness of the cortex, the degree of corticomedullary differentiation, and the structure of the intrarenal collecting system (i.e., calyces and renal pelvis).

The kidney usually has a smooth contour that resembles a bean although persistent fetal lobulation is a common normal variant. The spleen or liver may indent the upper pole of the kidney giving the impression of a dromedary hump. The adult renal cortex is thickest at the poles of the kidney where it is approximately 15 mm thick [1]. The renal medulla is principally comprised of 10–12 triangular renal pyramids that contain the collecting ducts and loops of Henle of the nephron. The pyramids are hypoechoic relative to the cortex and are separated from one another by fingers of interpyramidal renal cortex called the columns of Bertin. The rounded apex of each renal pyramid—called the papilla—projects into a minor calyx where it drains the urine flowing through its collecting ducts.

Renal Calyces and Pelvis

The 10–12 minor calyces then drain into 2–3 major calyces which coalesce to form the renal pelvis. The renal pelvis can assume a wide variety of normal shapes and may not be symmetric with the contralateral side. This pleomorphism can make diagnosing obstruction difficult at times. The renal

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calyces and pelvis are located in a central concavity in the kidney that is called the renal sinus. Fatty tissue is abundant in the renal sinus of adults and accounts for its hyperechogenic appearance on ultrasound [2]. In renal ultrasonography, the normal order of increasing tissue echogenicity is renal medulla, renal cortex, liver and spleen, pancreas, and renal sinus. Demonstration of the urothelium that lines all the collecting system is not always possible but, when it is visible, it should appear as a slightly hyperechogenic layer that is smooth, thin, and regular. The renal pelvis and calyces drain into the same retroperitoneal lymph nodes as the kidney: the left side drains primarily into the para-aortic, preaortic, and postaortic nodes while the right side drains principally into the paracaval and interaortocaval nodes.

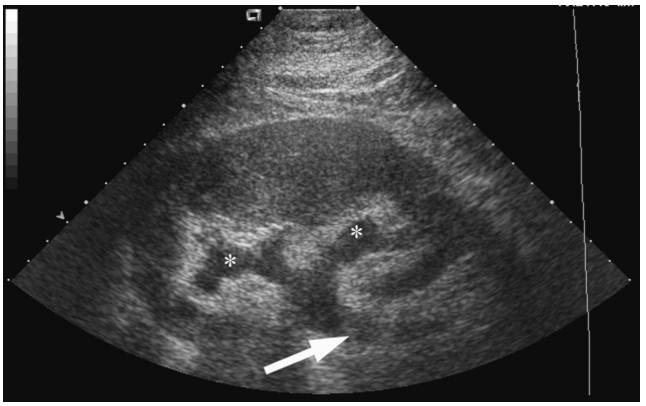

Fig. 11.1 Longitudinal ultrasound image of the left kidney demonstrates dilatation of the intrarenal collecting system (*asterisk*) with a dilated proximal ureter (*arrow*)

Ureter

Drainage of the renal pelvis into the ureter occurs at the ureteropelvic junction, a common site for both congenital and acquired obstructions. The ureter courses in the retroperitoneal space on top of the psoas muscle and is situated lateral to the vertebral pedicles until it deviates medially and crosses the common iliac artery (at the level of its bifurcation) to enter the pelvis. The retroperitoneal ureters should be at least 5 cm apart and should have a slight S shape. The pelvic portion of the ureter enters the trigone of the bladder posteriorly after passing in close proximity to the uterine artery and cervix in the female. Ureteral length varies with age, gender, and height but averages around 24 cm. Normal ureters are not routinely seen with ultrasonography but dilated ureters are. The lymphatic drainage of the ureters follows a course similar to the ureteral vasculature. The retroperitoneal portion of the left ureter drains medially into the para-aortic and presacral nodes whereas the right retroperitoneal ureter drains medially into the paracaval and interaortocaval nodes. Both pelvic ureters drain laterally into the internal iliac, external iliac, and common iliac nodes.

Upper Urinary Tract Obstruction

Renal ultrasonography (RUS) may be the first imaging modality used to investigate a patient with flank pain or hematuria, both of which may be presenting signs of an upper urinary tract tumor [3, 4]. The most frequent complication of an upper urinary tract tumor that can be seen with RUS imaging is urinary tract obstruction leading to *collecting system dilation* (Fig. 11.1). Though early account of RUS described an impressive sensitivity of 98% for diagnosing obstruction, the specificity was only 74% [5]. It was quickly recognized that the cause of the high false-positive rate was a number of non-obstructive entities that produce a dilation of the collecting system that can closely mimic obstruction [6]. Technological advances in ultrasonography have helped to reverse these early problems of diagnostic accuracy and the combination of higher ultrasound frequencies, better transducers, and better software has resulted in dramatically improved image resolution. The single most important development in renal ultrasound in the last 20 years, however, has been the acquisition of the capability to perform Doppler flow analysis [7]. The expansion of early Doppler technology has led to the clinical applications of waveform Doppler sonography, power Doppler sonography, and color Doppler sonography. This, in turn, has allowed the ultrasonographer to measure the *renal resistive index* and *ureteral jets* (Fig. 11.2) [8–10], both of which can help to diagnose veritable renal obstruction.

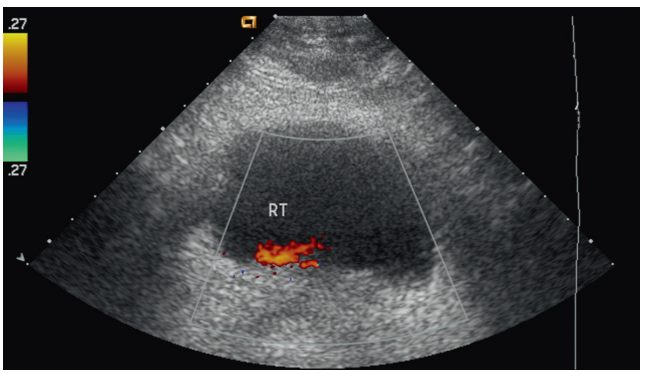

Fig. 11.2 Transverse Doppler ultrasound image of the bladder demonstrates a normal right ureteral jet. The left ureteral jet is absent suggestive of left sided obstruction

Renal Pelvic Tumors

If large enough, urothelial tumors of the renal pelvis can be visualized directly by ultrasound. Although finding a mass in the renal collecting system can sometimes be very difficult with ultrasound, an equally important task is ruling out a number of non-malignant pathologies that can cause a mass lesion in the renal pelvis (Table 11.1). A recent manuscript provides an excellent review of the diagnostic imaging features of lesions of the renal sinus [11].

Separation of the Central Echo Complex

Renal pelvic tumors can cause separation of the normally echodense central renal sinus if they are large enough [2, 12, 13]. The appearance of separation of the central echo seen in upper tract tumors is similar to what is seen in hydronephrosis but can be distinguished from the former by the presence of residual echoes and the absence of the acoustic enhancement (Fig. 11.3) [12]. The presence of a central renal mass of moderate echogenicity that is separated from the renal parenchyma by a rim of highly echogenic renal sinus fat should be considered a malignant urothelial tumor until proven otherwise [2, 13].

Table 11.1 Differential diagnosis for a collecting system filling defect

Calculi
Calyceal papilla
Cancer
Clots
Contrast air bubble
Cyclical endometriosis
Contamination/cultures
Fungus ball (mycetoma)
Schistosomiasis
Tuberculosis
Chronic inflammation
Cystic ureteropyelitis
Malakoplakia
Leukoplakia/cholesteatoma
Congenital
Vascular imprint
Kinks

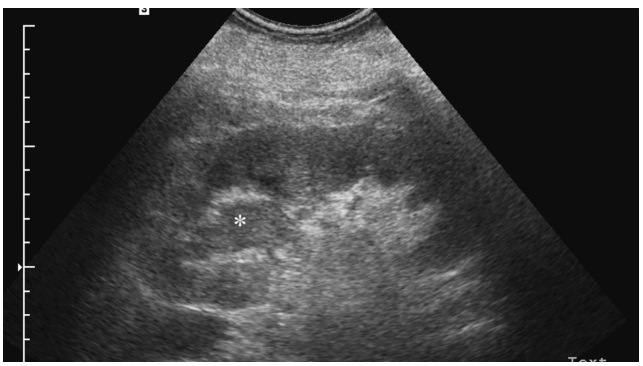

Fig. 11.3 Longitudinal ultrasound image of the right kidney demonstrates soft tissue with similar echogenicity as the renal parenchyma (*asterisk*) separating the normal renal sinus fat. The findings are due to a large TCC in the upper pole of the kidney

Echogenicity

Urothelial tumors tend to have an echogenicity that is similar to the renal cortex but less than the normal renal sinus [12, 13]. Blood clots can have varying degrees of echogenicity and may be quite difficult to differentiate from a tumor [14, 15]. Renal calculi tend to be more echogenic than tumors and, due to their high density, calculi usually demonstrate acoustic shadowing (the cone-dome) characteristic of calcium deposition [15–18]. Calcification may also be present in tuberculous and schistosomal infection of the urinary tract [19–25]. However, it should be kept in mind that rare urothelial tumors may present with intratumoral calcification in a pattern that has been described as coarse and punctate [26]. Furthermore, certain upper urinary tract tumors—particularly squamous cell carcinomas—arise in the context of chronic irritative renal urolithiasis [27–31]. One group has even reported acoustic shadowing in a tumor [32]. Therefore, though the presence of calcification, a renal pelvic stone, or acoustic shadowing does not absolutely rule out a renal pelvic tumor, it certainly does suggest alternate diagnoses.

