The Development of Computed Tomography Urography for Investigating Haematuria

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Submission for the degree of Doctor of Medicine

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Abstract

This thesis addresses the three principal questions concerning the development of CT urography for investigating haematuria and each question is the subject of a separate chapter. The questions are:

1. What is the reasoning behind using CT urography?
2. What is the optimum diagnostic strategy using CT urography?
3. What are the problems with using CT urography and how may solutions be provided?

Haematuria can signify serious disease such as urinary tract stones, renal cell cancer, upper tract urothelial cancer (UTUC) and bladder cancer (BCa).
CT urography is defined as contrast enhanced CT examination of kidneys, ureters and bladder. The technique used here includes unenhanced, nephrographic and excretory-phases for optimized diagnosis of stones, renal masses and urothelial cancer respectively.
The reasoning behind using excretory-phase CT urography for investigating haematuria is based on results showing its high diagnostic accuracy for UTUC and BCa.
Patients with haematuria are classified as low risk or high risk for UTUC and BCa, by a risk score, determined by the presence / absence of risk factors: age > 50 years, visible or nonvisible haematuria, history of smoking and occupational exposure.
The optimum diagnostic strategy for patients at high risk for urothelial cancer, uses CT urography as a replacement test for ultrasonography and intravenous urography and as a triage test for flexible and rigid cystoscopy, resulting in earlier diagnosis and potentially improving prognosis. For patients at low risk, ultrasonography, unenhanced and nephrographic-phase CT urography are proposed as initial imaging tests.
Problems with using CT urography include false positive results for UTUC, which are eliminated by retrograde ureteropyelography-guided biopsy, an innovative technique, for histopathological confirmation of diagnosis.
Recommendations for the NHS and possible future developments are discussed.
CT urography, including excretory-phase imaging, is recommended as the initial diagnostic imaging test before cystoscopy for patients with haematuria at high risk for urothelial cancer.

Acknowledgements

So many people have helped in so in many ways to make this work possible and I would like to sincerely thank them all.

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Finally I would like to acknowledge and thank the anonymous donor who generously provided the funding for the original Voxar 3D software. The CT urography research programme was based on the analysis of 3D CT datasets using the software. I remain most grateful.

Thank you again to all mentioned above. Your help was, is and always will be appreciated. You helped change clinical practice with reference to imaging investigation for haematuria. This thesis represents the end of one of life's chapters. The exciting thing about the end of a chapter is that it means that another one begins .....

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List of keywords from Medical Subject Headings (MeSH®) 2012

Keyword
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"Biopsy"
"Bladder cancer"
"Carcinoma, renal cell"
"Carcinoma, transitional cell"
"Computed tomography, x-ray"
"Cost effectiveness"
"Cost savings"
"Costs and cost analysis"
"Cystoscopy"
"Cytology"
"Diagnosis"
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"Diagnostic imaging"
"Diagnostic techniques and procedures"
"Diagnostic techniques, urological"
"Diagnostic tests"
"Disease-free survival"
"Early detection of cancer"
"Early diagnosis"

List of keywords

"Educational assessment"
"Educational techniques"
"Hematuria"
"Incidental findings"
"Kidney calculi"
"Kidney neoplasms"
"Neoplasm grading"
"Neoplasm staging"
"Prognosis"
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"Urinary bladder neoplasm"
"Urinary bladder neoplasms"
"Urinary calculi"
"Urography"
"Urolithiasis"

Introduction

Original concept

Front line high-tech imaging for haematuria and patient centred diagnosis

The thesis is based on an original concept that clinical quality may by optimized by placing a new high-tech imaging test, CT urography, at the front of the diagnostic pathway for investigating haematuria.

Traditionally in clinical practice, when a new diagnostic imaging test becomes available, the new test is added on to the end of the existing diagnostic pathway. The concept of this thesis, challenges such an approach. By using the test with the highest diagnostic accuracy as a front line event, the total number of imaging investigations is reduced, rendering other tests redundant.

The new strategy consists of same day consultation, clinical examination, CT urography and flexible cystoscopy (FC) for selected patients presenting with haematuria. A truly integrated, one-stop haematuria clinic is the goal.
Substituting CT urography for ultrasonography and intravenous urography (IVU) has many potential advantages (Nolte-Ernsting & Cowan, 2006) (Van Der Molen et al., 2008) (Cowan, 2012). The potential benefits are improved diagnostic accuracy, earlier diagnosis, improved patient experience and reduced overall cost.

Weinstein et al 2005 in the paper 'Clinical evaluation of diagnostic tests' describes three pieces of information a clinician needs to determine if a diagnostic test should or should not be requested.

1. From the patient's previous medical history, previous and recent exposures, current signs and symptoms, and results of other screening and diagnostic tests performed, what is the probability that this patient has the disease (the pretest probability)?
2. How accurate is the diagnostic test being considered (sensitivity and specificity)?
3. Could the results of this test affect the patient's management?

This thesis will provide the relevant information for clinicians to answer the three questions given above (Weinstein, Obuchowski, & Lieber, 2005).

Purpose

The purpose of the thesis is to evaluate the development of a new test, known as CT urography for investigating haematuria, within a reconfigured diagnostic pathway. The technique of CT urography is assessed with respect to diagnostic accuracy and diagnostic strategy. Diagnostic accuracy is calculated and compared with other tests. The pathway is assessed by analysis of many contributing factors including time taken from presentation to diagnosis. Problems arising from the implementation of the new technique and diagnostic pathway are given and solutions provided. For a new test and new strategy to become accepted for general clinical use and change clinical practice, the test should be better, quicker, easier, safer, cheaper and more pleasant for the patient.

Investigating haematuria

Definition of visible and nonvisible haematuria

Haematuria is defined as the presence of red blood cells in urine, and can signify a serious disease such as bladder cancer (BCa), upper urinary tract urothelial cancer (UTUC), renal cell cancer (RCC) or urinary tract stones (Sutton, 1990) (Khadra, Pickard, Charlton, Powell, & Neal, 1999) (Edwards, Dickinson, Natale, Gosling, & McGrath, 2006). If the blood is visible it is considered a symptom; nonvisible haematuria is considered a sign.

The criteria used to diagnose nonvisible haematuria and for referral to a nephrologist or urologist vary widely (Kelly, Fawcett, & Goldberg, 2009; Malmström, 2003). Nonvisible haematuria can be detected on a chemical dipstick or microscopy. Haemoglobin, either free in the urine or within urinary red blood cells, catalyses the oxidation of substances on a chemical dipstick, resulting in a colour change that indicates haematuria. Urinary dipsticks are useful for detecting nonvisible haematuria, with a sensitivity of 91–100%, but they have a low specificity, ranging from 65–99% (Sutton, 1990). Myoglobin, free haemoglobin and oxidizing contaminants in the urine, such as povidone-iodine, can provide false positive results on dipstick analysis.

Dipstick alone is the most common method of diagnosing haematuria in UK primary care (Rodgers et al., 2006a). The American Urological Association Best Practice guidelines recommend confirmation of a positive dipstick test with microscopy, and define nonvisible haematuria as ≥ 3 red blood cells per high-power field on evaluation of the urinary sediment from two of three properly collected midstream urine specimens (Grossfeld et al., 2001b).

Risk factors for urothelial carcinoma

The risk factors for developing urothelial carcinoma are numerous and include a history of smoking; occupational exposure to chemicals, dyes, benzenes or aromatic amines; history of visible haematuria; age > 40 years; history of a urological disorder or disease; history of irritative voiding symptoms; history of urinary tract infection resistant to antibiotic treatment; analgesic abuse, for example phenacetin; or history of pelvic irradiation or cyclophosphamide therapy (Chow, Dong, & Devesa, 2010).

When should patients with haematuria be referred to a nephrologist or urologist?

For patients at high risk of urothelial cancer, the current UK guidelines suggest that after one urinalysis, patients should be referred to a urologist for full evaluation of the upper and lower urinary tracts, principally to exclude life-threatening malignancy (Rodgers et al., 2006a) (Grossfeld et al., 2001a) (Grossfeld et al., 2001b).

Current standard of care for patients with asymptomatic nonvisible haematuria is to undergo urinalysis on at least two separate occasions, whereas those with symptomatic nonvisible haematuria or visible haematuria are referred immediately after one positive urinalysis and exclusion of transient causes of haematuria and urinary tract infection.
The next step is to determine whether referral to a urologist or nephrologist is most appropriate based on the results of renal function tests, and to determine if the haematuria originates in the nephron (glomerular or tubular) or from the epithelium. A nephrological referral is recommended in the presence of proteinuria, red cell casts on microscopy, elevated serum creatinine, or elevated of blood pressure.

The clinical and economic significance of haematuria

Patients with haematuria constitute a massive clinical workload for both urology and radiology departments, as well as a huge requirement for health care resources. The clinical significance of haematuria is demonstrated by the underlying high prevalence of serious disease in patients presenting with visible and nonvisible haematuria (Table 1).

Table 1. Disease prevalence in patients with visible and nonvisible haematuria evaluated initially with US and IVU

	Prevalence (%)	
Disease	**Visible haematuria**	**Nonvisible haematuria**
Bladder cancer	16.5-19.3	3.7-4.8
Renal cell cancer	0.9-2.0	0.3-1.0
Prostate cancer	0.6	0.2
UTUC	0.1-0.5	0.1-0.2
Stones	3.2-8.8	4.0-7.8
UTI	13.0	13.0
Nephrological disease	10.3	9.4
No disease found	52.5-72.2	68.2-87.3

Data combined from two studies, Khadra et al 1999 and Edwards et al 2006.

Abbreviations: UTUC, upper urinary tract urothelial carcinoma; UTI, urinary tract infection; IVU, intravenous urography; US, ultrasonography.

Visible haematuria is a common presenting symptom for patients referred to urological clinics (Edwards et al., 2006) (Khadra et al., 1999) with an estimated community prevalence of 2.5% (Mariani et al., 1989). Patients with visible compared with nonvisible haematuria, have a higher prevalence of malignancy, stone and medical renal disease

(Edwards et al., 2006) (Khadra et al., 1999) (Sutton, 1990). The main purpose of clinical and imaging investigations for haematuria is to diagnose treatable causes at the earliest opportunity to improve prognosis, in particular for renal cell carcinoma, UTUC, bladder and prostate cancer (Hall et al., 1998) and stones.

Bladder cancer is the third most common cancer in men and the eleventh most common in women in the United States (Siegel, Naishadham, & Jemal, 2012). Bladder cancer has the highest lifetime treatments costs per patient of all cancers, followed by colorectal, breast, prostate and lung cancer (Botteman, Pashos, Redaelli, Laskin, & Hauser, 2003). Data regarding renal pelvis and ureter cancer are unclear because cancers of the kidney and renal pelvis are often grouped together (Konety, Joyce, & Wise, 2007).

Renal cell carcinoma is the most common malignancy of the kidney, and is diagnosed in 1-4% of patients presenting with visible haematuria (Edwards et al., 2006) (Khadra et al., 1999) (Sutton, 1990). Up to 60% of patients with renal cell carcinoma present with haematuria, but renal cell carcinoma is being increasingly diagnosed incidentally as an asymptomatic small renal mass.

UTUC arising from the renal pelvis or ureter accounts for 0.1%-0.8% of patients with visible haematuria (Edwards et al., 2006) (Khadra et al., 1999) (Sutton, 1990). Early diagnosis of UTUC significantly changes the management allowing surgical excision by nephroureterectomy.

The total annual cost for urinary tract stone disease in the USA in 1995 was estimated to be $1.83 billion (Clark, Thompson, & Optenberg, 1995).

It is clear that there are huge clinical and economic implications for our health care systems with respect to the diagnosis and treatment of the underlying medical conditions responsible for haematuria (Stenzl et al., 2009) (Roupret et al., 2013) (Ljungberg et al., 2010) (Clark et al., 1995) (Shih et al., 2011).

The advantages of early diagnosis

If the diagnosis of UTUC is made early when the primary tumour is at a low stage, before local invasion and distant spread to lymph nodes or other sites, the outcomes of radical nephroureterectomy, the surgical standard of care for UTUC, measured in terms of recurrence free survival and cancer specific survival are improved (Waldert et al., 2010). Theoretically, the risk of tumour progression and upstaging increases with increasing delay before treatment by radical nephroureterectomy. A biological event such as a

mutation or shedding of a micrometastatic cell may potentially happen at any time. Therefore delay is assumed to have a detrimental effect on outcome, unless radical nephroureterectomy is ineffective or UTUC does not progress. The key question realistically is not whether a delay in diagnosis and subsequent delay to radical nephroureterectomy affects outcome, but by how much a particular delay increases the risk.

Tumour stage is one of the most important predictors of survival in patients with UTUC (Margulis 2010 JUrol 184 453-458). Upper tract urothelial cancer can spread by direct invasion, epithelial seeding, blood borne and lymphatic routes. Metastatic potential increases and therefore prognosis worsens with advancing tumour stage (Margulis 2009 Cancer, Langner 2006 Mod Pathol, Novara 2010 Eur Urol, Novara 2007 Cancer) (Hall et al., 1998). For UTUC, the overall prognosis is heavily dependent on the stage at diagnosis, with 5 year survival rates ranging from 100% for Stage Ta and Tis tumours to 40% for Stage T3 tumours (Hall et al 1998). It makes sense that early diagnosis improves prognosis.

Other prognostic factors

UTUC tumour grade is currently classified as papillary urothelial neoplasia of low malignant potential, low-grade carcinoma or high-grade carcinoma. Until 2004, the WHO classification of 1973 was used, which distinguished three grades (G1, G2, G3) (Lopez-Beltran & Montironi, 2004). High-grade tumours are more likely to invade into the underlying connective tissue, muscle and surrounding tissues and are also more likely to be associated with concomitant carcinoma in situ (Brien et al., 2010). Recent series using the 2004 WHO grading system have found high tumour grade to be a strong independent prognostic factor for UTUC (Margulis, McDonald, Tamboli, Swanson, & Wood, 2009) (Margulis et al., 2010) (Remzi et al., 2009). Other recently reported variables indentified as potential prognostic factors associated with outcomes following radical nephroureterectomy for UTUC include age, gender, lymphovascular invasion, sessile tumour architecture, concomitant carcinoma in situ (Cha et al., 2012).

Improved risk stratification and accurate individual prediction of postoperative recurrence and survival outcomes can help guide patient counselling, follow-up scheduling, administration of adjuvant chemotherapies and design of clinical trials.

Description and discussion of conventional diagnostic strategies

Conventionally, intravenous urography and ultrasonography were the imaging techniques of choice for the initial investigation. In 1990, Khadra et al reported one of the few large observational series on the subject, comprising 1,930 patients. They concluded that all patients with haematuria should undergo cystoscopy and if an upper tract tumour is suspected then a combination of ultrasonography and intravenous urography (Khadra et al., 1999). In another large series reported by Edwards et al. in 2006, the recommendation was the ubiquitous use of ultrasonography with selective intravenous urography for men aged > 50 years, with visible haematuria or a positive repeat dipstick urine analysis when initial tests were negative (Edwards et al., 2006). The relative merits of ultrasonography or intravenous urography as the initial imaging investigation for haematuria have been the subject of much debate (Webb, 1994). Traditionally further imaging was considered if no cause for haematuria was found initially, using a combination of ultrasonography, intravenous urography and flexible cystoscopy, CT or renal angiography (Webb, 1997). In 2006, a Health Technology Assessment review concluded that there was insufficient evidence available to draw any firm conclusions regarding the diagnostic accuracy of imaging studies in determining the cause of haematuria, and that there was insufficient data available to derive an evidence-based algorithm of the diagnostic pathway for haematuria (Rodgers et al., 2006a). Since then, data have been steadily accumulating supporting the use of CT urography as an initial one-step imaging modality for the investigation of haematuria.

Development of CT urography

Definition of CT urography

CT urography is a developing diagnostic imaging technique made possible by recent advances in CT technology. In 2008, the European Society of Urogenital Radiology Working Group for Urography defined CT urography as CT examination of the kidneys, ureters and bladder with at least one series of images acquired during the excretory-phase of intravenous contrast media (CM) enhancement (Van Der Molen et al., 2008). Iodinated CM is administered intravenously and enters the kidney via the renal arterial system. CM is filtered at the glomerulus passing into the renal tubules, collecting ducts, renal collecting system and ureter en route to the bladder. Images may be acquired during various phases of CM enhancement. Each phase is defined by the anatomical location of CM during its passage through the kidney at the time of image acquisition. Now, partly in response to subsequent rapid advances in CT technology, a broader definition is proposed, giving greater emphasis to the whole spectrum of contrast enhanced phases and range of CT urography techniques:

CT urography is contrast enhanced CT examination of the kidneys, ureters and bladder

This means that at least one phase of CM enhancement must be included in the examination for it to be called CT urography and that the excretory-phase although the most commonly included in clinical practice is now not mandatory. The timing of image acquisition for each phase measured from the start of CM injection should be specified. The unenhanced-phase is acquired before CM injection. The nephrographic-phase is acquired at 100s when CM is located in the renal tubules. The excretory-phase is acquired at 300-900s when CM is in the renal collecting system, ureter and bladder.

The diagnostic accuracy of CT urography for a particular disease depends on which phases are included in the examination as the diagnostic accuracy of each phase varies greatly for different diseases. For example, the diagnostic accuracy of the unenhanced-phase is highest for stones, the nephrographic-phase highest for solid renal masses and renal cysts and the excretory-phase highest for UTUC.

Image acquisition should be optimised for multiplanar reconstruction so images can be reviewed in orthogonal planes to maximise diagnostic accuracy.

The development of CT technology from concept to isotropic

CT is a logical conceptual progression from conventional radiography, translating the two dimensional information of radiographic images into three dimensions. The first CT machine - an invention credited to Godfrey Hounsfield - was introduced into clinical practice in 1973. The subsequent development of multidetector CT represents a major landmark in the evolution of CT. By late 1998, all major CT manufacturers were marketing multidetector CT machines capable of acquiring at least four body sections per gantry rotation. By 2007, CT machines capable of acquiring 320 body sections per gantry rotation were available for clinical use. By increasing the number of detector rows, the data acquisition capability of the machine and the efficiency of the x-ray tube was greatly improved, producing image quality far surpassing that of Hounsfield's original invention.