Mobility

One feature that can distinguish a urothelial tumor from other potential intraluminal masses is its lack of mobility. While necrotic papillae, blood clots, and certain calculi may move with a change in patient position, tumors are fixed to the urothelium and should not move [12].

Contour

Though by no means absolute, urothelial tumors of the renal pelvis tend to be poorly defined and have irregular contours while blood clots and stones tend to have sharp smooth contours [12]. Considerable overlap exists, however, and stones can be ragged and tumors smooth. Another problem is that contours are difficult to assess with ultrasonography. For these reasons contours are often of little use in diagnosing urothelial tumors by ultrasonography [33].

Blood Flow

The demonstration of blood flow within a urothelial mass is pathognomonic for a neoplastic process [33–38]. Of the few reported upper tract urothelial carcinomas that have been evaluated by Doppler ultrasonography, most have shown a Doppler shift greater than 2 kHz [34, 35].

Large Tumors

Large tumors of the central kidney that are clearly invading both the collecting system and the renal parenchyma are nearly impossible to categorize with certainty using ultrasonography [39]. These lesions can represent a renal tubular neoplasm that has invaded the collecting system or a urothelial neoplasm that has grown into the renal parenchyma. CT scanning may perform better than ultrasonography in this setting but is by no means a perfect technique [40, 41]. If treatment decisions are to be influenced by the histologic tumor type, a pretreatment biopsy should be considered.

Ureteral Tumors

Ultrasonography has not been traditionally considered a good way to assess for ureteral tumors. Whereas other imaging modalities can show a variety of imaging findings in cases of ureteral tumors, ultrasonography typically demonstrates two things: a ureteral mass or its associated hydronephrosis [37, 42, 43]. Ureteral tumors have similar features to the renal pelvic tumors described earlier in that they are of moderate echogenicity, show no acoustic shadowing, and are rarely calcified. Evidence of Doppler flow in a ureteral mass is likewise considered pathognomonic for tumor [38]. Comparative studies of the various imaging modalities for ureteral tumors are rare but at least one group has shown ultrasonography to be superior to CT in detecting these uncommon tumors [42].

Advantages of Ultrasonography

Ultrasonography is probably not the best overall method for evaluating the upper urinary tract for cancer. Nonetheless, it does have certain advantages that deserve special mention.

Noninvasive

Unlike all other methods of evaluating the upper urinary tract, ultrasonography does not require intravenous access, a percutaneous nephrostomy, or a ureteral catheter. The risk of iatrogenic injury to the body is therefore practically nonexistent.

No Contrast

All other forms of urography require the administration of potentially toxic and allergenic contrast agents. Contrast-associated side effects are not a minor problem and will be discussed in more detail in the section Intravenous Pyelography.

Renal Insufficiency

Patients with impaired renal function are at high risk for contrast nephrotoxicity and should generally be spared contrast if possible. If the kidney is non-functional because of severe tumoral obstruction or some other process, contrast excretion will be markedly impaired and the quality of the imaging will suffer dramatically. Ultrasonography can be used safely and effectively in patients with renal failure.

Radiation

Ultrasonography does not use ionizing radiation to image the body and is generally considered to be free of significant side effects [44]. This important fact makes it the ideal imaging study for pregnant women. It should also be remembered that imaging-related neoplasia is a possibility for diagnostic imaging modalities that use ionizing radiation [45–48]. This may be particularly relevant for cancer patients who undergo repeated imaging tests.

Cost

Along with IVP, ultrasonography is probably the most inexpensive diagnostic test for evaluating the upper urinary tract.

Disadvantages of Ultrasonography

Calculi

Ultrasonography is not very sensitive for diagnosing renal calculi [49–52]. Since most patients with upper tract tumors are initially evaluated for flank pain or hematuria and stones are a much more common cause of these symptoms than urothelial tumors, the initial evaluation of flank pain and

hematuria should employ a technique that is very sensitive for detecting stones (such as noncontrast CT) [53–55].

Staging

If a urothelial tumor is detected on initial imaging, staging the tumor then becomes a very important consideration. Conventional ultrasonography is inferior to CT and MRI for detecting retroperitoneal and pelvic lymph node enlargement [56–60], for detecting hepatic metastases [61–63], and for evaluating the lungs [64–66]. There is one particular advantage to ultrasonography for tumor staging, however: evaluation of the renal vein. Like renal cell carcinomas, urothelial carcinomas can invade the renal vein and spread to the inferior vena cava, albeit much less frequently [67]. Color Doppler imaging may be more accurate than CT in identifying tumor thrombus in the renal vein or vena cava [68–71].

Operator Dependence

Ultrasonography is operator dependent: the better the ultrasonographer, the better the accuracy [72–76]. Cross-sectional imaging modalities appear to have better interobserver reproducibility than ultrasonography.

New Advances in Ultrasonography

Endoluminal Ultrasonography

The use of intraureteral ultrasonography was first reported in the 1990s and the first report of the diagnosis of ureteral tumor occurred shortly thereafter [77, 78]. Endoluminal ultrasonography has not been widely adopted in the 15 years since it was introduced despite the refinement of smaller and more accurate probes. Its use has been principally limited to the diagnosis of crossing vessels at the ureteropelvic junction in a few select medical centers [79–83]. There have been just a few reports of its employment in diagnosing urothelial tumors of the ureter and renal pelvis [77, 84, 85]. The authors of these studies cite the principle benefit of better preoperative staging of the tumor due to more accurate identification of the ureteral mucosa and musculature. This staging advantage would only benefit the minority of patients with upper tract tumors that are considering endoscopic management. Newer modifications of the technique involve 3D reconstruction of the upper urinary tract [86, 87].

Microbubble Contrast Agents

One of the most exciting advances in ultrasonography has been the development of the technique of contrast-enhanced ultrasonography that has the potential to greatly improve diagnostic accuracy [88, 89]. The contrast agents that have been developed for ultrasound consist principally of small air bubbles measuring 3 μm in diameter that can be injected into the bloodstream or the urinary tract. At high ultrasound frequencies these microbubbles are over a thousand times more echogenic than the surrounding normal tissues [90]. Applications that are relevant to urothelial tumors include improved visualization of liver metastases [91, 92], improved imaging of tumor microvascularity [93], retrograde imaging of the ureter without radiation [94–96], molecular imaging [97], and the delivery of drugs to specific targets [88].