The two principal clinical advantages of multidetector technology are increased speed of imaging and increased spatial resolution. Increased speed is particularly useful for studies in which patient motion is a limiting factor. Increased spatial resolution makes true isotropic imaging possible - sometimes described as the Holy Grail of medical imaging. Isotropic imaging is achieved when the reconstructed image is equally sharp in any plane of the examined volume. Production of isotropic images requires careful attention to image acquisition and reconstruction parameters. The truly isotropic 3D radiograph has perfect cubic voxels of less than 1 mm in diameter, acquired over large volumes with very short acquisition times, within a single breath hold.

When reconstructing an image for isotropic resolution, the reconstructed slice thickness must equal the pixel size. The image matrix is the number of pixels found across the display field of view and is usually fixed at 512 for most CT machines. It follows, by simple algebra that the display field of view required to be set up on the CT machine to provide isotropic imaging is given by multiplying the reconstructed slice thickness by the matrix. For example, if the reconstructed slice thickness is 0.625 mm and the matrix is 512, then the display field of view required to give isotropic voxels is 320 mm (Mahesh, 2009a) (Mahesh, 2009b). Isotropic resolution with multiplanar viewing is integral to the high diagnostic accuracy of CT urography for UTUC, small stones and renal masses,

allowing images to be reviewed without the step reconstruction artifact that can simulate disease. With only axial review it is easy to overlook small tumours of the upper urinary tract or bladder, especially those with their long axis in the axial plane. Many CT applications using isotropic resolution (CT angiography, CT colonography and CT urography) are developing rapidly in clinical practice (Mahesh, 2009a) (Mahesh, 2009b). Rapid developments in multidetector CT technology have increased the speed of image acquisition and also spatial resolution making possible multiplanar review of isotropic datasets providing high resolution CT urography studies.

Early reports of CT urography for detecting urinary tract abnormalities including stones, (Smith, Rosenfield, Choe, & et al, 1995) (Smith, Verga, McCarthy, & Rosenfield, 1996) (Sourtzis et al., 1999) (Fielding, Silverman, Samuel, Zou, & Loughlin, 1998) renal masses (Bosniak, 1991) (Silverman et al., 1994) (Zagoria, 2000) (Warshauer et al., 1988) and UTUC were very encouraging (Caoili et al., 2002), (Chow & Sommer, 2001) (Kawashima et al., 2004) (Anderson, Murphy, Rennie, & Cowan, 2006), (Nolte-Ernsting & Cowan, 2006) (Dillman, Caoili, & Cohan, 2007) (Silverman, Lyendecker, & Amis, 2009).

When multiplanar reformatted images of excretory-phase CT urography became a clinical reality for diagnosing UTUC and not just a mythical quest, there was much excitement amongst uroradiologists. The exquisite detail now possible with this new diagnostic imaging technique is demonstrated in the examples provided (Figures 1 - 5).

Figure 1. Unenhanced, nephrographic and excretory-phase CT urography showing an upper tract urothelial carcinoma of the right renal pelvis

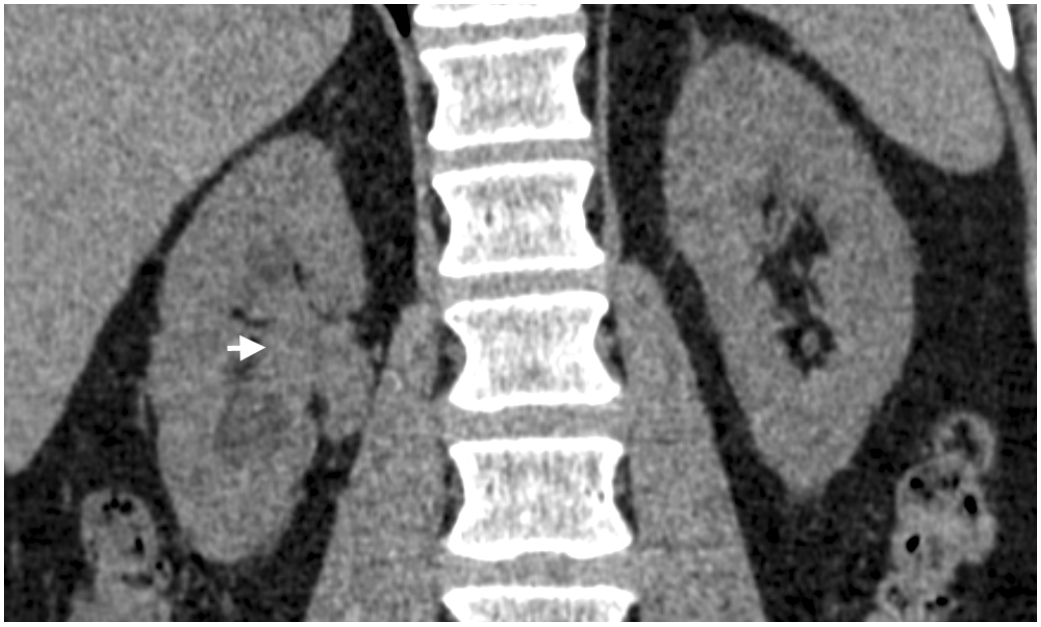


Figure 1a. Unenhanced coronal reformatted image of the kidneys. The mass in the right renal pelvis (white arrow) is difficult to visualize without the administration of intravenous contrast media.

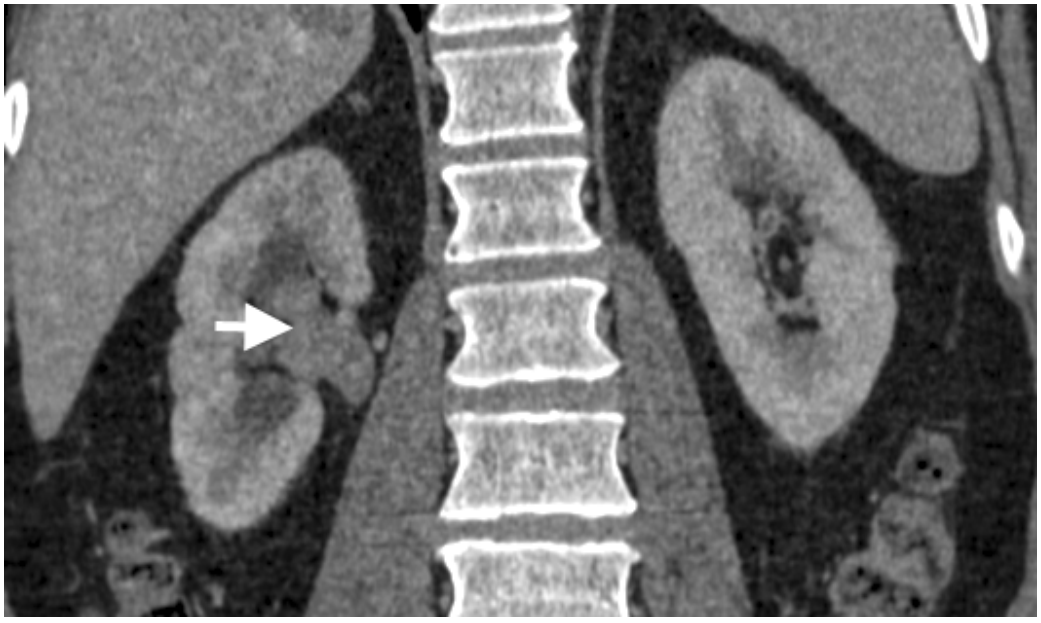


Figure 1b. Nephrographic-phase, contrast enhanced coronal reformatted image of the kidneys. The mass in the right renal pelvis is visible but is much more clearly depicted on the excretory-phase image, Figure 1c.

Figure 1. Unenhanced, nephrographic and excretory-phase CT urography showing an upper tract urothelial carcinoma of the right renal pelvis

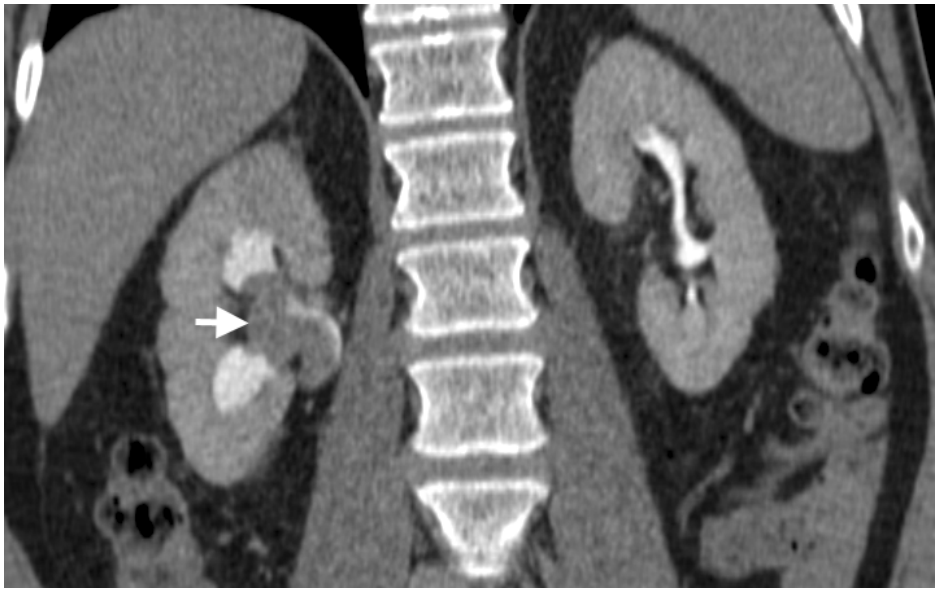


Figure 1c. The mass in the right renal pelvis is most clearly demonstrated during the excretory-phase. The mass was a urothelial carcinoma, G2, pTa. The patient underwent nephroureterectomy.

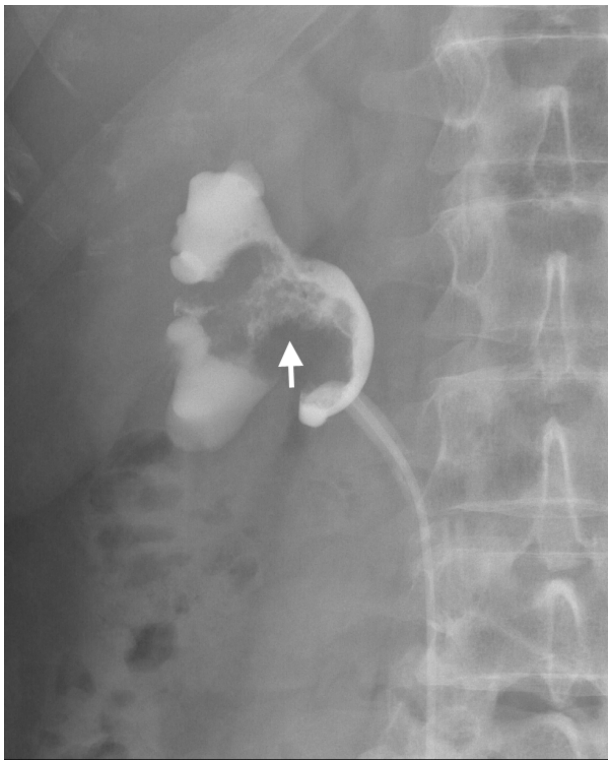


Figure 1d. Retrograde ureteropyelogram showing the large right renal pelvic mass, with irregularity and destruction of the epithelium.

Figure 1. Unenhanced, nephrographic and excretory-phase CT urography

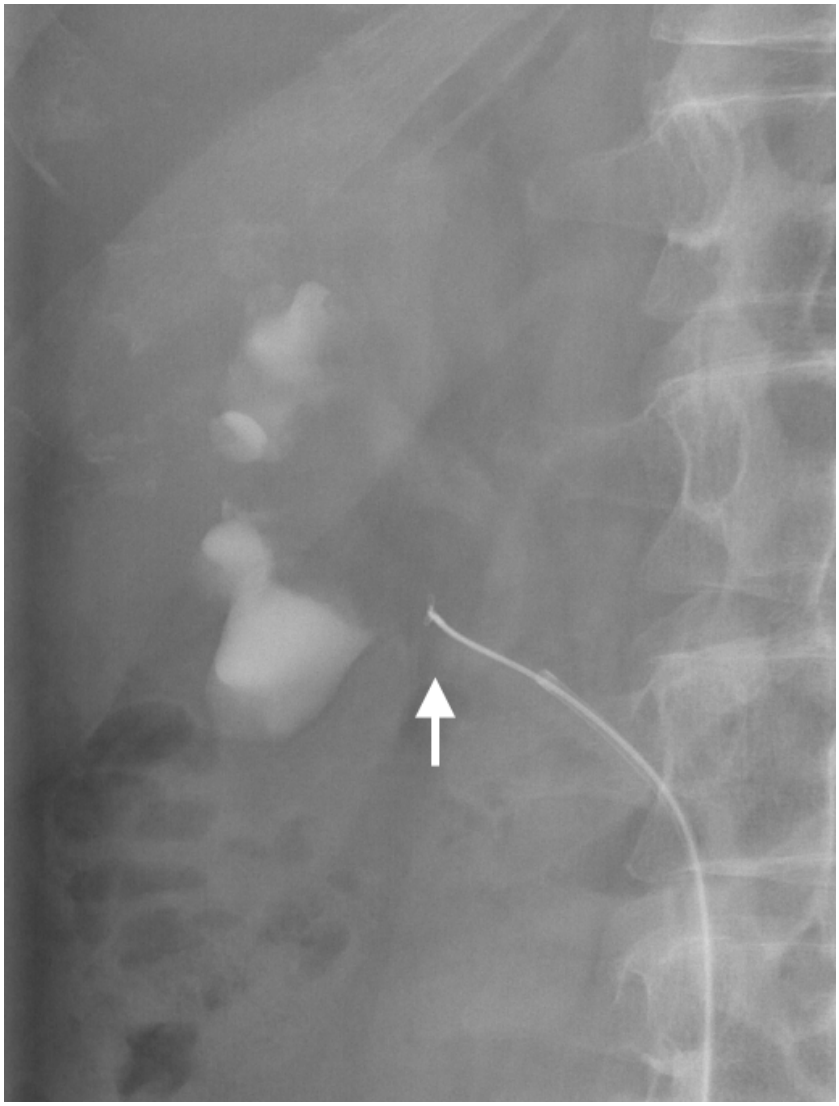


Figure 1e. Retrograde ureteropyelography-guided biopsy of the right renal pelvic mass, using ureteroscopic biopsy forceps. The biopsy result was G2-3, pTa urothelial carcinoma.

Figure 2. Urothelial carcinoma of the upper pole of the left kidney

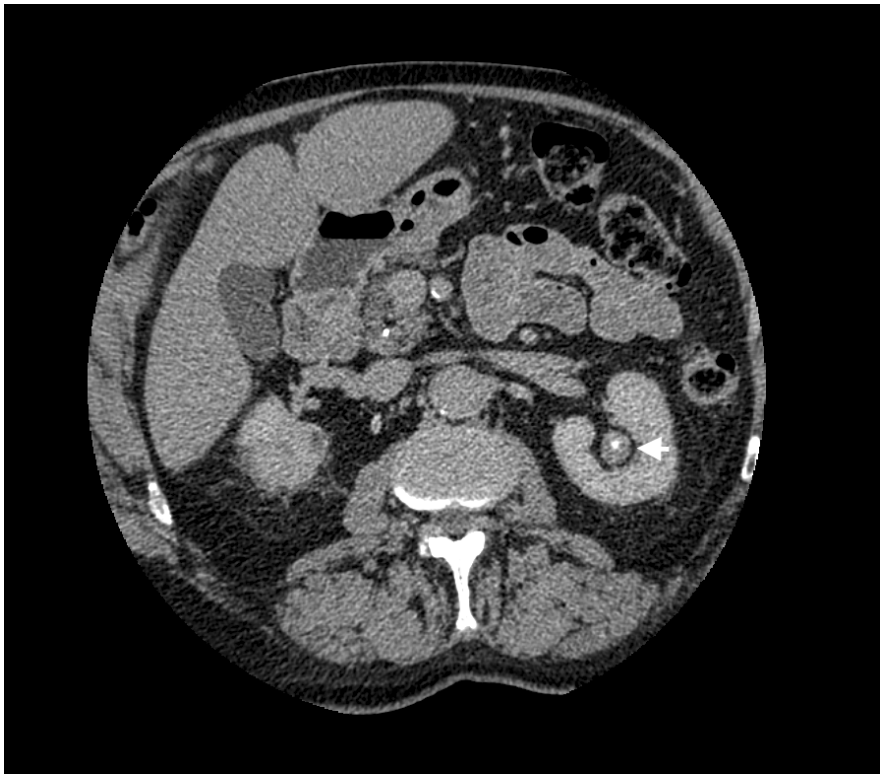


Figure 2a. Axial CT urogram of an 83M, presenting with visible haematuria. The upper pole shows urothelial thickening with epithelial irregularity.

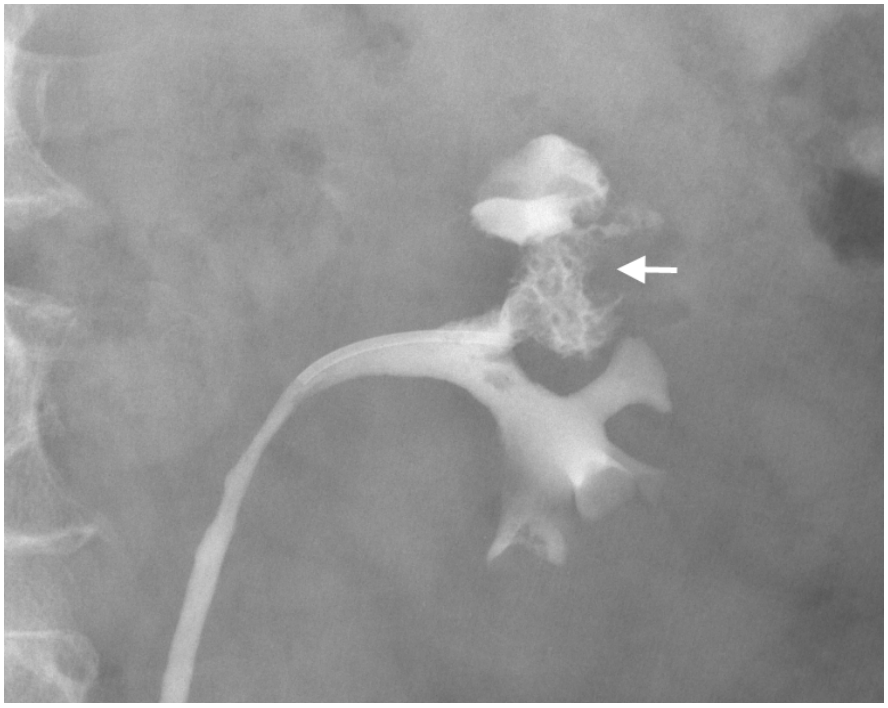


Figure 2b. Retrograde ureteropyelogram showing upper pole epithelial irregularity and destruction. Fluoroscopically-guided biopsy showed the mass to be a urothelial carcinoma, G2, pTa.

Figure 3. CT urogram showing urothelial carcinoma of the left pelvic ureter

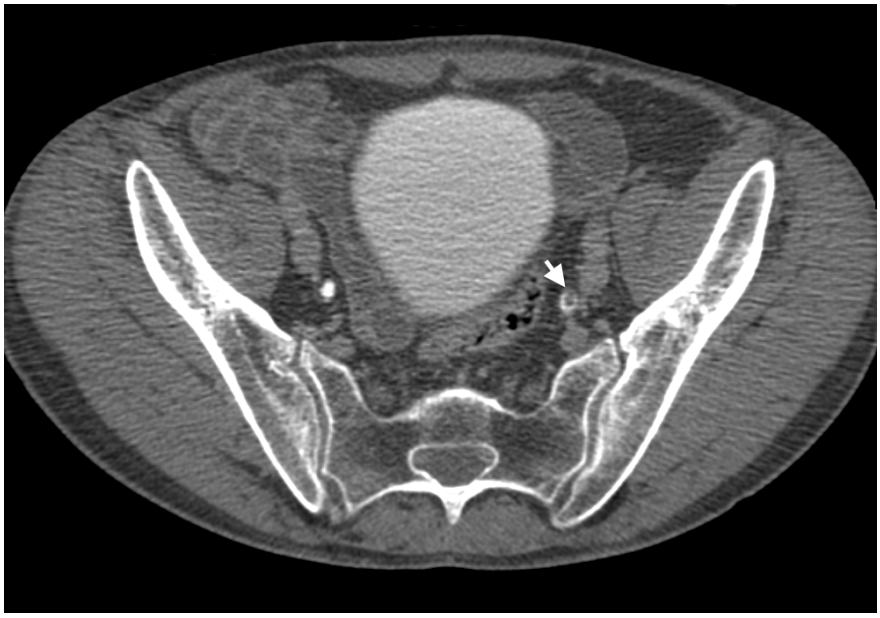


Figure 3a. Axial CT urogram of a 66M, presenting with visible haematuria, showing a solid filling defect in the left pelvic ureter.

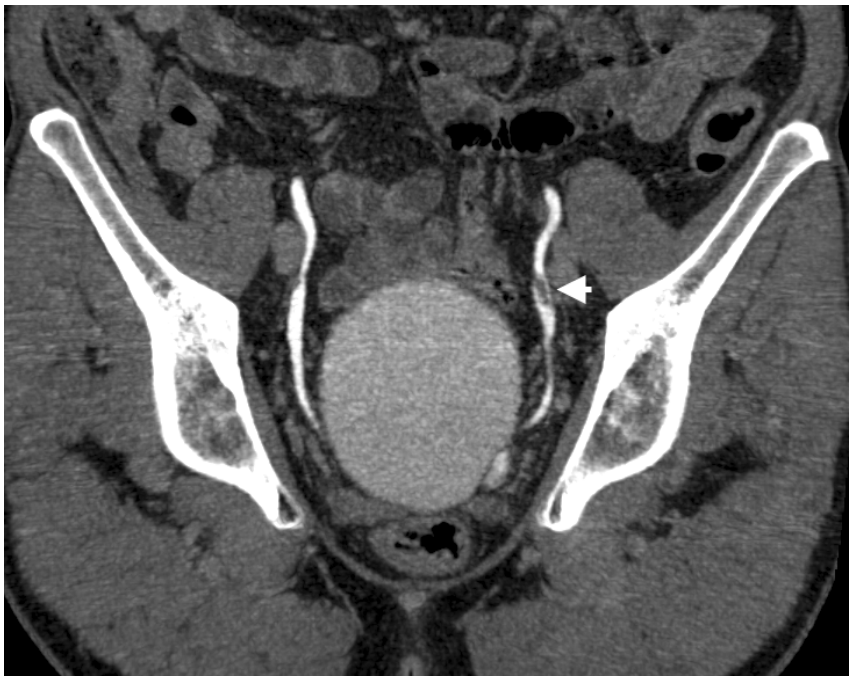


Figure 3b. Coronal reconstruction of the same examination, again demonstrating a mass in the left pelvic ureter.

Figure 3. CT urogram showing urothelial carcinoma of the left pelvic ureter

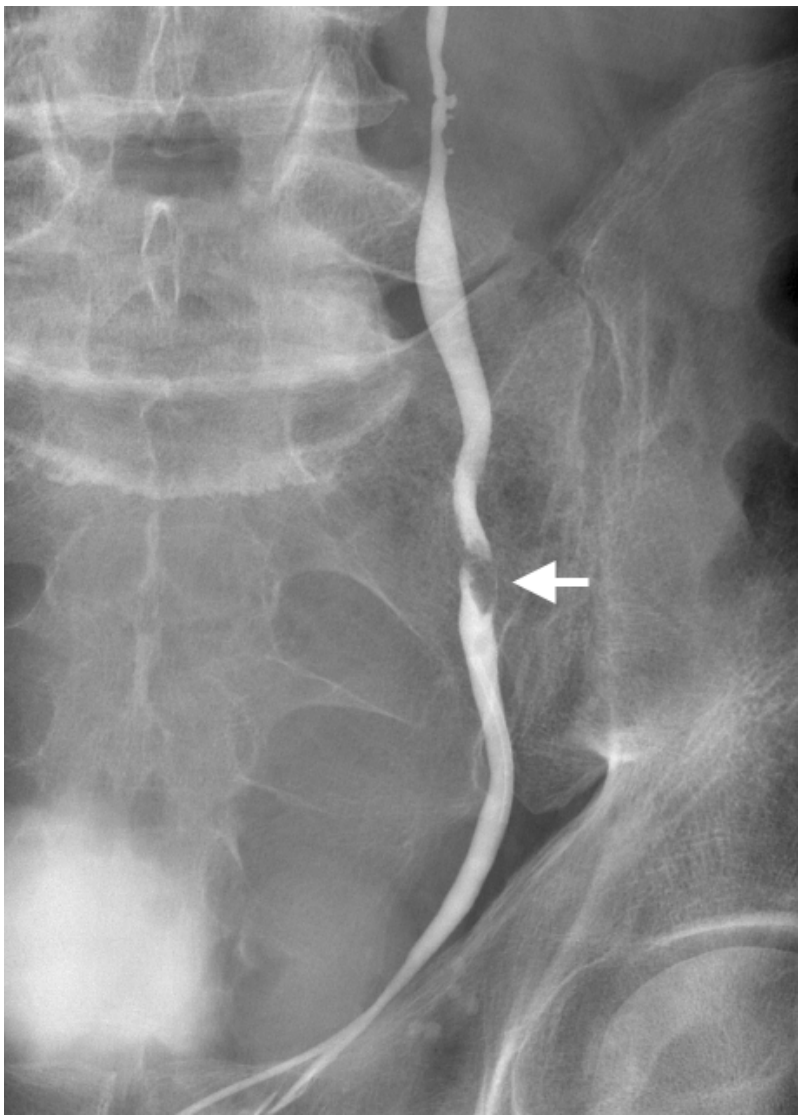


Figure 3c. Retrograde ureteropyelogram, immediately prior to biopsy showing urothelial carcinoma of the left pelvic ureter, G2, pT1.

Figure 4. CT urogram and retrograde ureteropyelogram showing a sessile UTUC of the abdominal ureter in a 78F with presenting with visible haematuria

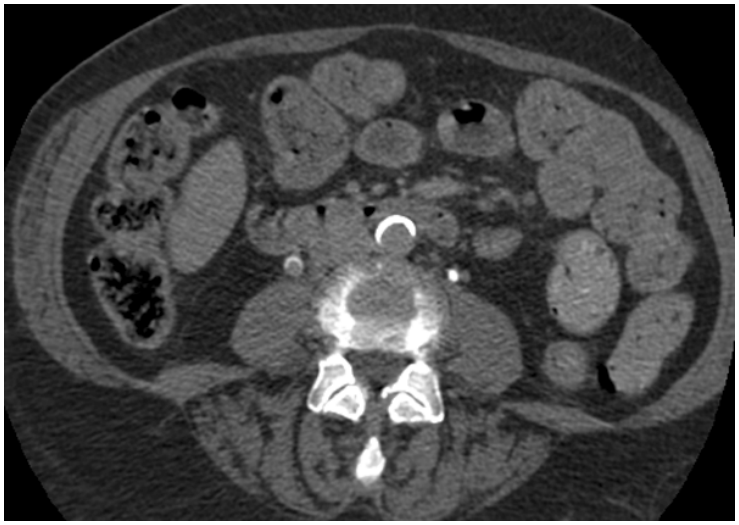
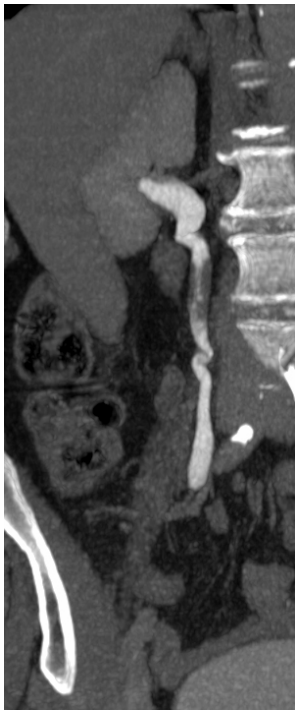


Figure 4a. Axial excretory-phase CT urogram showing a soft tissue mass in the right abdominal ureter



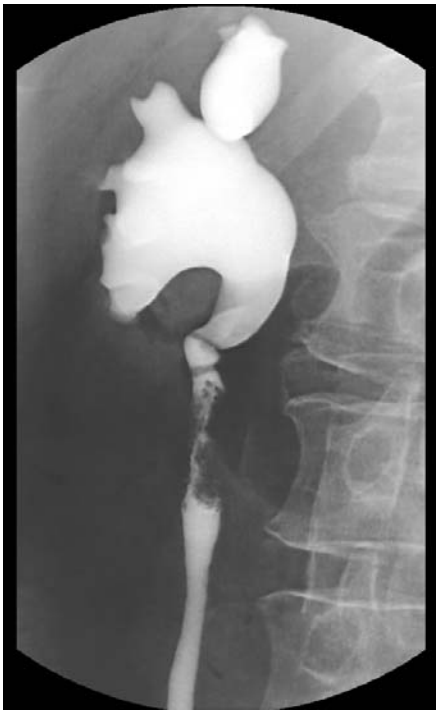


Figure 4b and 4c. Coronal reconstruction of the excretory-phase CT urogram and a corresponding retrograde ureteropyelogram showing a sessile urothelial carcinoma

Figure 5. CT urogram and retrograde ureteropyelogram showing a pendunculated urothelial carcinoma of the ureter in a 60M with visible haematuria

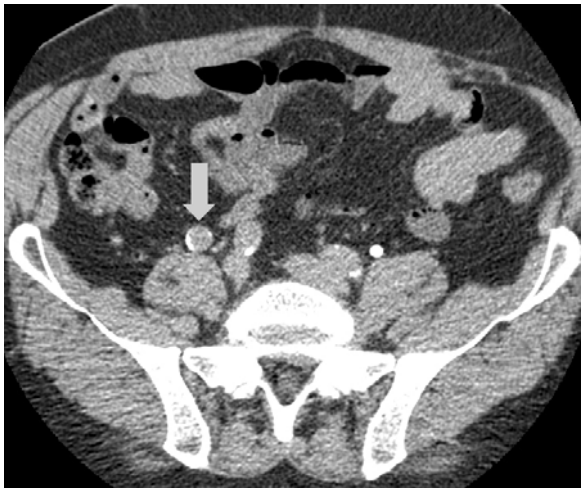


Figure 5a. Axial excretory-phase CT urogram
showing a soft tissue mass in the lower right abdominal ureter

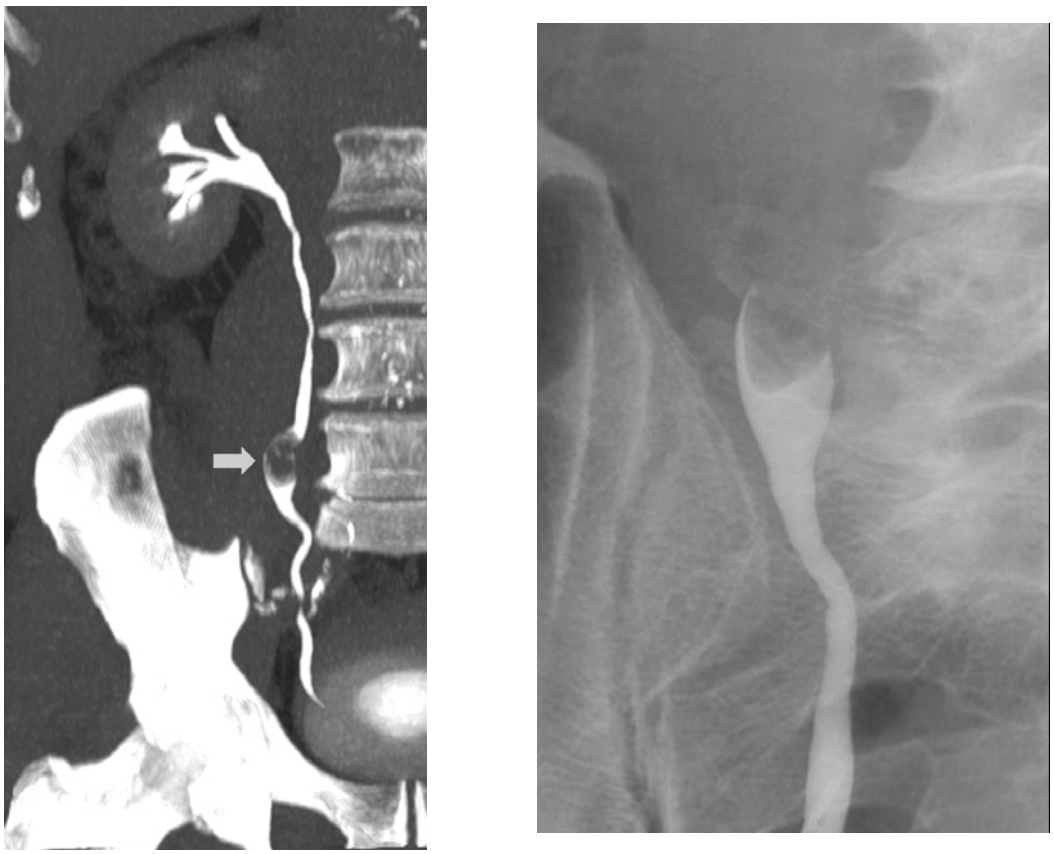


Figure 5b. A coronal reformatted image showing a pedunculated urothelial carcinoma in the lower right abdominal ureter. Figure 5c shows the corresponding retrograde ureteropyelogram, demonstrating the "goblet sign".

The first set of guidelines from the Upper Urinary Tract Imaging Group of the European Society of Urogenital Radiology were published in 2008 (Van Der Molen et al., 2008).

Indications and contra-indications for CT urography

The indications for CT urography remain controversial and consensus has not been reached on the subject (Nolte-Ernsting & Cowan, 2006). The principal indication is investigating haematuria, the subject of this thesis. Other indications will not be discussed further here (Table 2). A working knowledge of the indications for a particular diagnostic test and three other key pieces of information should be understood before making a request to avoid redundant requesting. Firstly, the clinician should use existing clinical knowledge of the patient to estimate the probability that the patient has the disease in question (the pretest probability). Secondly, the clinician should be aware of the sensitivity and specificity of the diagnostic test and finally the physician must consider whether the results of the test will affect the patient's management (Weinstein et al., 2005).

Contraindications are few but centre around whether iodinated contrast media or radiation should be avoided (Stacul et al., 2011).

Table 2. Indications for CT urography

1.	Haematuria (UTI excluded)
2.	Staging and follow-up of urothelial cancer, UTUC and BCa
3.	Iatrogenic injury to the ureter and bladder
4.	Trauma to the genitourinary tract
5.	Investigation of fistulae
6.	Unexplained hydronephrosis
7.	Planning for percutaneous nephrolithotomy
8.	Living related donor assessment
9.	Recurrent UTI's

Iodinated contrast media for CT urography

The iodinated contrast media (CM) used in this work was iohexol (Figure 6a) or iopamidol (Figure 6b) which are classified nonionic monomers.

Their molecular structure is based on the triiodinated benzene ring, they are water soluble (hydrophilic) and do not dissociate in solution.