Intravenous Pyelography (IVP)

Brief History

After the development of medical X-rays by Roentgen in 1895, the first step toward the development of intravenous pyelogram was the development of radiocontrast. Radiocontrast was first used to visualize the urinary collecting in the form of retrograde pyelography (see discussion below) [98]. Early contrast agents—such as colloidal silver, thorium, and colloidal silver iodide—were toxic irritants that harmed the urinary tract and occasionally resulted in patient deaths. A major advance occurred in 1918 when Donald Cameron from the University of Minnesota introduced sodium iodide as a new contrast agent [99]. This agent was remarkable because it was much less toxic than other contrast agents available at the time. Mayo Clinic physicians Earl Osborne (Fig. 11.4), Charles Sutherland, Albert Scholl, and Leonard Rowntree (Fig. 11.5) used intravenous sodium iodide to produce the first intravenous pyelogram in 1918 and reported the results of their initial series in 1923 [100]. The result was a revolution in medical imaging and the next 75 years were spent trying to find contrast agents with better imaging characteristics and lower toxicity. German physician Leopold Lichtwitz was key to the development of novel contrast agents. He recruited American physician Moses Swick to a fellowship position in his laboratory in Hamburg, and the young American physician began screening multiple new agents as potential contrast agents. Swick soon moved to Berlin and began working with Alexander von Lichtenberg, the discoverer of the retrograde pyelogram, on newer and better agents. They teamed up with Arthur Binz, a Berlin chemist that had provided chemicals to Swick while he was in Hamburg,

Fig. 11.4 Earl Osborne, Mayo Clinic dermatology resident, 1918–1923

Fig. 11.5 Leonard Rowntree, Mayo Clinic internist, 1920–1932

and eventually the ionic compound Uroselectan (Iopax) was developed [101]. Uroselectan was eventually replaced by ionic monomers (e.g., diatrizoate, iothalamate) then by triiodinated nonionic compounds (e.g., iohexol/Omnipaque), and finally by iso-osmolar nonionic compounds (e.g., iodixans/Visipaque). With these newer agents, IVP has become a safer and better diagnostic test.

More recently, questions have surfaced as to whether IVP is dead, dying or neither [102–106]. Though IVP may no longer be the primary diagnostic modality for evaluating the urinary tract, we argue that it certainly has its place in current practice. CT and MR urography simply do not demonstrate the anatomic detail of the renal pelvis and ureter that IVP and retrograde pyelography offer [107]. These techniques are still useful and need not be abandoned.

Technique

Patient preparation is not routinely required for IVP but certain key points should be observed. Patients should be well hydrated and have adequate renal function (see section Disadvantages of IVP) and an empty bladder. The following film sequences are a suggestion for a typical case but it should be recalled that IVP should be tailored to each clinical circumstance [108]. A summary of the IVP procedure that we use at the Mayo Clinic has been previously published [109]. A scout film is first obtained and is followed by 300–600 mg/kg of contrast medium injected as a bolus into the bloodstream. An initial film coned to the kidneys can be obtained at 1 minute to demonstrate the nephrogram. A second film is obtained at 5 minutes to assess the progress of opacification of the parenchyma and collecting system. This film should include the inferior margin of the symphisis pubis and the suprarenal region. A third film is obtained at 10 minutes to view the collecting system which should be filled with contrast by this point in time. Visualization of the collecting system on this film can be improved by abdominal compression or by Trendelenberg positioning (Fig. 11.6). We routinely commence our abdominal compression shortly after contrast injection and center it at the iliac crest where the ureters can be compressed against the bony pelvis. If the collecting system is not seen perfectly, oblique films may be of use. It is recommended that at least two images of any collecting system defect be obtained. A fourth film of the ureters and full bladder can be obtained at 10–15 minutes (after release of abdominal compression) followed by a fifth post-micturition film. If there is evidence of obstruction and the collecting system has not filled adequately, delayed films should be sought.

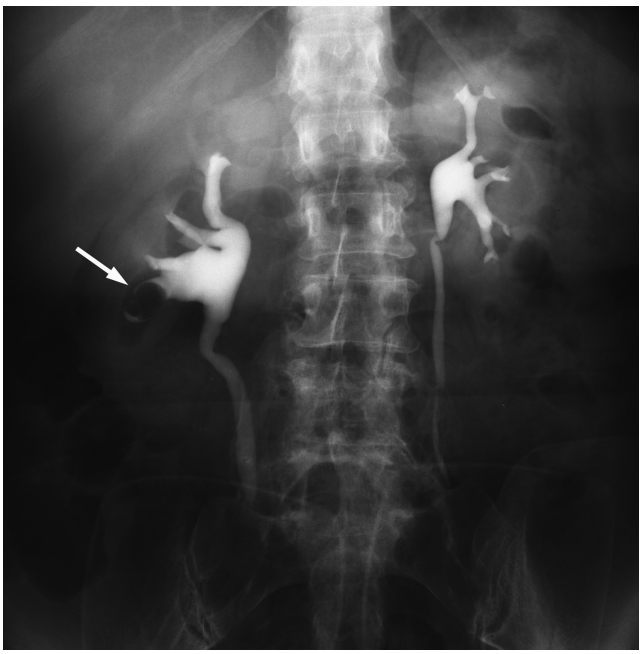

Fig. 11.6 Image from an intravenous pyelogram demonstrates a TCC in a lower pole infundibulum of the right kidney (*arrow*). External compression, as in this case, is useful for optimal distension of the intrarenal collecting system

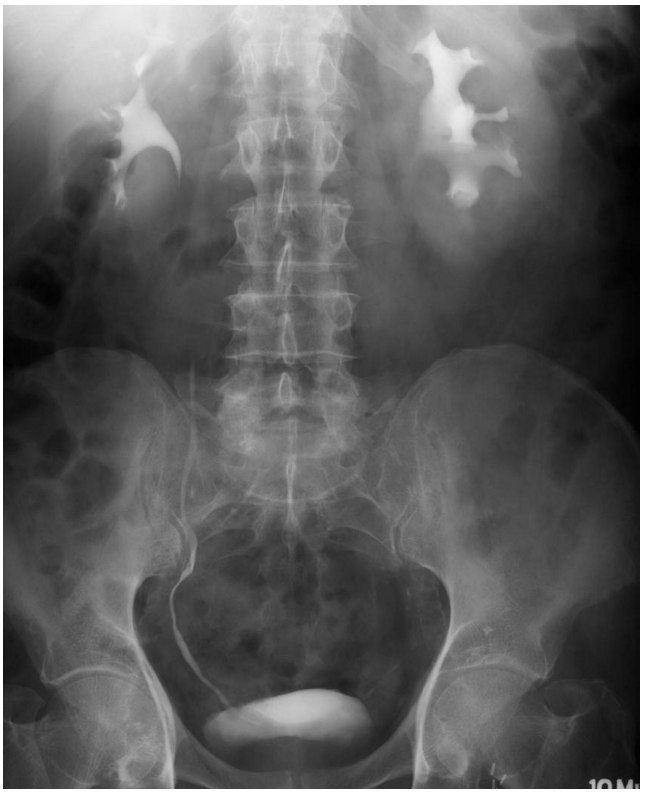

Fig. 11.7 Image from an intravenous pyelogram demonstrates left renal enlargement, dilation of the left renal collecting system and absence of filling of the left ureter

Imaging Features

Calcification

Calcification in upper tract tumors and their mimics is discussed in section Renal Pelvic Tumors. Calcification is sought on the scout film and its position confirmed following contrast injection.

Delayed Nephrogram

When the collecting system of one of two kidneys is obstructed, compensatory hemodynamic changes lead to a reduction in its glomerular filtration rate predominantly through afferent arteriolar vasoconstriction [110–114]. The reduced renal blood flow delays the passage of radiocontrast from the renal artery to the nephron and the imaging result is a delay in the nephrogram. The delay is usually best appreciated by comparing the normal unobstructed kidney to the obstructed kidney. It is noteworthy that renal units that are obstructed bilaterally or that are solitary and obstructed may not show this imaging feature because they undergo a different series of hemodynamic responses to obstruction [113].

Increased Renal Size

Obstruction of the renal collecting system usually (but not always) results in progressive dilation of the ureter and renal pelvis. The dilated kidney appears larger during the nephrographic phase of the IVP (Fig. 11.7).

Distortion of the Renal Contour

The interpapillary line is the curved line that joins the tips of the minor calyces [108]. A change in parenchymal thickness can be appreciated by comparing the distance from the interpapillary line to the edge of the renal parenchyma visualized on the nephrogram of the kidney. When the parenchyma is thickened and the underlying collecting system is abnormal, a renal mass lesion should be suspected. Renal masses can also produce a double contour that is best appreciated at tomography. Parenchymal beaking occurs when there is thickening of the parenchyma at the margins of an intraparenchymal renal lesion and indicates the presence of a slow-growing mass. Non-enhancing parenchymal thickening is typical of a renal cyst.