Figure 6. The molecular structure of low osmolar contrast media

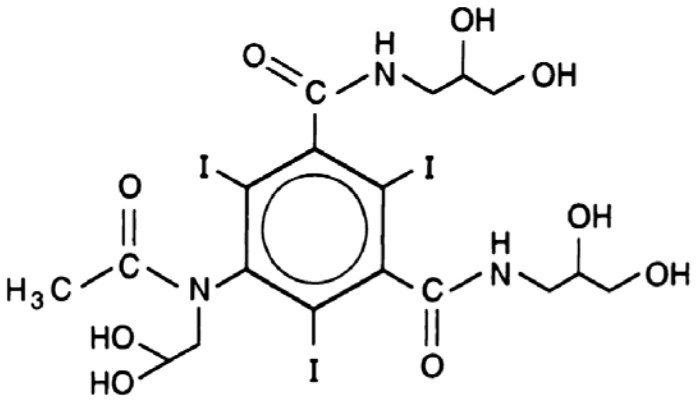


Figure 6a. The molecular structure of iohexol (Omnipaque)

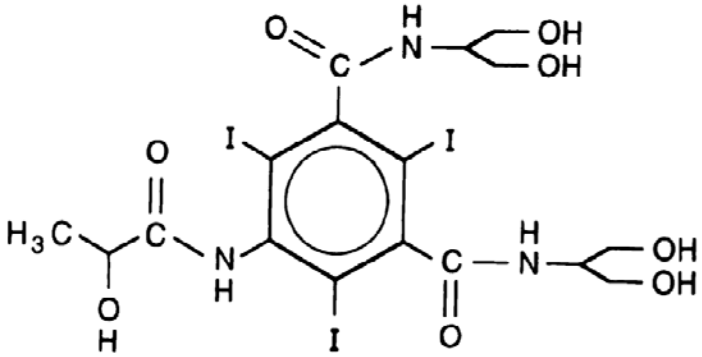
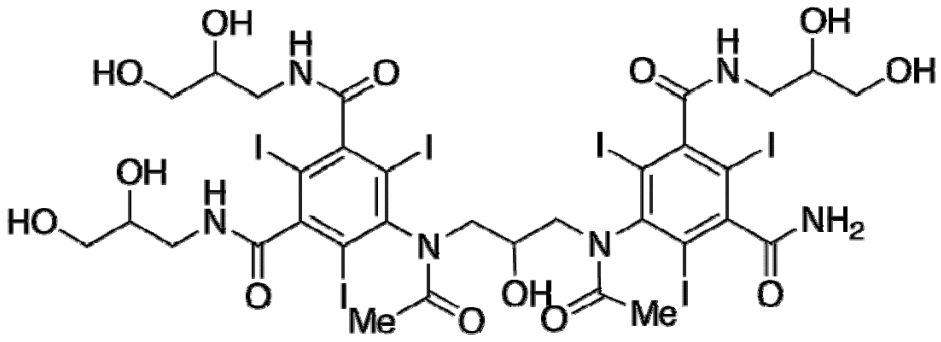


Figure 6b. The molecular structure of iopamidol (Niopam) (McClennan, 1990)

Figure 7. The molecular structure of iso-osmolar contrast media (iodixanol)



They were built on the concept that radiopaque contrast media should not double their osmolality by dissociation in solution, so virtually eliminating all haemodynamic effects due to the osmotoxicity of the agent.

The ratio of iodine atoms to dissolved particles is an important characteristic of contrast media which quantifies the important relationship between the attenuation effect of x-rays and the osmotic effect of the media. More iodine atoms per molecule means better opacification and fewer particles means lower osmotic effect, so a high ratio is preferred. Agents with a ratio of 1.5:1 are termed high osmolar contrast media (HOCM), agents with a ratio of 3:1 are low osmolar contrast media (LOCM) and agents with a ratio of 6:1 are termed isotonic contrast media (IOCM).

The history of iodinated radiographic contrast media for excretory urography began in 1923, when the first "nephrogram effect" was produced by giving a 10% solution of sodium iodide both orally and intravenously, (Osborne 1923, JAMA).

Intravenous use was limited by severe reactions. Continuous development led to the production of iohexol and iopamidol.

Pharmacokinetics of iodinated contrast media

Iodinated CM have pharmacokinetics similar to molecules known as "extracellular tracers". All of the current iodinated CM have very low lipid solubility and extremely low chemical reactivity with body fluids. Iodinated CM have molecular weights ranging from 600 to 1,650 Daltons. There is no evidence of passage of iodinated CM molecules through cell membranes into the interior of living cells, with the single exception of the proximal tubular cells of the kidney. When the CM molecules reach the systemic microcirculation, the molecules equilibrate quickly across capillary membranes (except the blood brain barrier). In the first phase of distribution, the increase in intravascular osmolality causes a rapid fluid shift across capillary membranes towards the hypertonic intravascular compartment. As the contrast medium molecules reach the capillary bed, rapid movement occurs through capillary pores and into the interstitial extracellular space as well as into the renal tubules.

The plasma concentration of iodine follows a biexponential decay curve. The first exponential term describes the mixing of contrast media in the plasma volume and then its distribution into the interstitial space. The second exponential term represents the clearance of contrast medium molecules from the body.

The clearance of x-ray contrast media and other extracellular tracers is primarily by glomerular filtration. There is no reabsorption or secretion by the renal tubules. Under normal physiological conditions very close to 100% of the contrast medium is eliminated through the kidney. The instantaneous rate of removal is equal to the glomerular filtration rate times the plasma iodine concentration.

Under normal physiological conditions, 99% of the water filtered through the glomeruli is reabsorbed in the renal tubules, with < 75% in the proximal tubules, 5% in the loops of Henle, 15% in the distal tubules and 5% in the collecting ducts.

The concentration of contrast material within the tubule depends on the concentration of contrast medium in the glomerular filtrate and on the amount of water reabsorbed as the filtrate passes down the tubule. The concentration of contrast medium in the initial filtrate is effectively the same as that in plasma, as protein binding of the modern urographic contrast media is insignificant. The final concentration of contrast in the urine may be 50 - 100 times that of plasma concentration.

The nephrogram is due to contrast material within the tubules. There is very little contribution to the nephrographic density from contrast medium in vascular structures.

Factors affecting the density of the nephrogram include the number of functioning nephrons, the volume of the nephron, the concentration of contrast material within the tubule, the GFR, the dose of contrast medium injected, the state of patient hydration and the type of contrast agents used. LOCM produce denser calyceal, ureteral and bladder opacification than HOCM. Urinary tract opacification depends on both the urinary concentration of iodine and the volume of contrast material in the urine (Katzberg, 1997).

As CT technology evolves so must the practice of CT intravenous contrast administration and scan timing evolve to optimize contrast enhancement (Bae, 2010).

Optimization of CT urography technique

It is helpful to classify CT urography protocols according to the method used for intravenous contrast administration. There are three main contrast administration protocols which depend on the number of boluses of contrast used (Table 3).

Table 3. CT urography protocols classified by bolus technique

	Bolus protocol	Indication
1	Single	Visible haematuria, patients at high risk for UTUC
2	Double	Bladder cancer follow-up, post-contrast series only
3	Triple	Living related kidney donor assessment Percutaneous nephrolithotomy assessment

The single bolus protocol is optimized for patients with haematuria at high risk of UTUC, renal masses and stones and is described in detail in the appendix. This protocol consists of three series of image acquisition**:** an unenhanced series optimized for detecting stones, a nephrographic series optimized for detecting renal masses and an excretory series optimized for detecting UTUC (Figure 1).

The double bolus protocol involves a lower radiation dose than the single bolus protocol. It uses less contrast than the single bolus protocol for demonstration of the nephrographic and excretory-phases and so may not demonstrate renal cell carcinoma and UTUC so clearly. For this reason, it is not currently recommended as an initial diagnostic test for patients at risk of UTUC, although many centres use it in this way. If the precontrast series is excluded, and the post-contrast nephrographic and excretory-phases are acquired in one series, a low dose examination is achieved which is recommended for the follow-up of patients with known bladder cancer or UTUC (Cowan, Turney, Taylor, McCarthy, & Crew, 2007; Turney, Willatt, Nixon, Crew, & Cowan, 2006; Anderson et al., 2006).

The triple bolus protocol is used for the assessment of living related kidney donors and patients undergoing percutaneous nephrolithotomy (Knox, Rivers-Bowerman, Bardgett, & Cowan, 2010). Although use of a triple bolus protocol for investigating haematuria has been described (Kekelidze et al., 2010), it is currently not recommended for routine use because the volume of contrast available for the excretory-phase is reduced by bolus splitting, which is likely to compromise diagnostic accuracy.

Many studies have evaluated techniques aimed at promoting complete opacification of the urinary tract during CT urography, in order to optimize the contrast between urine and urothelial disease. Currently there is no consensus regarding the optimum technique. A number of manoeuvres have been suggested that are often interrelated in a complex fashion so that adjustment of one will impact on the others. Such manoeuvres include oral administration of water, intravenous furosemide or saline to encourage urine flow, abdominal compression, varying the timing of the image acquisition, acquiring a second series of images in the excretory-phase, increasing the volume of contrast injected, and encouraging patient movement (walking or log rolling on the CT table) to promote mixing of contrast and urine.

Quality control

Continuous audit of opacification is required to maintain the standard of CT urography from day to day. All users of CT urography should employ comparable scoring systems. In one such scoring system, the urinary tract is divided into four anatomical components (collecting system and renal pelvis; abdominal ureter; pelvic ureter; and bladder), and each is given a score of 0 (no opacification), 1 (partial opacification) or 2 (complete opacification). The bladder is scored slightly differently, with 0 representing no opacification, 1 is used for regions of interest within the bladder at less than 100 HU, and 2 corresponds to all regions of interest in the bladder over 100 HU. Only by using a similar scoring system across different centres will it be possible to accurately compare different CT urography techniques (Cowan, 2012).

Radiation dose optimization strategies

There has been much recent interest in radiation dose optimization strategies (Brenner & Hall, 2007) (Brenner, Shuryak, & Einstein, 2011) (Kalra et al., 2004) particularly as the patient radiation dose at CT urography is greater than for conventional urography (Nawfel, Judy, Schleipman, & Silverman, 2004). There are many ways to reduce radiation exposure from CT while maintaining diagnostic accuracy. Such methods may be considered in three groups; reducing radiation exposure before the examination, during the examination and after the examination. The most effective way to reduce radiation exposure is to not perform the examination. Scrutiny of examination appropriateness is vital. Once the decision has been made to perform a CT examination, there are many available strategies to reduce radiation exposure. Use of size dependent protocols, automated tube current modulation, reduction of the number of passes (Morcos, 2007), reduction in duplicate coverage, reduction of mAs and kVp (Lee, Jung, Rha, & Byun, 2012) where possible, optimization of intravenous contrast infusion and possible use of external shielding. Methods of reducing radiation exposure after the examination include using postprocessing methods to decrease noise, such as smoother kernels for reconstruction, reconstruction at larger slice thickness and iterative reconstruction (Sodickson, 2012). These postprocessing techniques may improve image quality for a set radiation exposure so that CT images performed at reduced radiation dose may be brought up to diagnostic quality.

Principal questions

The thesis addresses the three principal questions concerning the development of CT urography for investigating haematuria:

1. What is the reasoning behind using CT urography?

2. What is the optimum diagnostic strategy using CT urography?

3. What are the problems with using CT urography and how may solutions be provided?

Each question is the subject of a separate chapter.

Chapter 1. Assessment and comparison of diagnostic accuracy

Introduction

Diagnostic accuracy of CT urography

The reasoning behind using excretory-phase CT urography for the investigation of haematuria ultimately depends on the high diagnostic accuracy of the excretory-phase for urothelial imaging and especially for UTUC (Figure 1). Early reports of the technique, illustrated the huge potential of CT urography for diagnosing UTUC. Some classical examples of UTUC demonstrated by CT urography are shown (Figures 2 - 5). The high diagnostic accuracy of the unenhanced and nephrographic-phases for stones and renal masses, is already well established. What is not well established is the diagnostic accuracy of CT urography for bladder cancer and UTUC. To justify its use in patients with haematuria, CT urography must be as good if not better in terms of diagnostic accuracy and patient acceptability than the alternative techniques for imaging urinary tract stones, renal cell cancer, bladder cancer and UTUC.

The results of studies evaluating the diagnostic accuracy of CT urography for haematuria are tabulated (Table 4). In 2002, Lang *et al*. reported a multicenter series of 350 consecutive patients with nonvisible haematuria and negative results on ultrasonography, intravenous urography, abdominal radiography and flexible cystoscopy, who subsequently underwent excretory-phase CT urography. A positive diagnosis rate of 45% was reported for all causes of haematuria, suggesting that excretory-phase CT urography was effective for diagnosing refractory cases of haematuria (Lang et al., 2002).

A number of studies have compared the diagnostic accuracy of intravenous urography and CT urography (Gray Sears et al., 2003) (O'Malley et al., 2003) (Albani, Ciaschini, Streem, Herts, & Angermeier, 2007) (Wang et al., 2010) (Jinzaki et al., 2011). Gray Sears *et al*. performed both intravenous urography and CT urography in 115 patients with asymptomatic haematuria. CT urography was found to be more accurate than intravenous urography for diagnosing the cause of nonvisible haematuria. A significant difference between the two imaging techniques was found for the detection of urinary calculi. Unenhanced CT is far superior to intravenous urography in terms of diagnostic accuracy for diagnosing stones. So far, this is the only study to directly compare CT

urography and intravenous urography prospectively in the same patients. The principal limitation of the study was the very small number of patients with UTUC in the sample population (n = 1). Although it is conceptually simple to design a study that compares two imaging techniques in the same patients, in practice it is very difficult to justify the increased radiation dose that such patients would receive. Studies using surrogate comparisons are now commonly reported, which require careful scrutiny to ensure that optimum CT urography is compared with optimum intravenous urography to mimic genuine clinical practice. It is also important to ensure that there are a sufficient number of patients with UTUC in each clinical cohort for an assessment of diagnostic accuracy for UTUC to be meaningful (O'Malley et al., 2003).

Albani *et al*. determined the usefulness of CT urography as an alternative to intravenous urography for the initial evaluation of patients with haematuria. Analysis of two separate unmatched groups of patients (*n* = 259 for CT urography; *n* = 253 for intravenous urography) revealed that CT urography was significantly more sensitive than intravenous urography for detecting upper tract disease (94.1% versus 50%). The cohort included an insufficient number of patients with UTUC for a meaningful comparison. The authors also reported low sensitivities (≤40%) for diagnosing lower tract lesions, which is most probably a reflection on the technique used for CT urography and reporting methods. Patient exercise and log rolling were not used (Albani et al., 2007).

In 2010, Wang *et al*. (Wang et al., 2010) performed a retrospective study of adult patients with haematuria who underwent both CT urography and intravenous urography over a 2.5 year period in a single institution. 19 of 60 patients had UTUC. The sensitivity, specificity and accuracy of intravenous urography were 0.750, 0.860 and 0.849 respectively, compared with 0.958, 1.000 and 0.996 for CT urography for UTUC. The authors concluded that CT urography should be the first choice noninvasive imaging technique for diagnosing UTUC in patients with haematuria. A similar study was reported by Jinzaki *et al*. in 104 patients with haematuria, 46 of whom had UTUC. Per-patient sensitivity, specificity, and overall accuracy for the detection of UTUC with CT urography (93.5%, 94.8%, and 94.2%, respectively) were significantly greater than the corresponding values for excretory urography (80.4%, 81.0%, and 80.8%; p = 0.041, 0.027, and 0.001 respectively (Jinzaki et al., 2011). Although the designs of these studies are theoretically imperfect, the results suggest that the diagnostic accuracy of CT

urography is greater than intravenous urography for upper urinary tract disease, especially UTUC.

Several retrospective studies report on the diagnostic accuracy of CT urography for UTUC (Fritz, Schoellnast, Deutschmann, Quehenberger, & Tillich, 2006) (Chow, Kwan, Olcott, & Sommer, 2007) (Sudakoff et al., 2008) (Wang, Wong, Chuang, Huang, & Pang, 2009) (Maheshwari, O'Malley, Ghai, Staunton, & Massey, 2010), against the reference standard of histopathology, cytology and clinical follow-up. Despite the variation in CT urography technique, most report high sensitivities and specificities for UTUC. Many studies using a double bolus protocol give the majority of the contrast volume in the second bolus, (Table 4), a manoeuvre that is likely to reduce the opacification scoring of the upper tract in the excretory-phase, as much of the contrast will not have been excreted into the collecting systems and ureter at the time of image acquisition.

In 2007, Cowan *et al.* (Cowan et al., 2007) compared the diagnostic accuracy of CT urography and retrograde ureteropyelography for diagnosing UTUC. The clinical cohort consisted of a selected group of 106 patients who presented with haematuria and initially underwent intravenous urography and flexible cystoscopy. Patients with equivocal or positive intravenous urography results and those with negative intravenous urography and flexible cystoscopy results but with persistent haematuria were investigated with CT urography and retrograde ureteropyelography. The reference standard was histopathology from biopsy or resected specimens and 3–5 year clinical follow-up. The sensitivity, specificity, positive predictive value and negative predictive value of CT urography and retrograde ureteropyelography for diagnosing UTUC were similar, (Table 7 and 8) which is an important result given that retrograde ureteropyelography is often regarded as the gold standard for imaging UTUC (Cowan et al., 2007). The authors concluded that the quantitative evidence provided by the study validated the use of CT urography for diagnosing UTUC.

Table 4. Diagnostic accuracy studies using CT urography for diagnosing UTUC and BCa

Study	n	Site	Se	Sp	PPV	NPV	Indications	Bolus / Timing	Manoeuvres
Fritz et al 2006	41/39	UUT	1.00	NR	NR	NR	Histologically verified UTUC	Single (1.5 ml/kg) 420-600 s	None
Chow et al 2007	8/500	UUT	1.00	0.99	0.80	1.0	Painless haematuria	Double (40 ml/80 ml) 360 s	900 ml oral water; compression
Sudakoff et al 2008	11/468	UUT	0.82	0.98	0.50	1.0	Unspecified haematuria	Double (40 ml/ 110 ml) 820 s	None
Wang et al 2009	39/115	Renal pelvis	0.94	0.99	NR	NR	Visible haematuria	Single (120 ml) 420-560 s	None
		Ureter	0.67	0.98	NR	NR			
Maheshwari et al 2010	9/200	UUT	1.00	0.99	0.82	1.0	Haematuria (all types)	Double (50 ml/80 ml) 420-560 s	1000 ml oral water, log roll on table; partially empty bladder
Jinzaki et al 2011	46/128	UUT	0.94	0.95	NR	NR	Haematuria (all types)	Single (2 ml/kg) 480 s	400–500 ml oral water
Cowan et al 2007	32/106	UUT (CTU)	0.97	0.93	0.79	0.99	Haematuria, equivocal or positive IVU, or persistent haematuria & negative IVU	Double (100 ml/50 ml) 700 s	750-1000 ml oral water; void before CT examination; walk and log roll
		UUT (RUP)	0.96	0.97	0.87	0.97			
Blick et al 2011	156/778	Bladder (CTU)	0.95	0.83	0.58	0.98	Visible haematuria, ≥40 years; no infection	Double (100 ml/50 ml) 700 s	750–1000 ml oral water; void before CT examination, walk and log roll
		Bladder (FC)	0.98	0.94	0.80	0.99			
Sadow et al 2008	54/373	Bladder (CTU)	0.83	0.94	0.71	0.97	Visible haematuria	Single (100 ml) 900 s	900 ml oral water, void before CT examination; 250 ml intravenous saline
		Bladder (CTU)	0.94	0.69	0.69	0.99			

Abbreviations: n, number of UTUC / number of patients; Se, sensitivity; Sp, specificity; PPV, positive predictive value, NPV, negative predictive value; CTU, CT urography; FC, flexible cystoscopy; IVU; intravenous urography; NR, not reported; RUP, retrograde ureteropyelography; UUT, upper urinary tract; UTUC, upper urinary tract urothelial carcinoma; BCa, bladder cancer.

From Cowan NC Nat Rev Urol 2012; 9: 218-226.

1.1 Assessment and comparison of the diagnostic accuracy of CT urography with retrograde ureteropyelography for upper urinary tract urothelial cancer

1.1 Abstract

1.1 Purpose

To evaluate and compare the diagnostic accuracy of CT urography with retrograde ureteropyelography for UTUC.

1.1 Patients and methods

The clinical cohort consisted of a selected series of adult patients presenting with haematuria and equivocal or positive signs for UTUC on conventional intravenous urography. Entry criteria were based on intravenous urography findings to ensure high prevalence for UTUC for valid retrospective comparison of the two diagnostic techniques. CT urography and retrograde ureteropyelography studies were performed on all patients in the clinical cohort and were scored for presence and absence of UTUC by two radiologists, retrospectively and independently. Demographic and clinical information was withheld. The reference standards were histopathology from biopsy or resection specimens and clinical follow-up for 3 - 5 years.

1.1 Results

CT urography and retrograde ureteropyelography were undertaken in 106 patients over a 24-month period. Retrograde ureteropyelography was attempted in 151 of 212 UUTs. The corresponding CT urogram for each UUT was reviewed. CT urography was true positive for urothelial tumour in 27, true negative in 108, false positive in 9 and false negative in 1 UUT. For CT urography for diagnosing UTUC, sensitivity = 0.96, specificity = 0.92, PPV = 0.75 and NPV = 0.99.

Retrograde ureteropyelography was technically successful in 96% of the UUTs (n=145/151). For diagnosing UTUC, retrograde ureteropyelography was true positive in 27, TN in 112, false positive in 5 and false negative in 1 UUT. For retrograde ureteropyelography for diagnosing UTUC, sensitivity = 0.96, specificity = 0.96, PPV = 0.84 and NPV = 0.99.

1.1 Conclusion

Similar results for the diagnostic accuracy of CT urography and retrograde ureteropyelography for diagnosing UTUC validates quantitatively the use of CT urography for diagnosing UTUC.

1.1 Introduction

Computed tomography is an established diagnostic imaging modality for detection and characterisation of urinary tract stones and renal masses (Israel & Bosniak, 2005) (Memarsadeghi et al., 2005).

Excretory-phase CT urography is a more recent technique made possible by multidetector CT technology and developed primarily for investigation urothelial lesions (Caoili et al., 2002).

CT urography may also detect significant extra-genitourinary pathology (Liu, Mortele, & Silverman, 2005) (Song, Beland, & Mayo-Smith, 2012) (Bromage, Liew, Moore, Raju, & Shackley, 2012).

The concept of CT urography for investigating haematuria is attractive as both the renal parenchyma, urothelium and extra-genitourinary diseases may be evaluated with a single relatively non-invasive comprehensive examination.

With careful attention to proper set up of CT acquisition parameters, production of isotropic voxels and high resolution multiplanar reformatted images is possible. Analysis of multiplanar reformatted images is a great advantage for the radiologist when reading CT urography, especially when looking at structures which have their long axis in the axial plane.

The 2001 American Urological Association guidelines also indicate that retrograde ureteropyelography is commonly considered by many to be the best imaging approach for detection of UTUC but again this opinion is not based on evidence (Grossfeld et al., 2001c).

1.1 Purpose

To evaluate quantitatively the use of CT urography for diagnosis of UTUC in patients with haematuria by comparison with retrograde ureteropyelography using histopathology and clinical follow-up as the gold standard.

1.1 Patients and methods

CT urography and retrograde ureteropyelography were performed to diagnose and stage UTUC in a selected series of patients presenting with haematuria. Initial investigations included intravenous urography and flexible cystoscopy in all. Patients with equivocal or positive intravenous urography, and patients with persistent haematuria, negative intravenous urography and flexible cystoscopy, were investigated for UTUC with CT urography and retrograde ureteropyelography. The examination were conducted over a 24 month period.

CT urography and retrograde ureteropyelography studies of the UUT were reviewed retrospectively and independently by two radiologists without knowledge of demographic details or clinical information. A decision relating to the presence or absence of UUT urothelial tumour was made. Results were analysed using 2 x 2 tables and the sensitivity, specificity, positive and negative predictive values were calculated for CT urography and retrograde ureteropyelography for diagnosing UTUC.

Reference gold standards were histopathology (obtained by biopsy or from resected specimens) and clinical follow-up through review of medical and pathological records for a 3 year to 5 year period.

1.1 Method for CT

CT examinations were performed on multidetector scanner (GE Lightspeed QX/i, GE Medical Systems, Milwaukee, Wisconsin, USA) 8 slice. All patients were given 500-750 ml of water to drink in the 20 minutes prior to the CT examination. No oral contrast was administered. The patient was placed in the supine position on the CT table.

Phase 1 was unenhanced from the top of the kidneys to 2 cm below the symphysis pubis on expiration using 8.0 x 2.5 mm collimation. A double bolus i.v. contrast administration protocol was used which was a variant of the protocol described by Chow and Sommer Phase 2 was a combined nephrographic and pyelographic-phase. A bolus of 100 ml of

3 ml / s and the patient was exercised in the CT room by walking and then touching their toes and finally by rolling on the table 720° in both clockwise and anticlockwise directions to mix thoroughly the contrast medium with urine in the UUT and bladder. At 10 minutes after the first injection, a second contrast bolus of 50 ml of the same contrast was given via a pump at a rate of 3 ml / s and the abdomen and pelvis scanned in expiration 100 s after the second bolus producing a combined nephropyelographic-phase. The scanning parameters are provided (Table 5).

Table 5. Acquisition and reconstruction parameters for CT urography

Se	C	n	SC	TS	P	SFOV	SW	RI	MX	DFOV
UE	KUB	8	1.25	16.75	1.675	500	2.5	1.25	512	320
R 1	A / P	8	1.25	16.75	1.675	500	5	5	512	320
R 2	A / P	8	1.25	16.75	1.675	500	2.5	1.25	512	320
R 3	A / P	8	1.25	16.75	1.675	500	1.25	0.625	512	320

Abbreviations: Se, series; C, coverage; n, detector configuration; SC, slice collimation (mm); TS, table feed (mm) / rotation; P, pitch; SFOV, scanned field of view (mm); SW, section width (mm); RI, reconstruction interval (mm); MX, matrix; DFOV, display field of view (mm).

kV, 120; Auto mA, UE 190-220, R 1-3, 100-300.

If the upper urinary tract opacification was incomplete when the first axial reconstruction was reviewed by attending radiologist, a second delayed excretory-phase scan in the prone position was performed. The prone position was selected in order to encourage complete upper urinary tract opacification and further mixing of contrast with urine. The unenhanced scans were reconstructed axially using 2.5 mm sections and 1.25 mm increments. The nephropyelographic-phase images were reconstructed axially initially using 5 mm sections at 5 mm intervals and then using 2.5 mm sections and 1.25 mm increments and at 1.25-mm sections and 0.625 mm increments in selected cases where multiplanar reformatted images were viewed in order to achieve isotropic voxels.

1.1 Method for retrograde ureteropyelography

Written informed consent was obtained from all patients and antibiotic prophylaxis (ciprofloxacin 500 mg orally) given. Lignocaine gel was used as a local anaesthetic and lubricant. Sedoanalgesia; diazemuls (2.5-10 mg i.v.) and pethidine (50-100 mg i.v.) was administered as required. The patient's pulse, blood pressure and oxygen saturation were continuously monitored during the procedure.

A flexible cystoscope was passed into the bladder and rotated through 180° to allow greater deviation of the end of the scope and facilitate identification of the ureteric orifices. A 0.035" straight hydrophilic guide wire (Terumo Corporation, Tokyo, Japan) was passed into the ureteric orifice under direct vision. The guidewire was manipulated into the renal pelvis using C-arm digital fluoroscopy for guidance (Siemens Polystar, Erlangen, Germany). The flexible cystoscope was removed and a 4F general purpose vascular catheter (Cordis, Miami, USA) placed over the wire into the renal pelvis. retrograde ureteropyelography was then performed using C-arm rotation and the table tilting facility (McFarlane, Cowan, Holt, & Cowan, 2001). Low osmolar non-ionic contrast media was used (Iopamidol 300) and diluted if appropriate with normal saline.

1.1 Image review technique

Examinations were reviewed and scored by two radiologists, without clinical information or knowledge of patient demographics. CT urography, axial, multiplanar reformatted images were constructed and reviewed at a workstation, running Voxar3D version 4.2 (Voxar, Edinburgh, U.K.) on abdominal and bone window settings. Using axial review of phase 1 and then phase 2, a diagnosis could be made in the majority of cases. Multiplanar reformatted images were only used in specific cases for clarification.

Retrograde ureteropyelography images were also reviewed on a workstation (eFilm 1.8.3). Individual UUT were reviewed retrospectively and independently by 2 radiologists and a consensus score was obtained. CT urography and retrograde ureteropyelography examinations were reviewed 3 months apart.

1.1 Results

CT urography and retrograde ureteropyelography were compared in 151 UUT in 106 patients with haematuria (male = 71, female = 35) (visible n = 77, nonvisible n = 29) over a 24 month period. The mean age was 64.9 years (range = 25.1 – 90.5 years).

CT urography was technically successful providing images of diagnostic quality in all 151 UUT. Retrograde ureteropyelography was technically successful in 96% (n=145/151) of the UUT attempted.

The aim of retrograde ureteropyelography is to provide diagnostic information about the entire UUT for an appropriate clinical management plan to be made. Tumour present in the bladder may prevent an adequate retrograde ureteropyelography study but does not necessarily indicate UUT involvement. In this study, 6 (4%) attempted retrograde ureteropyelography examinations were technically unsuccessful. UUT urothelial tumour was present in 4 and absent in 2. The reasons for technical failure were bladder tumour obscuring the ureteric orifice (n = 4), blood obscuring the ureteric orifice (n = 1) and tumour obstructing the lower ureter preventing passage of guidewire (n = 1).

Of all the retrograde ureteropyelography studies, 2 were classified as technically successful but non-diagnostic. In these 2 studies, there was complete occlusion of the ureter, making a diagnosis from the retrograde ureteropyelography images alone impossible. For the analysis these two UUTs were designated as disease positive as subsequent tests were needed to confirm the diagnosis. In one of the cases urothelial cancer was responsible for the ureteric occlusion and in the other it was due to pelvi-ureteric junction obstruction secondary to chronic pyelonephritis.

Of the 151 retrograde ureteropyelography studies attempted, 145 examinations were technically successful and of sufficient diagnostic quality to be included in the quantitative analysis.

The prevalence of UTUC in the study population was 30.2% (n = 32/106). Such a high prevalence is explained by the inclusion criteria for the study. The UUT tumour type, location and number are given (Table 6).

Table 6. Upper urinary tract tumour type, location and number

Tumour type	Location	Number
UTUC	Collecting system	8
	Renal pelvis	9
	Ureter (unifocal)	13
	Ureter (multifocal)	2
	Total	32
RCC		2
Metastases	To kidney from adenocarcinoma of the lung	1
	Total	3

Abbreviations: UTUC, upper urinary tract urothelial carcinoma; RCC, renal cell carcinoma.

1.1 Results for CT urography

Analyzing the results for CT urography compared with the reference standard of histopathology and follow-up, showed CT urography had a sensitivity of 0.96 and a specificity of 0.96, with a positive predictive value of 0.75 and negative predictive value of 0.99 for diagnosing UTUC in the population group, (Table 7 and 8).

The upper urinary tracts for which CT urography was false negative and false positive require comment.

CT urography was false negative for urothelial tumour in one UUT. The lower ureter was incompletely opacified at the site of a small urothelial tumour. Diagnosis from the CT urography was not achievable from the excretory-phase images.

CT urography was false positive for urothelial tumour in 9 UUTs. Debris in the collecting system was misinterpreted as tumour (n = 3). Circumferential ureter wall thickening was mistaken for tumour (n = 3). One of these cases was secondary to an iatrogenic injury at ureteroscopy for stone removal, another showed slight, circumferential wall thickening at the site of a ureteral kink, and the last may have been due to recent passage of a stone.

Renal cell carcinoma with collecting system invasion was interpreted as UTUC (n = 1). A vessel causing an indentation in an upper pole infundibulum was interpreted incorrectly as UTUC (n = 1). Another false positive CT urography showed a small filling defect on axial sections in the lumen of the lower ureter close to the ureterovesicle junction. The corresponding retrograde ureteropyelography showed a tumour-free ureter with fish-hooking as it passed over an exophytic bladder cancer (n = 1).

Table 7. CT urography compared with RUP for diagnosing UTUC

Disease positive for UTUC		CT urography		
(n = 28 / 145)		Positive	Negative	
RUP	Positive	26	1	27
	Negative	1	0	1
	Total	27	1	
Disease negative for UTUC		CT urography		
(n = 117)		Positive	Negative	
RUP	Positive	1	4	5
	Negative	8	104	112
	Total	9	108	

Abbreviations: RUP, retrograde ureteropyelography; UTUC, upper urinary tract urothelial carcinoma.

Table 8. Diagnostic accuracy of CT urography and RUP for UTUC

n=145		Disease (UTUC)		
		Positive	Negative	
CT urography	Positive	27	9	PPV = 0.75
	Negative	1	108	NPV = 0.99
		Se = 0.96	Sp = 0.96	
RUP	Positive	27	5	PPV = 0.84
	Negative	1	112	NPV = 0.99
		Se = 0.96	Se = 0.96	

Abbreviations: RUP, retrograde ureteropyelography; UTUC, upper urinary tract urothelial carcinoma.

1.1 Results for retrograde ureteropyelography

Analysing the results for retrograde ureteropyelography compared with histopathology and follow-up, with the technically inadequate studies excluded from analysis, retrograde ureteropyelography had a sensitivity of 0.96 and a specificity of 0.96 with a positive predictive value of 0.84 and negative predictive value of 0.99 for diagnosis of UTUC, (Table 7 and 8).

Retrograde ureteropyelography was false negative for UTUC when there was circumferential ureter wall thickening without epithelial irregularity which was detectable only on CT urography (n = 1).

Retrograde ureteropyelography was false positive for UTUC (n = 5). A vascular impression caused irregularity of the inferior margin of an upper pole infundibulum of the right kidney (n = 1). Subsequently CT arteriography confirmed these signs were due to a serpiginous vessel from as small arteriovenous fistula. Irregularity of the epithelium in the region of the PUJ was shown by CT urography to be secondary to an impacted calculus dislodged and not identified at retrograde ureteropyelography (n = 1). A solid renal cell carcinoma and a renal metastasis from adenocarcinoma of the lung were tumours that mimicked UTUC, both displaying invasion of the collecting system (n = 2). Abrupt cut off of the ureter in the region of the PUJ was secondary to chronic pyelonephritis. No tumour was found at nephroureterectomy.

1.1 Discussion

This paper sets out to evaluate quantitatively the use of CT urography for diagnosing UTUC. There are currently available very few studies comparing the performance of various diagnostic imaging modalities for the diagnosis of UTUC (Lang et al., 2002) (Gray Sears et al., 2003). High detection rates for UTUC on contrast enhanced CT images are suggested (Caoili et al., 2005) (Caoili et al., 2002) (Noroozian, Cohan, Caoili, Cowan, & Ellis, 2004) but such reviews are without statistical analysis. The American Urological Association Best Practice Policy Recommendations of 2001 states that retrograde ureteropyelography is generally considered the best imaging approach for the detection and characterization of ureteral abnormalities (Grossfeld et al., 2001c). This study evaluates CT urography for diagnosing UTUC and provides statistical analysis. CT urography is compared with retrograde ureteropyelography because retrograde

ureteropyelography is currently assumed to be the best diagnostic test for these tumours.

CT urography and retrograde ureteropyelography have similar high sensitivities for diagnosing UTUC. Sessile or pedunculated UTUC may be detected with similar sensitivity by both CT urography and retrograde ureteropyelography. Those urothelial tumours which show circumferential urothelial thickening with epithelial irregularity (Figure 8), may also be diagnosed by both diagnostic techniques. CT urography however, may detect urothelial wall thickening without epithelial irregularity. Such cases of UTUC will be missed by retrograde ureteropyelography, (Figure 9).

The single case of false negative CT urography for UTUC was due to incomplete ureter opacification by contrast medium. Diagnosis of UTUC depends on the difference in density between the tumour and surrounding contrast. In ureter segments in which there is incomplete opacification, the difference in density between tumour and ureter wall may be so small as to render small tumours undetectable (Figure 10). Complete and homogenous opacification of the collecting system and ureter with contrast medium is therefore desirable for optimum sensitivity of CT urography for diagnosing UTUC.