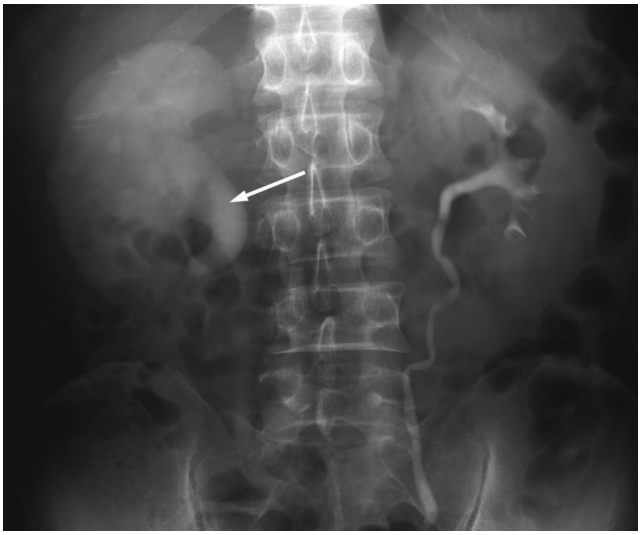

Fig. 11.8 Image from an intravenous pyelogram 45 minutes after injection demonstrates a dilated right intrarenal collecting system and upper ureter (*arrow*). There is persistence of the right nephrogram relative to the left. These secondary findings of obstruction were due to a distal right ureteral TCC (not shown)

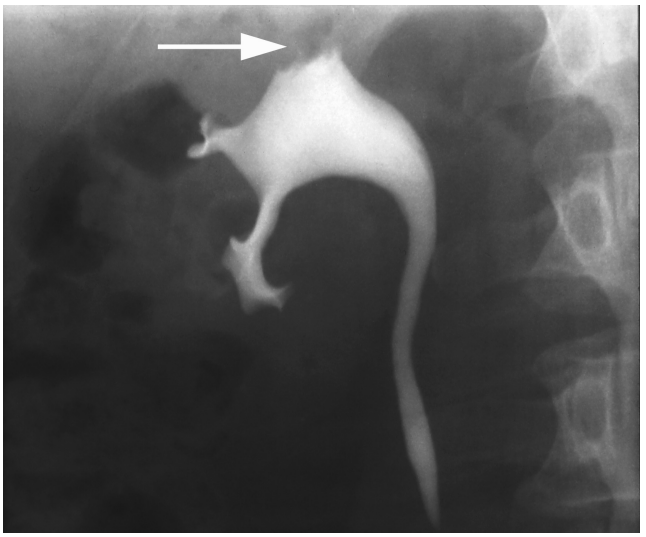

Fig. 11.9 Image from an intravenous pyelogram demonstrates an amputated calyx in the upper pole of the right kidney (*arrow*). This was shown to be due to an obstructing TCC in the upper pole infundibulum

Pyelocaliectasis

Dilation and distortion of the calyces and renal pelvis are usually signs of obstruction though there are many other pathologies that can affect the collecting system anatomy (Fig. 11.8). Pathologies that should be considered include infection and post-infectious scarring (particularly tuberculosis, fungal infections, and schistosomiasis) [19, 24, 115], papillary necrosis [116–119], calyceal diverticulae [120, 121], and infundibular stenosis. Papillary necrosis can be diagnosed by carefully evaluating the minor calyces for a series of suggestive signs while infections are ruled out by urinalysis and urine cultures.

Phantom Calyx

A phantom calyx (a.k.a. aborted calyx) is a calyx that does not fill with contrast on imaging (Fig. 11.9) [122]. It is thought that phantom calyces generally represent serious pathology in the kidney and the differential diagnosis includes tuberculosis, urolithiasis, neoplasia (usually originating from nephron or urothelium), and congenital malformation. A tumor-filled calyx that is non-visualized has been termed an oncocalyx [108].

Filling Defects

Filling defects are likely the most common imaging feature of urothelial tumors of the renal pelvis and may be the second most common feature of ureteral tumors (after hydronephrosis) (Fig. 11.10) [18, 123–126]. The differential

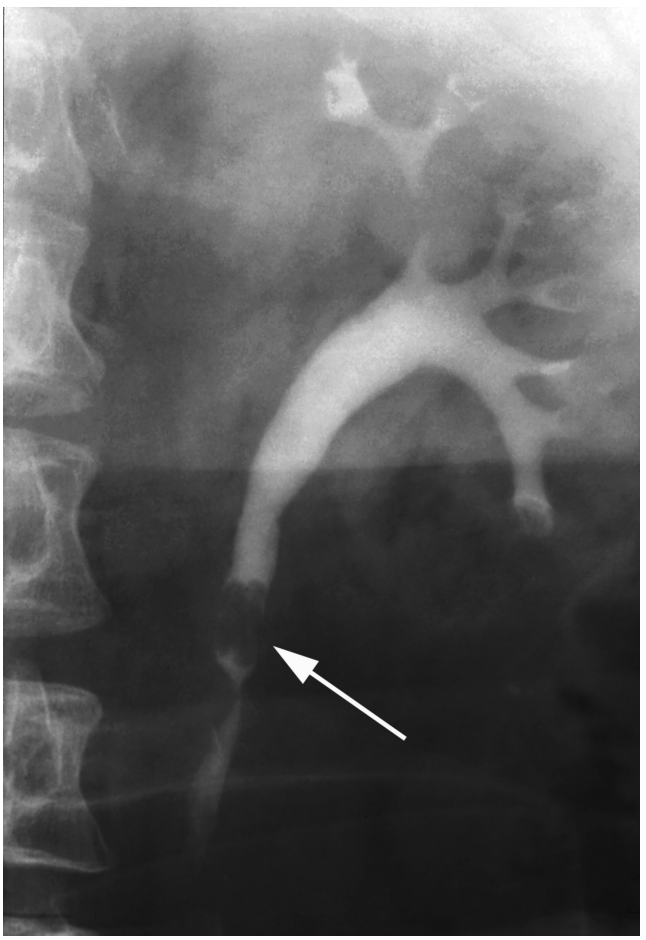

Fig. 11.10 Image from an intravenous pyelogram demonstrates a TCC in the upper left ureter (*arrow*)

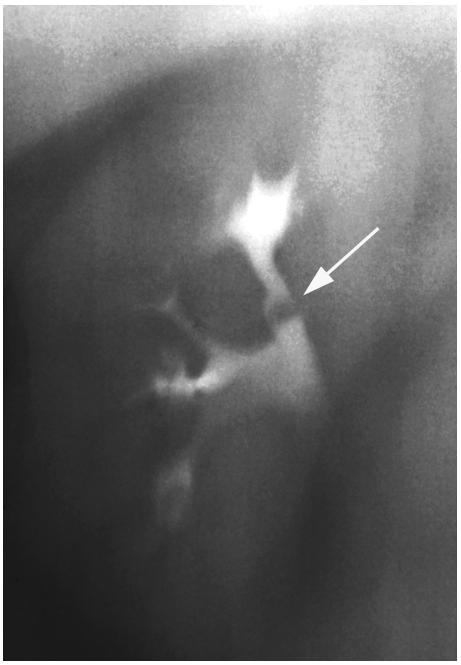

Fig. 11.11 Tomographic image from an intravenous pyelogram demonstrates a tiny TCC in an infundibulum in the upper pole of the right kidney (*arrow*)

diagnosis of collecting system filling defects is given in Table 11.1. Urothelial tumors are multifocal in 10–20% of cases and, therefore, should be high on the differential diagnosis of any process that produces multiple filling defects in the renal pelvis and ureter. Smaller filling defects may be better visualized with tomography (Fig. 11.11)**.**

Stipple Sign

The stipple sign occurs when contrast is trapped within the interstices of a tumor and produces a stippled appearance [127, 128]. The stipple sign is highly suggestive of urothelial carcinoma but can also occur with other pathologies such as blood clots and fungus balls.

Ureteral Deviation

The course of the normal ureter is described in section The Normal Upper Urinary Tract. In most instances, the cause of ureteral deviation is ultimately determined by cross-sectional imaging. On IVP, both the direction of the ureteral deviation and the level at which it occurs are important and can suggest potential etiologies (Table 11.2).

Ureteral Dilation or Narrowing

Though the normal ureteral caliber has been defined by some uroradiologists as a ureter that is less than 8 mm in diameter, the best way to determine dilation is usually comparison to the contralateral side (Fig. 11.12) [108]. The ureter is often slightly dilated just above the area where it crosses the common iliac artery, a segment that has been called the ureteral spindle. Causes of ureteral dilation are given in Table 11.3. Narrowing of the ureter should be interpreted with caution because normal peristaltic waves may give the false impression of a narrowed segment (hence the importance of obtaining two views of any suspected pathology). Determining intrinsic from extrinsic causes of ureteral narrowing can be helpful. Intrinsic infiltration typically produces an irregular and abrupt change in ureteral caliber that resembles an apple core. Extrinsic encasement tends to produce a smooth tapering of the ureter. Causes of ureteral narrowing are given in Table 11.4.