The most common technical error of CT urography is incomplete ureter opacification, most frequently of the distal ureter (Meindl et al., 2006). Various manoeuvres may promote complete opacification of the ureter including oral hydration prior to scanning (Kawamoto, Horton, & Fishman, 2006; McTavish, Jinzaki, Zou, Nawfel, & Silverman, 2002), intravenous furosemide administration (5-10 mg), exercising the patient immediately before scanning the excretory-phase (Anderson et al., 2006), test scanning at defined levels prior to performing the excretory-phase (Kemper, Regier, Stork, Adam, & Nolte-Ernsting, 2006) and undertaking further series (Kawamoto et al., 2006; Nolte-Ernsting & Cowan, 2006).

There is the theoretical risk of missing tumour at CT urography due to incomplete mixing of contrast medium with urine within the renal pelvis, ureters and bladder. Rolling on the CT table and exercising the patient just before the acquisition of the excretory-phase series encourages homogenisation of contrast and urine aimed at increasing the sensitivity of CT urography for diagnosis of UTUC.

The CT urography false positives for UTUC fall into three groups; those with urothelial abnormalities, those with luminal abnormalities and those with extra-urothelial abnormalities, simulating UTUC.

For urothelial abnormalities, in this study, an iatrogenic ureter injury at ureteroscopy led to circumferential urothelial thickening and was misdiagnosed as UTUC (Figure 11). Without the history, withheld from the reviewers under the conditions of the review process, this was not suspected. In the other case, mild circumferential urothelial thickening was identified at the site of a ureter kink. multiplanar reformatted review routinely would assist in differentiating UUT tumour thickening from artifactual wall thickening. Other causes of urothelial wall thickening include irritation by calculi or stent, fibroepithelial polyp or rare tumours such as the nephrogenic adenoma.

For luminal abnormalities, in four UUTs, debris was mistaken for UTUC (Figure 12). Lack of enhancement would help differentiate debris from tumour or repositioning and rescanning in the prone position at the specific site of interest to see if the debris shifted with repositioning. Intraluminal clot could be differentiated from tumour using these techniques.

For extraluminal abnormalities, vascular indentation upon an upper pole infundibulum is difficult to distinguish from tumour (Figure 13). CT arteriography or retrograde ureteropyelography would help clarify in this situation. Finally other tumour types sometimes mimic UTUC, such as renal cell carcinoma when invading the collecting system (Figure 14). The only method of determining the exact cell type under these conditions is by biopsy and histopathology review.

In principle, CT urography has many advantages over other imaging modalities for the investigation of patients with haematuria who are at risk for urological malignancy. CT urography may be used as a single non-invasive test for examination of the entire urinary tract. It provides information relating to the presence of stones, urothelial tumours, renal tumours and extra-genitourinary pathology (Liu et al., 2005). Recent work suggests it has a role for diagnosing bladder tumours (Turney et al., 2006).

CT urography when compared with retrograde ureteropyelography, offers less chance of physical trauma e.g. rupture of the collecting system, introduction of infection or irritation to the urinary tract, because of its non-invasive nature.

Figure 8. CT urogram and retrograde ureteropyelogram of a patient presenting with visible haematuria caused by an UTUC seen as with circumferential urothelial thickening

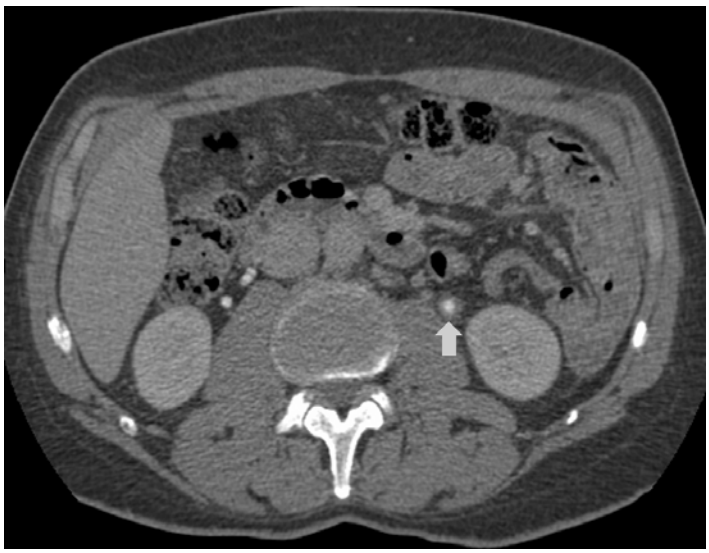


Figure 8a. Circumferential urothelial thickening of the ureter seen on an excretory-phase CT urogram due to urothelial cancer.

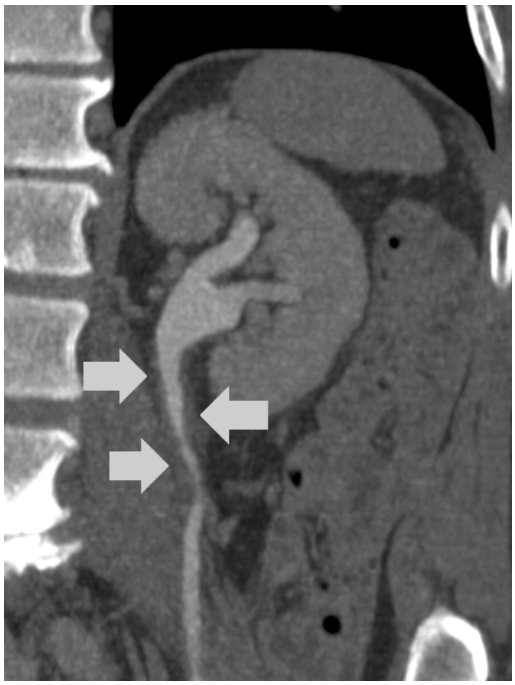


Figure 8b. Coronal multiplanar reformatted image of an excretory-phase CT showing circumferential urothelial thickening of the ureter.

Figure 8. CT urogram and retrograde ureteropyelogram of a patient presenting with visible haematuria caused by an UTUC seen as with circumferential urothelial thickening

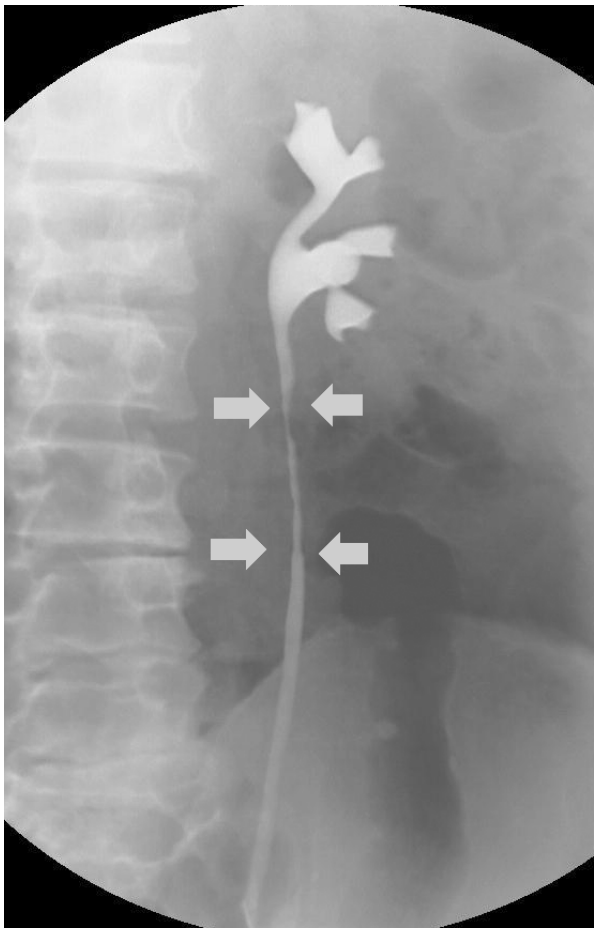


Figure 8c. Retrograde ureteropyelogram showing narrowing and minor but definite irregularity of the epithelium of the upper ureter due to urothelial carcinoma.

Figure 9. CT urography positive, RUP negative for urothelial cancer

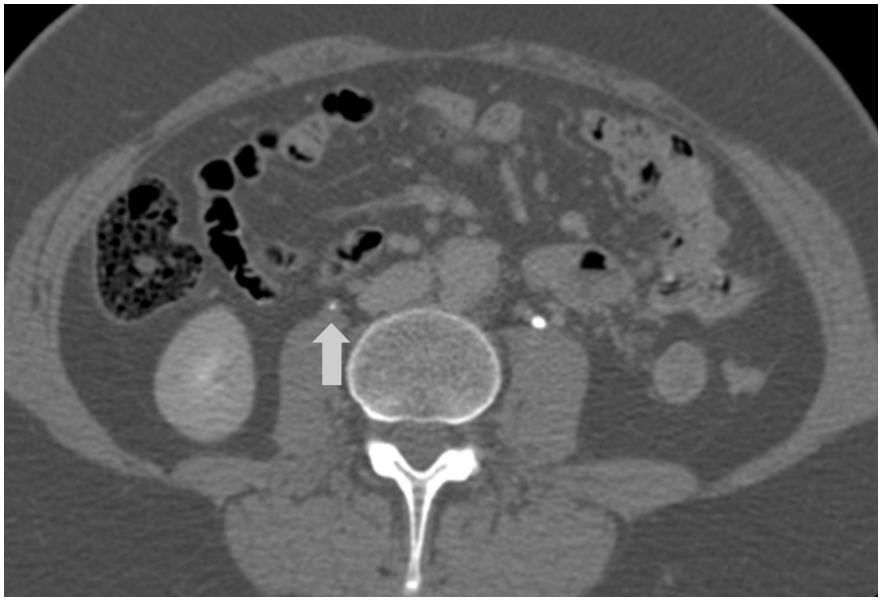


Figure 9a. Axial excretory-phase CT urogram showing circumferential wall thickening of the right ureter caused by urothelial cancer.

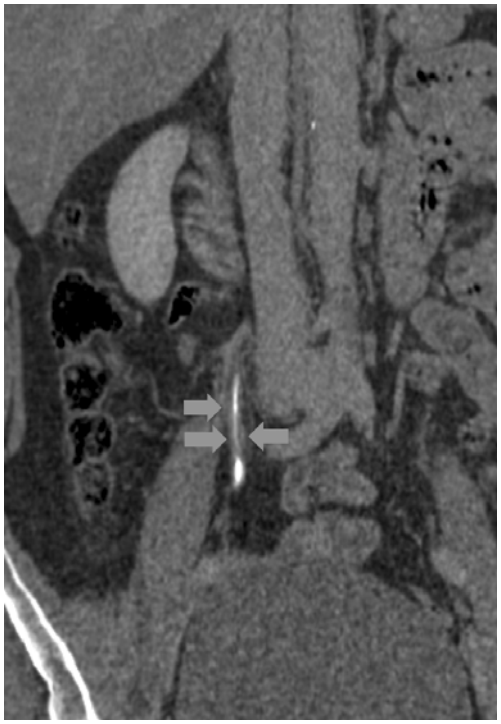


Figure 9b. Excretory-phase CT urography. Coronal multiplanar projection showing circumferential wall thickening of the right ureter due to urothelial cancer.

Figure 9. CT urography positive, RUP negative for urothelial cancer

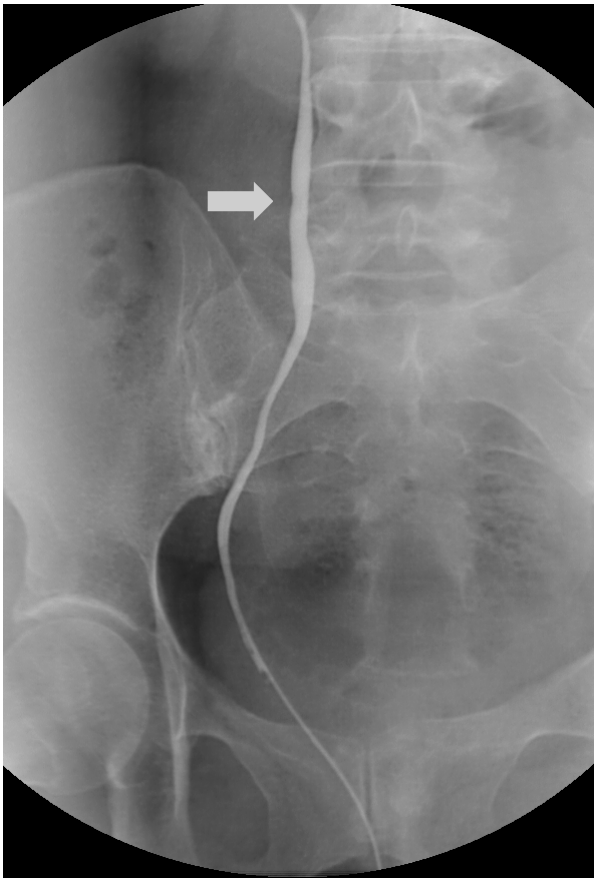


Figure 9c. Retrograde ureteropyelogram showing a smooth epithelium, masking the presence of urothelial cancer.

Figure 10. CT urography false negative for urothelial cancer

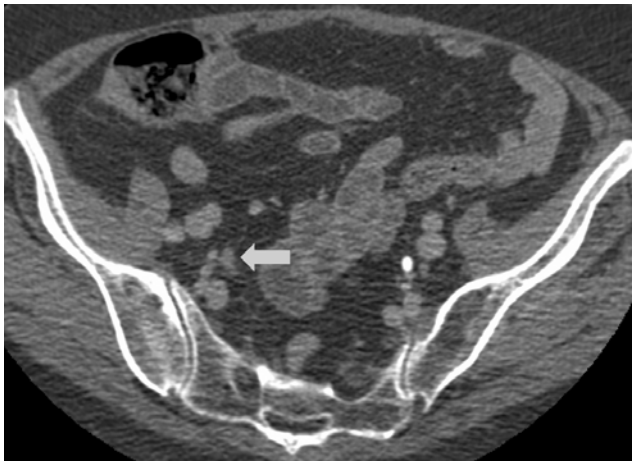


Figure 10a. Excretory-phase CT urography showing non-opacification of the right ureter without dilatation.

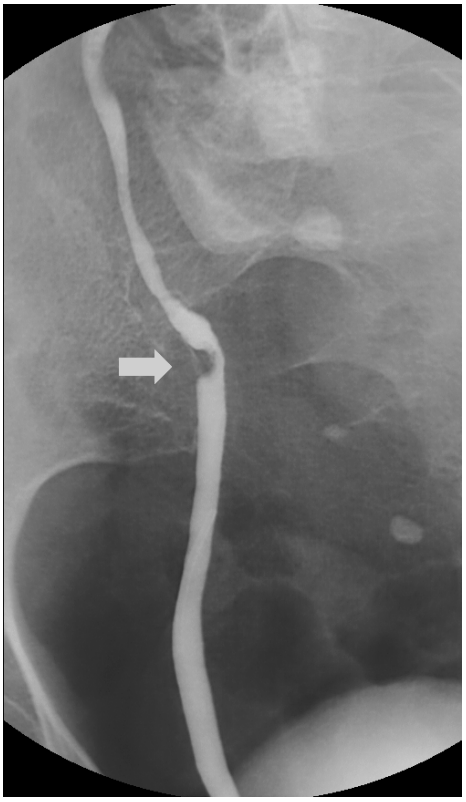


Figure 10b. Retrograde ureteropyelogram showing a lower ureteric filling defect proven to be a urothelial cancer following ureteroscopic biopsy.

Figure 11. CT urography false positive for UTUC - ureteroscopic trauma

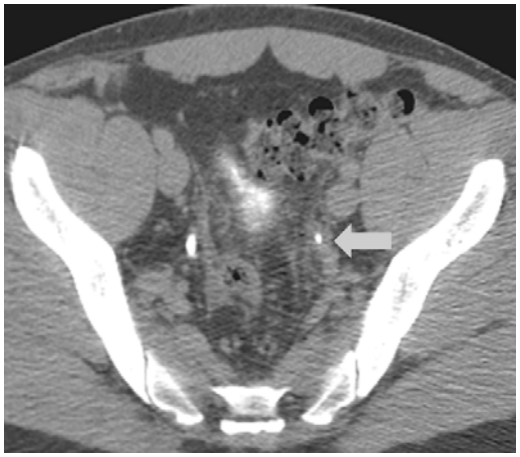


Figure 11a. Axial excretory-phase CT urography. Circumferential wall thickening of the left lower ureter was interpreted as urothelial cancer. In the study, a history of a difficult ureteroscopic stone removal was not available at the time of image interpretation.

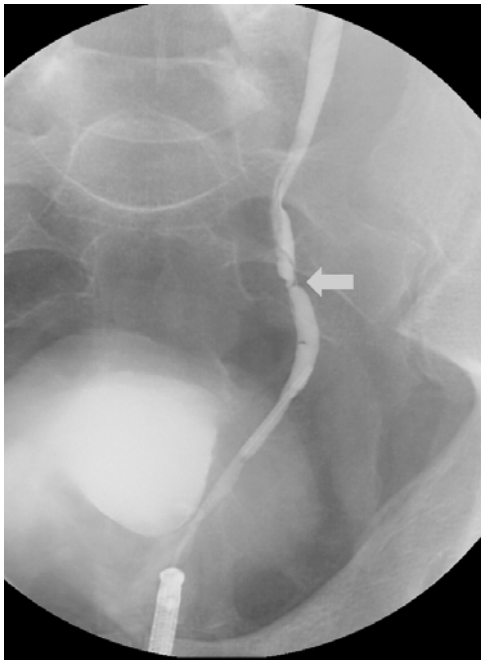


Figure 11b. Retrograde ureteropyelogram showing raised urothelial flap and a short lower ureteric stricture following ureteroscopy for stone removal but no evidence of urothelial cancer.

Figure 12. CT urography false positive for UTUC - debris

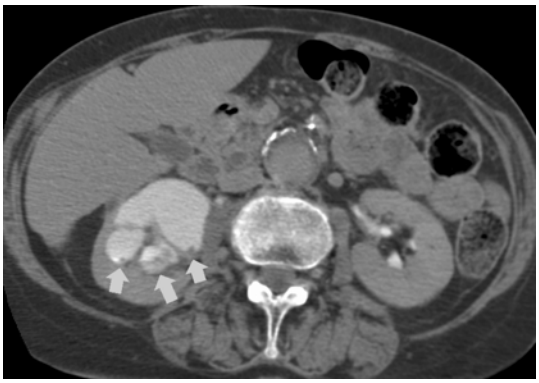


Fig 12a. Axial excretory-phase CT urography showing hydronephrosis of the right kidney and multiple small filling defects caused by debris, misinterpreted as multifocal urothelial cancer.