Table 11.2 Differential diagnosis for ureteral deviation

Upper ureter
Medial
Renal parenchymal mass
Renal pelvic mass
Lateral retroperitoneal mass
Retroperitoneal fibrosis
Retrocaval ureter
Lateral
Congenital malformation of kidney
Horseshoe kidney
Malrotation
Renal pelvic mass
Retroperitoneal mass or lymph nodes
Psoas hypertrophy or abscess
Aortic aneurysm
Prior retroperitoneal surgery
Lower ureter
Medial
Pelvic lymphadenopathy
Pelvic mass
Prior pelvic surgery
Pelvic prolapse
Bladder diverticulum
Inguinal ureteral herniation
Lateral
Pelvic mass
Iliac artery aneurysm
Urinoma/Hematoma
Prior pelvic surgery
Femoral ureteral herniation

Advantages of Ivp

Cost and Availability

Intravenous pyelography is inexpensive and can be obtained with a strict minimum of radiologic equipment. Even the most remote rural facilities can perform IVP if basic radiography is available.

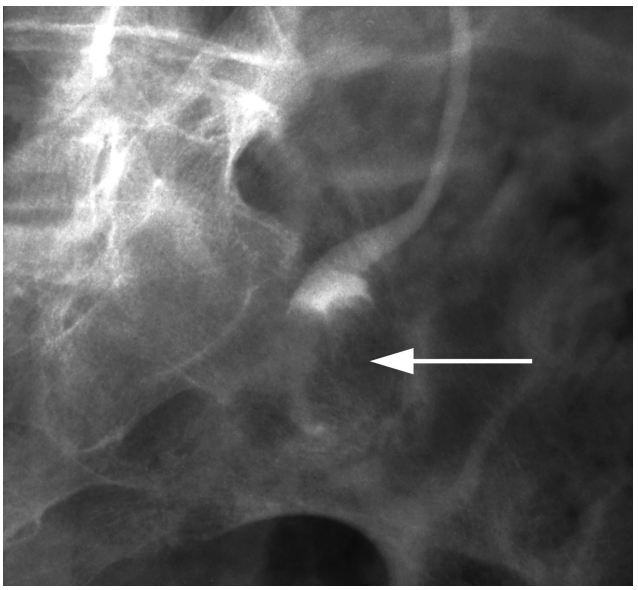

Fig. 11.12 Image from an intravenous pyelogram demonstrates a TCC filling the distal left ureter (*arrow*) with slight ureteral dilatation proximally

Table 11.3 Differential diagnosis for ureteral dilation

Obstructive
Intraluminal ureteral mass (see Table 11.1)
Extraluminal ureteral pathology
Ureteral stricture
Retroperitoneal or pelvic mass
Retroperitoneal fibrosis
Intravesical obstruction
Bladder tumor
Bladder calculus
Bladder infection (e.g., TB, schistosomiasis)
Neurogenic bladder (± detrusor-sphincter dysynergia)
Infravesical obstruction
Benign prostatic hyperplasia
Prostatic or urethral tumor
Urethral stricture
Non-obstructive
Pregnancy
Ureteral atony
Postobstructive residual dilation
Infection (endotoxin)
High urine flow
Polydipsia
Diabetes insipidus
Postobstructive diuresis
Congenital
Vesicoureteral reflux
Megaureter
Ectopic ureter
Ureterocele
Prune belly syndrome
Retrocaval ureter

Table 11.4 Differential diagnosis for ureteral narrowing

Normal
Ureteral peristalsis
Vascular imprinting
Neoplasia
Urothelial tumors
Retroperitoneal/pelvic tumor
Lymph nodes
Metastases
Stricture
Iatrogenic
Trauma
Radiation
Congenital
Infection
TB
Schistosomiasis
Inflammation
Malakoplakia
Endometriosis
Inflammatory bowel disease

Image Quality

Many physicians still regard IVP as one of the best tests for visualizing ureteral anatomy.

Disadvantages of IVP

Contrast Toxicity

A full discussion of the toxicities of radiocontrast is beyond the scope of this chapter and we provide only a brief overview here. The reader is referred to Bush and Lasser for a complete discussion [129]. Nephrotoxicity is probably the most important complication of IVP—though not the only one—and its incidence depends on the type and dose of contrast used, the underlying health of the patient at study, and the medication used by the patient. Numerous clinical

trials have been conducted in an attempt to find strategies to minimize this complication. European guidelines for the prevention of contrast nephrotoxicity have recently been published and propose the following important points [130]. Identifying individuals at risk of contrast nephrotoxicity prior to injecting contrast may reduce its incidence. Risk factors include diabetes, renal failure, congestive heart failure, dehydration, nephrotoxic drugs (e.g., NSAIDs, gentamicin), and age over 70. Physicians should try to minimize contrast nephrotoxicity by adopting a prevention strategy. Universal preventative measures include: ensuring adequate hydration (oral or IV), using low-osmolar contrast agents, minimizing contrast dose, maximizing time delay between contrast injections, stopping nephrotoxic drugs, avoiding diuretics, and avoiding contrast altogether if not necessary. Other interventions that have shown promise in randomized trials include intravenous bicarbonate infusions and *N*-acetylcysteine [131–134]. Another interesting investigational treatment with low toxicity is vitamin C [135].

Contrast Allergy

The incidence of anaphylactoid reactions to contrast media depends on the type of agent used and the patient's history of atopic reactions [136]. Most anaphylactoid reactions occur within minutes of contrast injection but some reactions may take up to 2 hours to develop [136]. Overall, the risk of any form of anaphylactoid reaction is 5% with ionic contrast and 1% with non-ionic contrast [136, 137]. Severe reactions are much less common, occurring in 1 in 750 patients injected with ionic contrast and in 1 in 3000 patients injected with non-ionic contrast [136, 137]. Risk factors for anaphylactoid reactions include asthma (RR=10), previous contrast reaction (RR=5), other allergies (RR=2.5), congestive heart disease, sickle cell anemia, anxiety, certain medications (β-blockers, IL-2, NSAIDs), and pheochromocytoma [136]. Patients with risk factors should receive a pre-contrast protocol of antihistamines and corticosteroids such as that supported by the European Society of Urogenital Radiology [138, 139].

Severe Obstruction

If the renal unit that is investigated is severely obstructed and no contrast is excreted into the collecting system by 10 minutes, delayed films will be required. Often these films do not adequately demonstrate the collecting system despite multiple radiation exposures, and alternative cross-sectional imaging studies become indicated. Unfortunately, the dose of contrast administered during IVP into the obstructed collecting system is quite high and may force delay of CT imaging by 1–2 days. This delay in diagnosis may prove quite distressing for both the physician and the patient.

Retrograde Pyelography

Brief History

Retrograde pyelography was described by the German physicians Fritz Voelcker and Alexander von Lichtenberg in 1906 and was the first technique used to specifically visualize the renal collecting system [98, 140]. The initial images of the ureter were the result of vesicoureteral reflux that occurred during a cystogram but this rapidly lead to the purposeful catheterization of the ureteral orifice and the retrograde injection of contrast media. The technique of retrograde pyelography was popularized in North America by William Braasch who practiced urology at the Mayo Clinic from 1907 to 1946 (Fig. 11.13). Braasch was a major advocate of retrograde pyelography and was responsible for describing the normal pyelographic upper tract anatomy and the use of pyelography for diagnosing malignant diseases of the genitourinary tract [141–143]. Improvements in contrast agents made over the next 100 years have made retrograde pyelography much safer for the patient.

Fig. 11.13 William Braasch, Mayo Clinic urologist, 1907–1946

Technique

Standard Single-Contrast Technique

Retrograde pyelography is a minimally invasive method of imaging the renal collecting system that generally requires cystoscopic visualization of the ureteral orifice, although there have been reports of performing the technique completely under fluoroscopic guidance [144, 145]. Regardless of the method employed, sterility is important because the introduction of bacteria directly into the renal collecting system and bloodstream is a potentially catastrophic complication. A small ureteral catheter, typically 4–7 F, is then slowly advanced into the distal intramural ureter. If urine collection, brush biopsy, or saline barbotage specimens are to be sent for cytologic analysis, as should routinely be the case if a tumor is on the differential diagnosis, these samples should be obtained prior to injecting contrast media into the collecting system. This is done because contrast media, particularly ionic agents with high osmolarity, can alter the cytologic appearance of normal urothelial cells resulting in a potential false-positive urine cytology [146–149]. Newer iso-osmolar contrast agents do not appear to have this problem [146]. Air bubbles in the ureteral catheter should be purged prior to inserting the catheter into the ureter because these can create the false impression of a filling defect, and positioning the patient in the Trendelenberg position may result in better opacification of the renal calyces. A scout film should be obtained prior to contrast injection to assess for mass effects and calcification. Under fluoroscopic guidance, 5–10 mL of diluted contrast media is then slowly injected at low pressure into the ureteral catheter. The ureter and renal pelvis are then assessed systematically. Rotating the fluoroscopy head can provide alternate views of the intrarenal collecting system and prove vital to correctly diagnosing pathology.

Double-Contrast Technique

The use of gas to visualize the urinary collecting system is called gas pyelography and the combination of a gas and a liquid contrast agent is referred to as double-contrast pyelography [150–154]. Several options exist for gas pyelography including oxygen, carbon dioxide, room air, and other inert gases. Carbon dioxide is preferred because it is safest. The technique for catheterizing the ureter is the same as described above with the exception of patient positioning: the reverse Trendelenberg position is preferred [154, 155]. A volume of 15–20 mL of gas is injected into the renal pelvis immediately following the injection of 5 mL of radiocontrast media. Though the risk of gas embolism with gas pyelography is not known with certainty, it has certainly been described and should be avoided at all costs [155–157]. The risk of gas embolism and little gain in diagnostic accuracy have made gas pyelography a largely unused procedure.

Imaging Features of Ureteral and Renal Pelvic Tumors

The imaging features of ureteral and renal pelvic tumors visualized with retrograde pyelography are generally the same as described earlier with intravenous urography. Tumors appear as filling defects, irregular stenoses, nonvisualized calyces, and hydronephrosis. The advantages of retrograde pyelography over other imaging modalities are discussed below. Two imaging features of ureteral tumors that are best detected with retrograde pyelography are the so-called goblet sign and Bergman's sign.

Goblet Sign

The goblet sign (a.k.a. chalice sign) refers to a cup-shaped collection of contrast media that is seen just distal to the intraluminal filling defect and suggests the presence of a tumor (Figs. 11.14 and 11.15) [158]. The slow growth of an intraluminal tumor causes proximal as well as distal expansion of the ureter [159]. Additionally, a pedunculated tumor may also be pushed distally during peristalsis only to return to its normal cephalad position between contractions [160]. Presence of the goblet sign suggests a superficial (i.e., less aggressive) tumor [158].

Bergman's Sign

Bergman's sign (a.k.a. catheter coiling sign) refers to the coiling of a ureteral catheter in the infratumoral ureter [159]. Its interpretation and cause are exactly the same as the goblet sign.

Advantages of Retrograde Pyelography

Fluoroscopic Monitoring

Fluoroscopic monitoring allows this imaging modality to better visualize the pathology in the urinary tract because the patient or fluoroscopy head can be repositioned to provide an optimal view of the problem. Often a slight change in the angle of view can result in a dramatically better picture of the pathologic process.

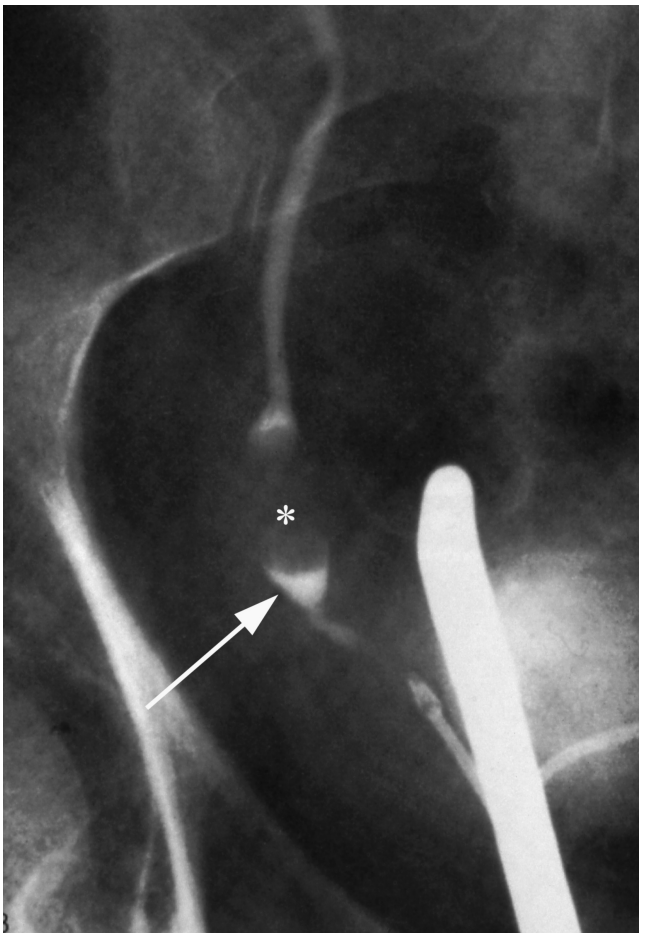

Fig. 11.14 Image from a retrograde pyelogram demonstrates a TCC filling the distal right ureter (*asterisk*) with slight ureteral dilatation distally (*arrow*). The distal ureteral dilation is known as the "chalice sign" or the "goblet sign"

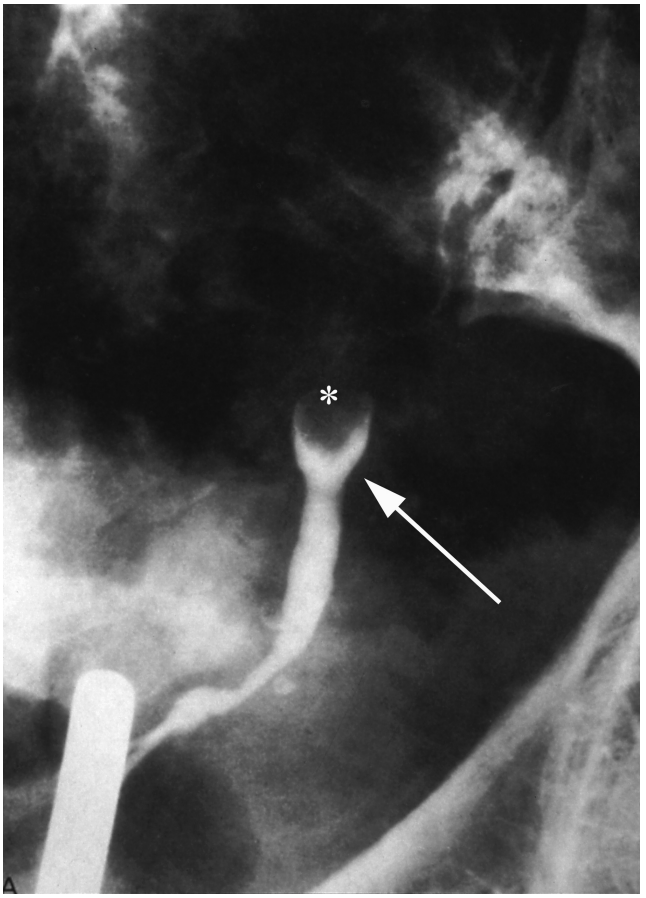

Fig. 11.15 Image from a retrograde pyelogram demonstrates a TCC filling the distal left ureter (*asterisk*) demonstrating the "goblet sign"

Intracavitary Filling

More contrast is instilled in the ureter and renal pelvis with retrograde pyelography than is possible with any intravascular imaging technique. This can sometimes be very useful in opacifying the phantom calyces seen on IVP. Many physicians feel that retrograde pyelography provides the best quality images of the renal pelvis and the most accurate measure of the extent of a ureteral tumor (i.e., length of ureteral involvement and multifocality) (Fig. 11.16).

Renal Failure

When renal function is so severely impaired that the kidney cannot excrete the contrast media or when intravascular contrast media risks worsening stable renal impairment, retrograde pyelography can be of use. As noted below, retrograde pyelography can worsen renal function, although this occurs very rarely. Most urologists and radiologists would agree that retrograde contrast injection is unlikely to cause significant renal dysfunction.