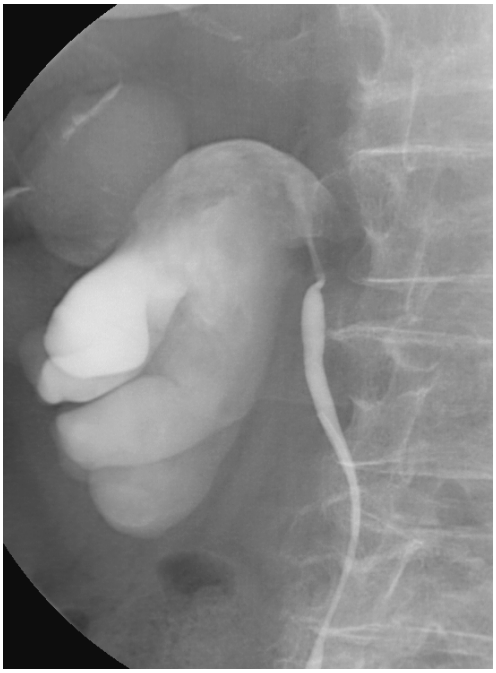


Fig 12b. Retrograde ureteropyelogram (RUP) showing tight pelvi-ureteric junction obstruction and hydronephrosis of the right kidney.
The filling defects seen on CT within the collecting system were not identified at RUP.

Figure 13. CT urography false positive for UTUC - vascular impression

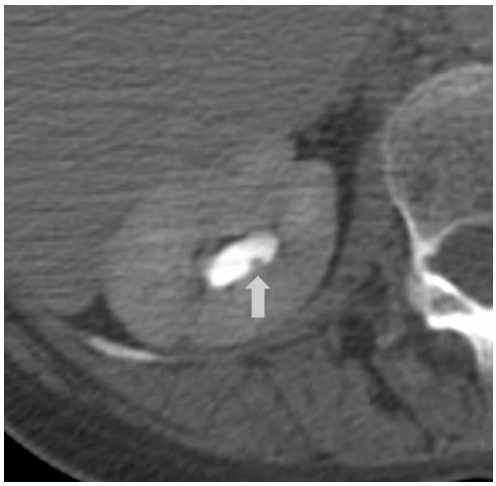


Figure 13a. Axial excretory-phase CT urogram.
The small impression on the upper pole infundibulum (arrow) was recorded as urothelial tumour.

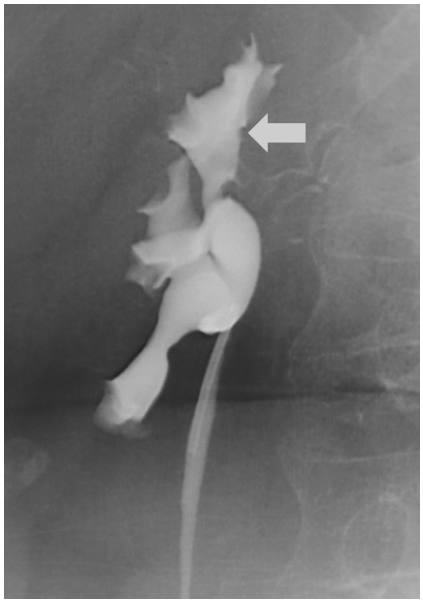


Figure 13b. Retrograde ureteropyelogram showing upper pole infundibulum with smooth indentation (arrow) characteristic of a vascular impression.

Figure 14. CT urography false positive for UTUC - renal cell cancer metastases

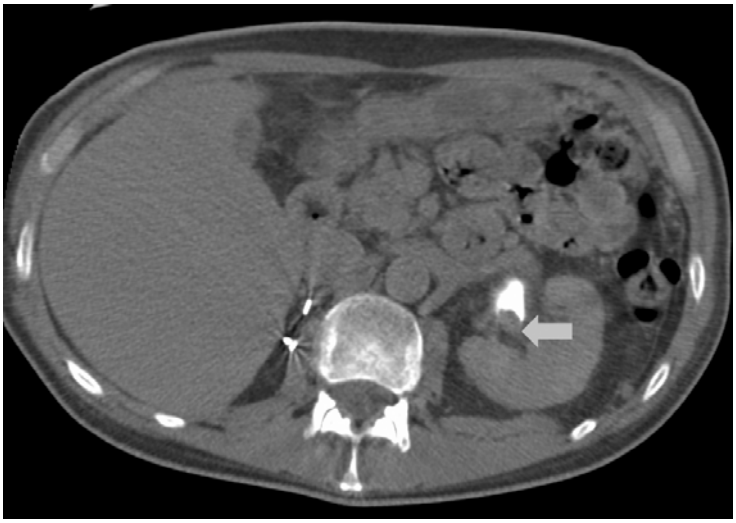


Figure 14a. Axial excretory-phase CT showing a soft tissue density mass indenting the infundibulum. The patient had previous right nephrectomy for renal cell carcinoma. This was reported as a urothelial cancer without the benefit of the clinical history.

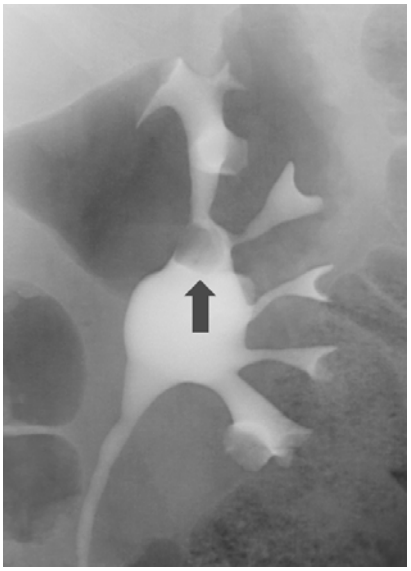


Figure 14b. Retrograde ureteropyelogram showing a filling defect with a smooth margin indenting the superior part of the renal pelvis. The lesion was reported as a urothelial cancer.

The principal disadvantage of CT urography is the increase in radiation dose to the patient when compared with intravenous urography or retrograde ureteropyelography (Hellawell, Cowan, Holt, & Mutch, 2002; Nawfel et al., 2004). For patients with possible malignancy the increased radiation risk of CT urography is considered to be justified because it has equivalent sensitivity and specificity for diagnosis of UTUC when compared with retrograde ureteropyelography but offers the additional benefits of being non-invasive, quicker, less labour intensive, cheaper, associated with fewer complications, and allows simultaneous diagnosis and staging of UTUC.

For young patients in whom malignancy is unlikely and for those with benign disease, CT urography may be performed as a last resort test only if those other imaging tests are negative with continuing symptoms or equivocal (Nolte-Ernsting & Cowan, 2006).

The most effective method of radiation dose reduction is to decrease the number of acquisitions or series. If CT urography could be limited to a single series through the abdomen and pelvis or unenhanced through the kidneys followed by a single series post intravenous contrast administration including abdomen and pelvis, then the effective dose of CT urography would fall within the range of conventional urography (Nawfel et al., 2004) making CT urography an even more attractive investigation.

This paper provides a quantitative evaluation of CT urography for detecting UTUC in adult patients presenting with haematuria. The results are significant because the increased sensitivity and similar specificity of CT urography for detecting UTUC compared with retrograde ureteropyelography means that CT urography is now performed before retrograde ureteropyelography in our institution. Retrograde ureteropyelography is no longer used for clarification of an equivocal intravenous urography or ultrasonography examination but instead we perform CT urography. The change in practice was brought about by this work. In those centres in which CT urography is performed, CT urography is often used as a problem solving technique when the other imaging provides equivocal or normal results in the presence of continuing haematuria (Nolte-Ernsting & Cowan, 2006). This paper adds to the evidence that CT urography could be used as a first-line imaging investigation in those groups of patients where the risk of disease outweighs the risk of radiation exposure. The most appropriate patients are those at high risk for urological cancer. If CT urography is used

as a first-line test, ultrasonography and intravenous urography may be avoided and retrograde ureteropyelography used only if CT urography findings are equivocal or non-diagnostic e.g. in the unusual case of incomplete ureter opacification. The overall result of making this readjustment is acceleration of the diagnostic imaging pathway for diagnosing UTUC.

1.1 Study limitations

The method of retrograde ureteropyelography used is unusual as it is performed under sedoanalgesia in the radiology department using high quality digital C-arm fluoroscopy (McFarlane et al., 2001). The retrograde ureteropyelography images are of higher quality when compared with those obtained using a mobile unit. As this method is not widely used, it makes this study difficult to replicate. Retrograde ureteropyelography was followed by ureteroscopy and biopsy when retrograde ureteropyelography was positive for urothelial tumour. A few reports suggest that ureteroscopy and biopsy is more sensitive than retrograde ureteropyelography for diagnosing urothelial lesions (Chen, El-Gabry, & Bagley, 2000). It is assumed that 3 year to 5 year clinical follow-up provided in this study will be sufficient to allow diagnosis of all UUT tumours in the population group.

1.1 Conclusion

CT urography and retrograde ureteropyelography show similar diagnostic sensitivity and specificity for diagnosing UTUC which validates quantitatively the use of CT urography. CT urography should therefore be undertaken before retrograde ureteropyelography as it is a single non-invasive comprehensive test which allows simultaneous diagnosis and / or staging. Retrograde ureteropyelography should be restricted to patients with a non-diagnostic CT urography (usually due to incomplete ureter opacification) or with impaired renal function and hence a predisposition to contrast induced nephropathy.

If CT urography replaces ultrasonography, intravenous urography and retrograde ureteropyelography for investigation of haematuria in specific groups of patients in whom the increased radiation dose is justified, the imaging pathway for diagnosing UTUC may be accelerated by reducing the number of diagnostic episodes without a reduction in diagnostic accuracy.

1.2 Assessment and comparison of the diagnostic accuracy of CT urography with ultrasonography for upper urinary tract disease in patients presenting with visible haematuria to a one-stop, purpose-designed hospital haematuria clinic

1.2 Abstract

1.2 Objectives

To evaluate and compare ultrasonography with CT urography for diagnosing upper urinary tract disease in patients attending a rapid diagnosis hospital haematuria clinic.

1.2 Methods

The clinical cohort consisted of 100 consecutive patients presenting with visible haematuria, ≥ 40 years of age, with infection excluded. Same day ultrasonography and CT urography were performed and reported by radiologists blinded to findings of the other examination. Reference standard included histopathology from biopsy or surgical resection for upper urinary tract tumours, unenhanced CT for stone disease, and 6-12 month imaging and histopathology follow-up.

1.2 Results

Disease prevalence for renal cell carcinoma was; n = 3/100 patients, UTUC; n = 2/100 patients, and renal calculi; n = 20/200 kidneys. For renal cell carcinoma, ultrasonography diagnosed 2/3, and CT urography 3/3 cases, giving for ultrasonography, sensitivity = 0.67 and specificity = 1.0 and for CT urography, sensitivity = 1.0 and specificity = 1.0. For UTUC, ultrasonography diagnosed 0/2 and CT urography 2/2 cases, giving for ultrasonography, sensitivity = 0.0 and specificity = 1.0 and for CT urography, sensitivity = 1.0 and specificity = 0.99. For diagnosing renal calculi using ultrasonography, sensitivity = 0.40 and specificity = 0.96.

1.2 Conclusion

CT urography is preferred to ultrasonography on the basis of greater diagnostic accuracy for renal cell cancer, UTUC and stones, as the first-line diagnostic imaging examination for investigating patients with visible haematuria at high risk for urological cancer. The role of ultrasonography for investigating haematuria needs to be re-examined.

1.2 Introduction

CT urography for investigating visible haematuria has been compared with intravenous urography and retrograde ureteropyelography (Wang et al., 2010) (O'Malley et al., 2003) (Cowan et al., 2007), but few studies have compared the diagnostic accuracy of CT urography with ultrasound, with the exception of stone disease (Ripolles et al., 2004) (Fowler, Locken, Duchesne, & Williamson, 2002). For bladder cancer, CT urography has superior sensitivity and similar high specificity compared with ultrasound (Knox, Cowan, Rivers-Bowerman, & Turney, 2008).

1.2 Purpose

To evaluate and compare the diagnostic accuracy of ultrasonography with CT urography for UUT disease, including renal cell carcinoma, UTUC and stones.

1.2 Materials and methods

A research ethics committee opinion was not required following consideration and approval by the local chairman. Informed consent was obtained.

The clinical cohort consisted of 100 consecutive patients attending a rapid diagnosis hospital haematuria clinic over a 7 month period from June 2009 to January 2010. All patients were aged 40 years or above presenting with visible haematuria, in the absence of infection, and were referred directly to the clinic by their primary care physician. Each patient was initially assessed by a clinical nurse specialist and underwent same-day ultrasonography, CT urography, and flexible cystoscopy. The ultrasonography and CT urography examinations were independently performed and reported by different radiologists blinded to the findings of the other examination.

1.2 Ultrasound

Transabdominal ultrasound of the kidneys and upper ureters was performed, using an Acuson Sequoia 512 machine (Siemens Medical Solutions, Malvern, USA) using a 1-4MHz curvilinear (4C1) transducer. The examinations were performed and interpreted by one of two consultant radiologists with 8 and 11 years experience in ultrasound respectively.

The presence or absence of renal mass, renal cyst, stones, hydronephrosis, hydroureter and abnormalities of renal size, outline or cortical thickness were recorded for each kidney. The location, maximum diameter and reflectivity characteristics of any renal mass, cyst or stone detected were also recorded.

1.2 CT urography

All CT urography examinations were performed using the same protocol. Patients were given 600-900 ml of water to drink 30 minutes prior to examination. CT urography was performed using a 64-slice Lightspeed VCT machine (General Electric, Milwaukee, USA). The patient was placed in the supine position on the CT table. An unenhanced series from the top of the kidneys extending to 2cm below the pubic symphysis on expiration was obtained. An intravenous injection of 150 ml Iohexol at 300 mg Iodine/ml was then delivered by pump injection at 4 ml/s via an intravenous cannula in the antecubital fossa. At 100 s following contrast injection, the nephrographic-phase was obtained from the top of the liver to bottom of the kidneys. At 12.5 minutes following contrast injection, excretory-phase images were taken from the top of the kidneys to 2 cm below the pubic symphysis. At 15 minutes following contrast injection, the patient was turned prone, and a prone series which covered only the pelvis was obtained. All series were obtained with the following parameters: x-ray tube voltage = 120 kV, current = 170-260 mA, table speed = 39.38 mm / rotation, beam collimation = 16 cm, pitch = 0.984, slice thickness = 0.625 mm, 512 x 512 matrix, scanned field of view (FOV) = 50 cm, display FOV = 32 cm.

CT images were reviewed on an Advantage Windows workstation 4.04 as axial and multiplanar reformatted images by a consultant uroradiologist with 10 years experience of interpreting CT urography. The presence or absence of a renal or ureteric mass, renal cyst, stones, hydronephrosis, hydroureter was recorded for each kidney and ureter.

1.2 Follow up and statistical analysis

Patients with a solid renal mass diagnosed on ultrasonography or CT urography underwent subsequent biopsy or surgical excision, with the histological diagnosis serving as the reference standard. UTUC diagnosed on ultrasonography or CT urography underwent further investigation in the form of retrograde ureteropyelography with fluoroscopic-guided biopsy prior to surgical excision or follow-up. The histological diagnosis was used as the reference standard. In patients with stone disease, the

diagnosis on CT urography was the reference standard. Imaging and histopathological database follow-up was obtained for 6 - 12 months on all patients and was used as the reference standard for patients with normal imaging of the kidneys and upper ureters.

The sensitivities, specificities, PPV and NPV of ultrasonography and CT urography respectively for each of renal cell carcinoma and UTUC were calculated from 2 x 2 contingency tables. The sensitivity, specificity and diagnostic accuracy of ultrasonography for stone disease on a per kidney basis was also calculated from a 2 x 2 contingency table.

1.2 Results

The 100 patients included 82 males and 18 females, with a mean age of 66 years (range 40 - 95 years). 3 cases of renal cell carcinoma and 2 cases of UTUC were diagnosed, giving 5% prevalence of upper tract cancers in this population.

All 3 cases of renal cell carcinoma were detected on CT urography, while 2 cases were detected on ultrasonography. In one case an 8 cm mass in the left kidney closely approximated the contour of the left kidney and was not detected on ultrasonography (Figure 15). There were no false positives for renal cell carcinoma with CT urography or ultrasonography.

The diagnostic accuracy of CT urography for diagnosing renal cell carcinoma was calculated; sensitivity = 1.0, and specificity = 1.0 and for ultrasonography; sensitivity = 0.67 and specificity = 1.0, (Table 9).

Both cases of UTUC were diagnosed on CT urography. However, both cases were missed on ultrasonography. Hydronephrosis was not present in either case (Figures 16 and 17). There was one false positive which was diagnosed as urothelial cancer on CT urography, histology of the resected specimen showed there was no evidence of malignancy but of chronic obstructive nephropathy (Figure 18). For diagnosing UTUC using CT urography the sensitivity was 1.0, specificity 0.99 and diagnostic accuracy 0.99. For ultrasonography the sensitivity was 0.0, specificity 1.0 (Table 10).