Contrast Toxicity

The injection of contrast media into the collecting system is associated with a very low adverse event rate. Despite this, there have been reports of a variety of contrast-related complications that deserve mention. Contrast nephrotoxicity can occur after retrograde pyelography and seems to be associated with bilateral obstruction, the presence of backflow (see later), and contrast-induced mucosal edema [161–163]. The course of resolution appears similar to that observed in cases of intravenous contrast nephrotoxicity.

Contrast Allergy

There is a very low rate of anaphylactoid reactions when contrast is administered directly into the urinary collecting system via retrograde injection. Though the urothelium

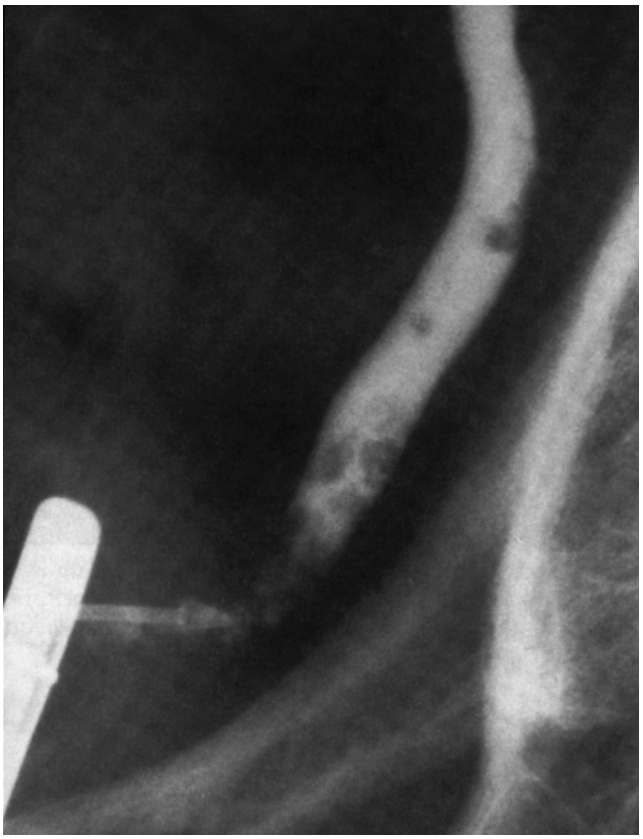

Fig. 11.16 Image from a retrograde pyelogram demonstrates multiple tiny papillary TCC in the distal left ureter

is considered a relatively impermeable barrier, contrast can be absorbed through the urothelium and enter the circulation [164–166]. Backflow mechanisms may also be involved in certain cases. A variety of allergic presentations have been described in patients undergoing cystography and retrograde pyelography, ranging from simple urticarial rashes to circulatory collapse [167–170]. Non-ionic contrast agents cause much fewer adverse reactions than ionic agents. It is unknown whether or not prophylaxis regimens are efficacious or indicated for preventing anaphylactoid reactions in patients undergoing cystography or retrograde pyelography [171]. Our bias is to err on the side of caution and administer prophylaxis to patients who have previously developed a reaction or that are at high risk of one.

Ancillary Diagnostic Procedures

Selective ureteral cytologies, saline barbotage, brush biopsy, and ureteroscopy can all be done in the same setting as retrograde pyelography. Combining all these diagnostic modalities provides a better chance of diagnosing difficult cases and is recommended in the follow-up of patients at high risk for an upper tract urothelial tumor [172].

Drainage

A ureteral stent can be placed into the ureter to relieve obstruction and symptoms caused by the tumor at the same time as retrograde pyelography.

Disadvantages of Retrograde Pyelography

Difficult Ureteral Orifice

All urologists with significant experience will recall occasions where ureteral cannulation was simply not possible. Some of the more common causes of difficult ureteral catheterization include a reimplanted ureter, the presence of a urinary diversion, a large prostate, a tumor at the ureteral orifice or previous transurethral resection thereof, a bladder diverticulum, extensive hematuria, an obstructing ureteral calculus, and looping dilated ureters. There are many tricks and tools that can assist in these situations but in certain cases the most rapid solution is to abort the procedure and obtain a percutaneous nephrostomy tract.

Iatrogenic Trauma

Though cystoscopy is a routine procedure for the urologist, inserting an instrument into the urethra should not be taken lightly. Many serious complications have occurred during cystoscopy and ureteral catheterization. Some of the more common complications include perforation of the urinary tract (urethra, bladder, ureter, or the renal pelvis) [173, 174], stricture with secondary obstruction [175–177], and infection/sepsis [178]. Although controversial, percutaneous nephrostomy is generally preferred over ureteral catheterization in the context of infected urine [179–182].

Backflow

Excessive injection pressure or trauma to the urothelium can result in the leakage of radiocontrast media into lymphovascular spaces [183–185]. This process is known as backflow and five distinct varieties have been described. *Pyelovenous backflow* occurs when contrast leaks into the venous drainage system of the kidney [186, 187]. It provides a direct route for contrast, air, and bacteria to enter the bloodstream. This is likely the point at which anaphylactoid reactions occur. Air embolism is a rare complication of retrograde pyelography that is related to pyelovenous backflow [157]. *Pyelolymphatic backflow* occurs when contrast leaks into the fine lymphatic channels that line the renal sinus and

migrates toward the hilar and retroperitoneal lymph nodes [186, 188]. Renal tubular toxicity has been reported to occur through this mechanism [163]. Backflow into a tumor has been termed *pyelocancerous backflow* [189, 190]. It is rare and of unknown significance. Intrarenal backflow refers to two things: pyelotubular backflow and pyelointerstitial backflow. *Pyelotubular backflow* occurs when contrast leaks into the collecting ducts and enters the nephron in a retrograde manner whereas *pyelointerstitial backflow* occurs when contrast leaks into the renal interstitium [184, 191]. Intrarenal backflow has been associated with impending renal transplant rejection [191, 192], renal ischemia [193–195], and prolonged obstruction [184]. The last form of backflow to be discussed is *pyelosinus backflow*. This form of backflow occurs when small tears in the calyces and renal pelvis develop and allow leakage of contrast into the renal sinus and the retroperitoneal space [196, 197]. The main clinical problems associated with this type of backflow are the development of a urinoma or retroperitoneal abscess [196, 198]. Though backflow can be prevented in most instances by keeping the intrapelvic pressure below 30 mmHg, some normal individuals will have backflow despite a perfect low-pressure technique.

Staging

Retrograde pyelography cannot establish extraureteral extension or the distant spread of a detected tumor. Occasionally retrograde pyelography will identify ureteral deviation caused by retroperitoneal lymph nodes or renal parenchymal invasion by a urothelial tumor, but these are the exceptions and always require cross-sectional imaging confirmation.

Carcinogenesis

A condition of historical interest is thorium-induced urothelial carcinoma. Thorotrast and Umbrathor were contrast agents composed of thorium dioxide, first introduced in 1915 and used routinely from the 1930s to the 1950s [199]. Thorium dioxide is mildly radioactive (it emits α-particles) and has a half-life of over 400 years. Small deposits of thorium (that are detectable by CT) occasionally formed under the urothelium of patients treated with this agent and many people developed cancers of the kidney and collecting system secondarily, 20–30 years after their exposure [200–204]. Newer contrast agents have not had this problem.

Antegrade Pyelography

Brief History

Percutaneous access to the upper urinary tract had its beginning in France in 1949 and was popularized by other groups in the mid-1950s [205–209]. The technique was initially used to diagnose and treat patients with severe hydronephrosis but has since been adapted to serve a wide variety of diagnostic and therapeutic needs [210]. Ultrasound or fluoroscopy guidance is now routinely used to help place the needle in the desired calyx [211–214].

Technique

Antegrade pyelography is generally reserved for patients that cannot receive intravenous contrast and that failed an attempt at retrograde pyelography. It can also be used as a primary imaging modality for patients with an obstruction of the upper urinary tract because the obstruction can be treated and its cause diagnosed.

Antegrade Pyelography

A quick focused medical history, a urine culture, and a coagulation profile are recommended prior to commencing this procedure. The patient is placed in the prone or prone-oblique position. Some form of imaging, usually ultrasonography or fluoroscopy, is used to guide the initial needle puncture into the desired renal calyx. When imaging or manometry are the only goals, a small 22- or 24-gauge needle may be sufficient to inject the contrast material and measure intrapelvic pressures. Strict sterility must be adhered to if infectious complications are to be avoided. To minimize the risk of bleeding complications, the needle tract is ideally placed through the relatively avascular line of Brödel on the posterolateral surface of the kidney [215, 216]. It is also generally preferred to target a posterior calyx in order to minimize the risk of bleeding and colonic injury [217, 218]. Similarly, infracostal puncture of a lower pole calyces is preferred over supracostal puncture of an upper pole calyx because of the risk of puncturing the pleura and the lung [219, 220]. Direct puncture of the renal pelvis should be avoided because of the risk of trauma to the central renal vasculature and the risks of urinoma and urinary fistula formation. Local anesthetics are usually adequate for pain control and their presence in the vicinity of the renal capsule is usually appreciated by the patient. Once the needle enters the collecting system, its position can be confirmed by the

respiratory motion of the needle and the appearance of the aspirated urine. Urine cultures and cytologies are almost always appropriate. Final confirmation of needle position is obtained by injecting a small dose of contrast into the collecting system and confirming its location with fluoroscopy.

Percutaneous Nephrostomy

When the renal unit in question is obstructed, it may be desirable to leave a nephrostomy tube to decompress the kidney and permit recovery of renal function. The nephrostomy tube can be used at a later date for performing antegrade pyelography or for endourologic access to the tumor. The technique for obtaining renal access is the same as that described above except that a slightly different needle is used. Once the needle is confirmed to be in the collecting system, a guidewire is inserted into the needle and positioned within the renal pelvis and ureter. The nephrostomy tract is then progressively dilated until an appropriately sized nephrostomy tube can be placed. Great care must be taken not to overdistend or puncture the renal pelvis during this procedure because serious bleeding and infection may result. The nephrostomy is then fixed to the skin in a manner that prevents inadvertent kinking, removal, or traction [221–223].

Imaging Features of Ureteral and Renal Pelvic Tumors

Urothelial tumors have essentially the same imaging characteristics with antegrade pyelography as with IVP and retrograde pyelography. As with retrograde pyelography, some physicians feel that direct injection of contrast into the collecting system provides for optimal anatomic detail (Fig. 11.17).

Advantages of Antegrade Pyelography

Success Rate

The success rate for establishing a percutaneous nephrostomy tract is over 99% and is relatively constant if the operator performs more than 10 nephrostomies per year [224–227]. The technique is therefore a very reliable way of diagnosing patients that have failed other imaging modalities.

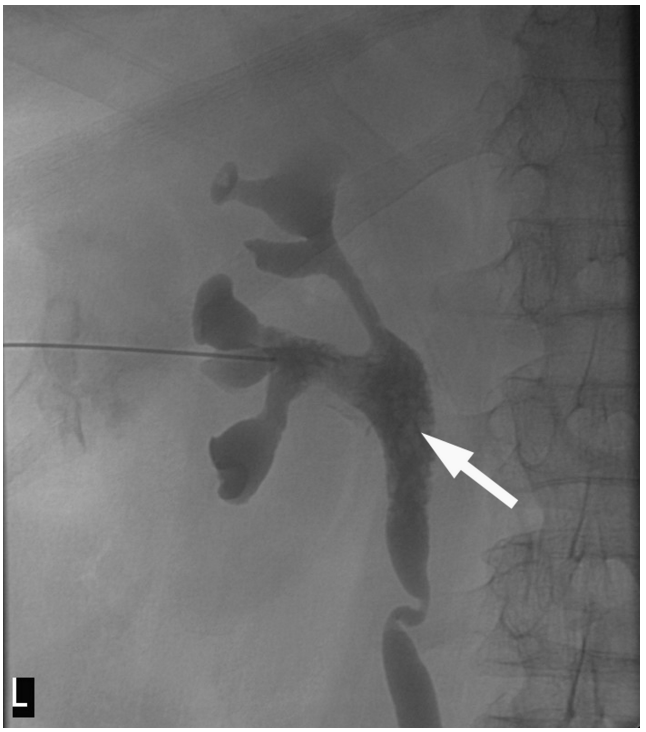

Fig. 11.17 Antegrade pyelogram demonstrating multiple tiny filling defects carpeting the right renal pelvis and upper right ureter (*arrow*) found to multifocal TCC at surgery

Drainage

The ability to leave a drainage nephrostomy catheter can be a major benefit, particularly for the patient with infected urine. There has been concern about the potential for tumor seeding along the nephrostomy tract [228–230]. This phenomenon appears to be quite rare and not all groups have observed it [231–235]. Nonetheless, for patients who eventually undergo nephroureterectomy, it may be wise to excise the nephrostomy tract. Brachytherapy has also been used to treat the nephrostomy tract in patients undergoing endourologic treatment [236].

Ancillary Diagnostic Procedures

As with retrograde pyelography, urine cultures, cytologies, and brush biopsies can all be obtained via the nephrostomy access [232]. A pressure-flow (Whittaker) study can also be performed if obstruction is questionable [237–242].

Treatment

The nephrostomy tract can be used for endourologic management of renal pelvic and upper ureteral tumors and chemotherapy and BCG can be dripped into the collecting

system safely via the nephrostomy [230, 231, 233, 235, 243–245].

Disadvantages of Antegrade Pyelography

Nearly all the disadvantages of this imaging approach are due to the potential complications associated with percutaneous renal access.

Bleeding

Hematuria is nearly universal after percutaneous needle puncture of the kidney but serious hemorrhage is fortunately uncommon. The incidence of major bleeding is directly related to the size of the nephrostomy tract. For small nephrostomy tracts (<12 F) the reported transfusion and/or intervention rates generally range from 1 to 4% while large tracts (>12 F) may have rates up to 20% [224, 225, 246–250]. The estimated average blood loss from a large nephrostomy tract ranges from 16 to 28 g/L [251, 252]. Risk factors for increased blood loss other than increasing nephrostomy tract size include renal pelvic perforation [251, 252], multiple renal punctures [251, 252], anterior calyx access [217], supracostal access [217, 220], diabetes [252], dilation of the nephrostomy tract without a balloon [248], and the lack of imaging guidance [213, 252]. Most renal hemorrhages can be handled non-operatively and we suggest a stepwise approach to management. Simple maneuvers such as clamping the nephrostomy tube and balloon tamponade should be considered first [249, 253, 254]. For procedures conducted in the operative setting, simple cauterization of the bleeding vessel or the application of fibrin glue may be of value [255–258]. If these methods fail or if the bleeding is too brisk to warrant an initial conservative approach, vascular access and selective renal embolization should be attempted [247, 249, 259–264]. Renal embolization is generally well tolerated but renal infarction of varying degrees of severity can occur [265, 266]. Other complications that have been reported secondary to endovascular techniques include pseudoaneurysm or arteriovenous fistula formation at the access site [267–270], thrombosis and dissection of the aorta [271, 272], and embolization of the limbs [273]. Lastly, severe bleeding can be associated with the formation of a retroperitoneal hematoma [274, 275]. These hematomas can be a source of pain and a nidus for infection.

Arteriovenous Fistula

AV fistulae are usually clinical entities that escape clinical attention. The incidence of radiologic AV fistula occurring after nephrostomy is unknown but reaches 10–15% for renal biopsies [276–279]. Most of these cases resolve spontaneously within 6–12 months but may occasionally require embolization or surgical treatment [280, 281].

Iatrogenic Organ Injury

Any organ that lies in or near the retroperitoneum can be punctured while obtaining percutaneous access to the kidney. The most commonly injured organs are the renal pelvis [224], the colon [218, 282–285], the liver [286, 287], the spleen [286–289], and pleura/lung [219, 220, 250, 287, 290–293].

Death

The death rate from percutaneous nephrostomies is very low but is not zero. Large series report death rates in the 0.1–0.5% range [224, 250].

Conclusions

The traditional diagnostic modalities of IVP and retrograde pyelography are rapidly being replaced as first-line diagnostic modalities for flank pain and hematuria by CT and MR urography. In many circumstances, however, they may still be the optimal method of evaluating the upper urinary tract for the presence of a urothelial tumor. Table 11.5 shows the relative strengths and weaknesses of the various imaging techniques that can be used to identify upper urinary tract tumors.

Table 11.5 Strengths of various imaging modalities for upper urinary tract tumors

	IVP	Retrograde/antegrade	US	CT	MRI
Renal pelvis	+++	+++	+	++	++
Ureter	+++	+++	+	++	++
Calculi	++	++	+	+++	+
Staging	+	+	++	+++	+++
Cost	+++	+	+++	++	+
Radiation	++	++	+++	+	+++

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