Table 9. CT urography compared with US for diagnosing RCC

Disease positive for RCC			
		CT	
		Positive	Negative
US	Positive	2	0
	Negative	1	0

Disease negative for RCC			
		CT	
		Positive	Negative
US	Positive	0	0
	Negative	0	97

Abbreviations: RCC, renal cell cancer; UTUC, upper urinary tract urothelial cancer, US, ultrasonography; CT, computed tomography; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

For CT urography for diagnosing RCC;
Se = 1.0 (31-100%), Sp = 1.0% (95-100%), PPV = 1.0, NPV = 1.0

For US for diagnosing RCC;
Se = 0.67 (13-98%), Sp = 1.0% (95-100%), PPV = 1.0, NPV = 0.99

Table 10. CT urography compared with US for diagnosing UTUC

Disease positive for UTUC			
		CT urograpy	
		Positive	Negative
US	Positive	0	0
	Negative	3	0

Disease negative for UTUC			
		CT urograpy	
		Positive	Negative
US	Positive	0	0
	Negative	1	97

Abbreviations: UTUC, upper urinary tract urothelial cancer, US, ultrasonography; CT, computed tomography; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

For CT urography for diagnosing UTUC;
Se = 1.0 (19-100%), Sp = 1.0, PPV = 1.0, NPV = 1.0

For US for diagnosing UTUC;
Se = 0.0, Sp = 1.0 (95-100%), PPV = 1.0, NPV = 0.98

Renal calculi were present in 20 kidneys in 15 patients. Ultrasonography correctly identified stones in 8 kidneys. There were 7 false positive diagnoses of renal calculi on ultrasonography giving a positive predictive value of 0.53. Compared with CT urography on a per kidney basis, ultrasonography had a sensitivity of 0.40 and a specificity of 0.96 for stone disease (Table 11).

Table 11. Diagnostic accuracy of US compared with CT urography for upper tract stone disease

Stone disease		CT urography		
		Positive	Negative	
US	Positive	8	7	PPV = 0.53
	Negative	12	173	NPV = 0.94
		Se = 0.40 (20-64%)	Sp = 0.96 (92-98%)	

The kidney and ureter are evaluated separately on each side of the patient, making a total of 200 kidneys and ureters.

Abbreviations: US, ultrasonography; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Figure 15. Ultrasonography and CT urography for renal cell carcinoma

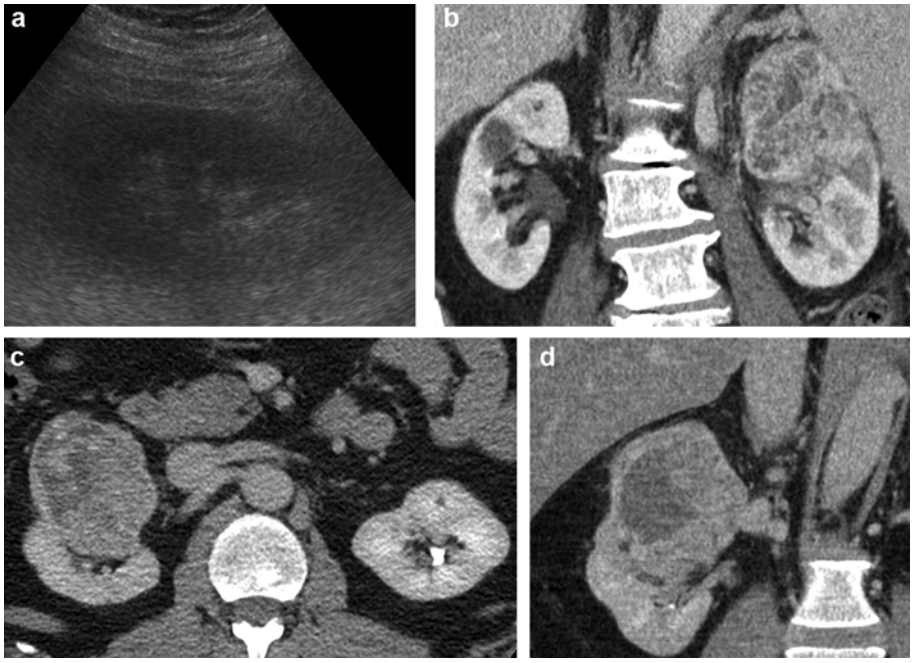


Figure 15. 74M with 8 cm renal cell carcinoma of the left kidney. On US (a) the mass is isoreflective to the renal parenchyma and closely approximates the renal contour, and was not identified. Coronal plane reformat of nephrographic-phase CT urography (b) demonstrates enhancing tumour in the upper pole.

A 44M with 7.6 cm renal cell carcinoma of the right kidney. Axial (c) and coronal (d) images from nephrographic-phase CT urography demonstrating exophytic tumour which was visible on US.

Figure 16. CT urography positive, ultrasonography negative for UTUC of the renal pelvis and ureter

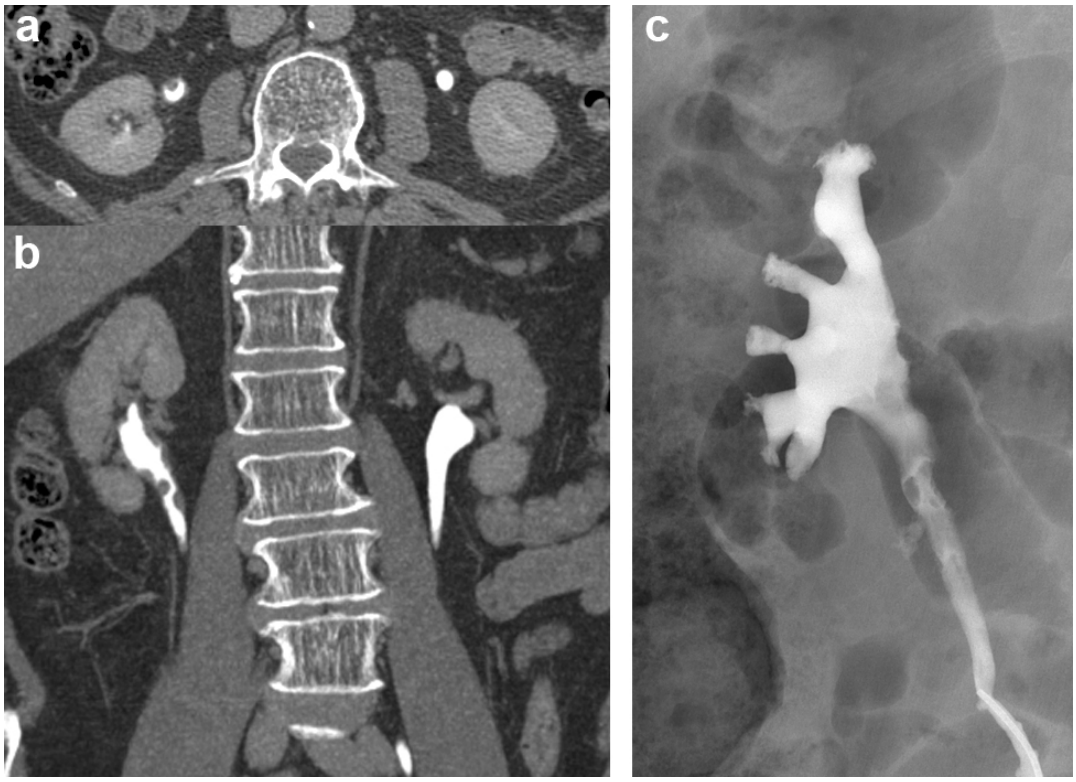


Figure 16. 75M with stage Ta UTUC of the right renal collecting system and stage T1 carcinoma of the bladder. (a) Axial and (b) coronal images from excretory-phase CT urography demonstrates tumour, confirmed on subsequent (c) RUP and biopsy.

Figure 17. CT urography positive, ultrasonography negative for UTUC of the ureter

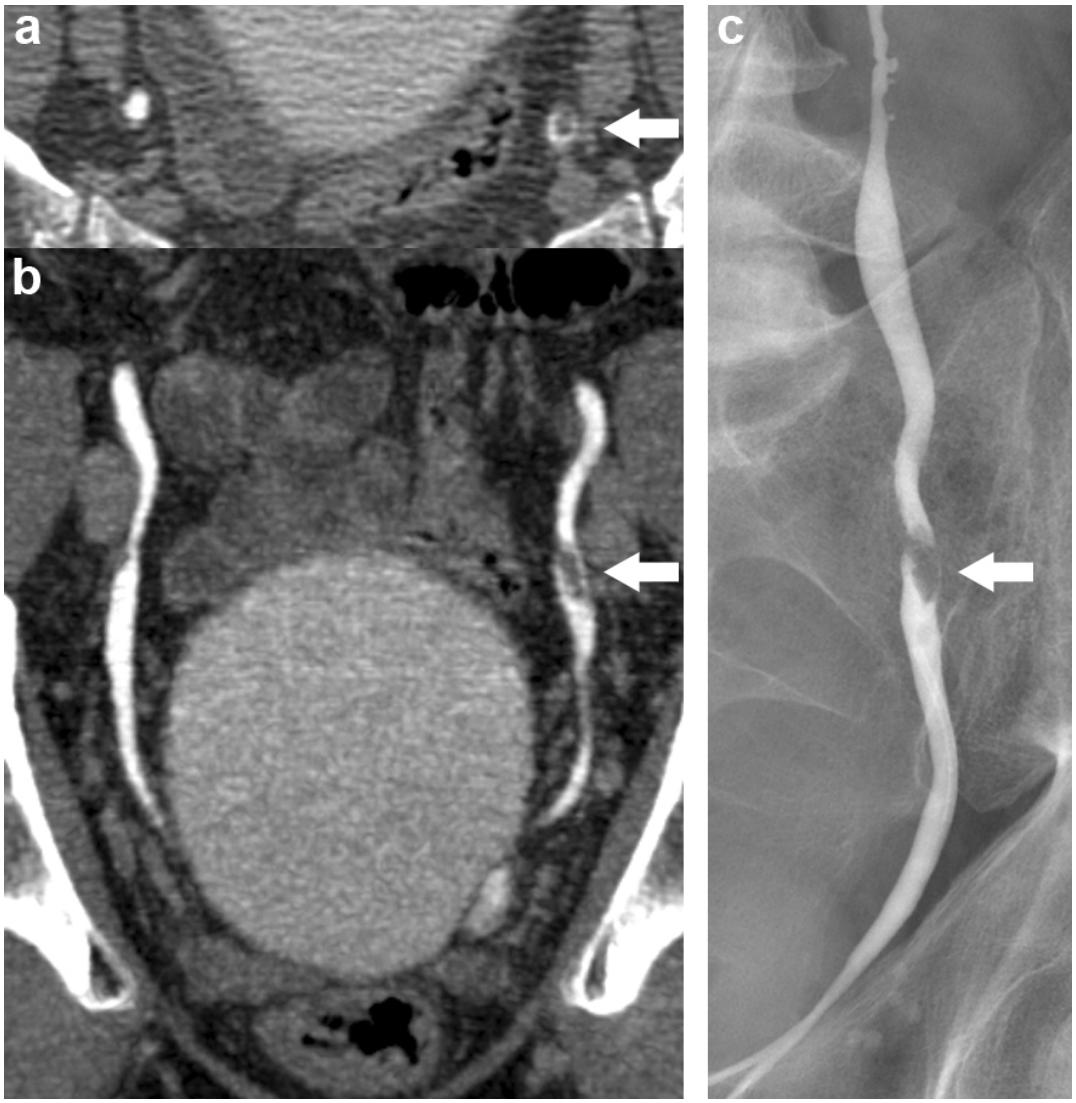


Figure 17. 66M with urothelial carcinoma of left ureter and bladder. (a) Axial and (b) coronal images from excretory-phase CT urography demonstrating filling defect in the ureter (arrows), with no associated hydronephrosis. (c) RUP and biopsy confirms UTUC.

Figure 18. CT urography false positive for UTUC

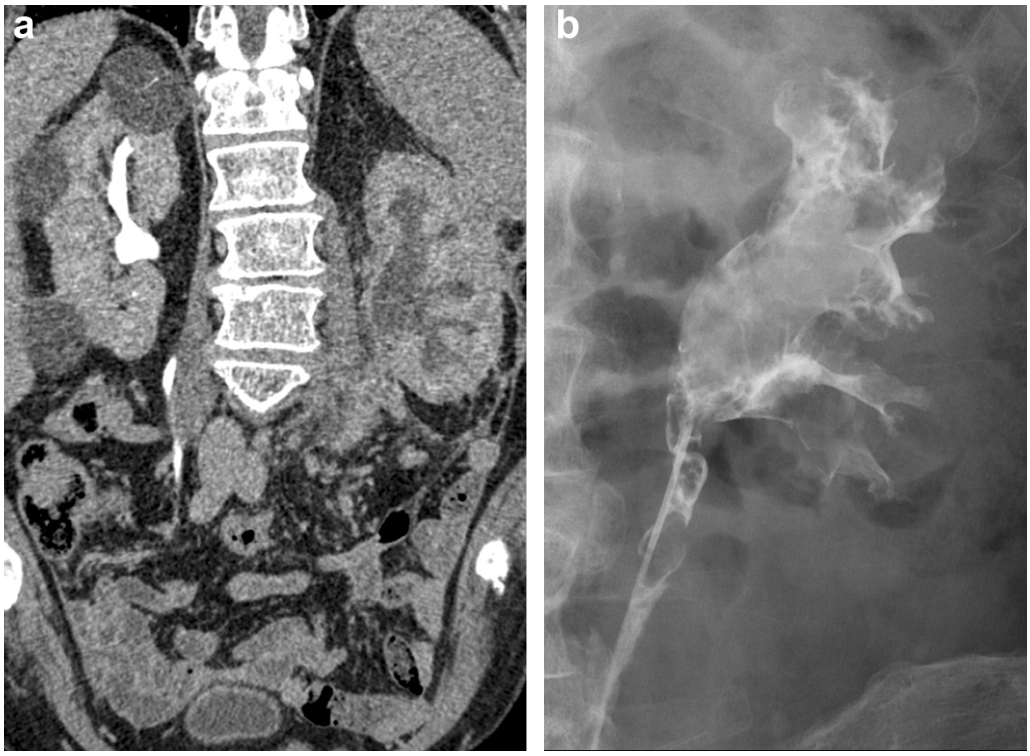


Figure 18. 78M (a) excretory-phase CT urography followed by (b) RUP demonstrate suspected tumour of left renal collecting system and upper ureter, histopathology of the resected specimen revealed chronic obstructive nephropathy only and no tumour.

1.2 Discussion

This study evaluated the use of CT urography and ultrasonography for diagnosing cancers and stone disease of the upper urinary tract in patients with visible haematuria over 40 years of age. This group of patients is at high risk of urological malignancy, most commonly of the bladder. In the study population the prevalence of renal cell carcinoma and UTUC combined is 5%, which is higher when compared with other studies with cohorts of patients with visible haematuria (Edwards et al., 2006) (Khadra et al., 1999) (Sutton, 1990). In particular, UTUC is normally considered rare, with a reported prevalence between 0.1% - 0.8%. In this study two cases of UTUC (2%) were diagnosed.

Of special note is the low sensitivity of ultrasonography for diagnosing UTUC. While UTUC of the renal pelvis can be seen on ultrasonography as soft tissue mass in the renal sinus and may cause focal hydronephrosis or proximal hydroureter, ultrasonography is limited by the inability to effectively evaluate the ureters. In both cases hydronephrosis and hydroureter were absent. In the study reported by Spencer et al. (Spencer, Lindsell, & Mastorakou, 1990) comparing ultrasonography with intravenous urography, there were no cases of UTUC among 155 patients with haematuria, therefore a valid comparison of ultrasonography and intravenous urography was not possible.

In the case of false positive UTUC on CT urography, the kidney was non-excreting (Figure 18). Although the appearance on retrograde ureteropyelography was also suspicious for UTUC, fluoroscopic-guided biopsy was negative. Given the kidney was non-functioning, after discussion with urological colleagues a nephroureterectomy was performed. Histology of the resected specimen revealed only chronic obstructive nephropathy.

For patients presenting with haematuria having UTUC, early detection allows early treatment which improved prognosis (Hall et al., 1998). CT urography has superior sensitivity and specificity for UTUC compared with intravenous urography, and similar sensitivity although more false positives when compared with retrograde ureteropyelography, the accepted gold standard (Wang et al., 2010) (Cowan et al., 2007). The sensitivity, specificity and accuracies reported were all close to 1.0, similar to the figures reported here.

In this study one renal cell carcinoma was seen as an 8 cm enhancing mass on CT urography but was not detected on ultrasonography (Figure 15). Although ultrasonography and CT urography are recognised imaging modalities for characterisation of renal masses, solid renal masses can be isoreflective relative to

normal renal parenchyma and so difficult to detect on ultrasonography. Higher sensitivity of CT, compared to ultrasonography, for detection of small renal masses less than 1.5cm is reported (Jamis-Dow et al., 1996). Although contrast enhanced ultrasonography (CEUS) using microbubble contrast agents is reported to have high sensitivity comparable to CT for characterisation of known renal masses (Nilsson, 2004) (Tamai et al., 2005), its sensitivity for detecting renal cell carcinoma as a first-line test has not been evaluated.

The poor sensitivity of ultrasonography for renal calculi compared with CT in this study is similar to that seen in previous studies (Ripolles et al., 2004) (Knox et al., 2008). The low sensitivity and positive predictive value greatly limits the usefulness of ultrasonography and CT urography remains the diagnostic standard.

Patients aged over 40 years presenting with visible haematuria are at high risk of urological disease, including cancers and stone disease of the urinary tract. This study shows that CT urography, compared with ultrasonography, has superior diagnostic accuracy for renal cell cancers, urothelial cancers of the upper tract, and provides the diagnostic standard for stone disease. Therefore, CT urography is the preferred examination for investigating visible haematuria in patients over 40 years. While ultrasonography will most likely continue to have a role in the diagnostic pathway for patients with haematuria, such as for detection of gross pathology or disease follow-up, its use as a first-line imaging investigation in this group of high risk patients needs to be re-examined.

Chapter 2. Evaluation of new diagnostic strategies

2 Introduction

2 Investigating haematuria

Haematuria, either visible or nonvisible, may indicate significant underlying disease such as urinary bladder cancer, upper tract urothelial cancer (UTUC), renal cell cancer or urinary tract stones (Edwards et al., 2006) (Khadra et al., 1999) (Sutton, 1990). Early and accurate diagnosis helps optimise prognosis but conventional diagnostic pathways are complicated and long, incorporating multiple imaging tests and many diagnostic algorithms exist without rigorous evaluation (Rodgers et al., 2006a). The concept of an integrated haematuria clinic, referred to as rapid diagnosis clinic in this paper, dates from as early as 1990 (Plail, 1990) and usually incorporates clinical examination, voided urine cytology, flexible cystoscopy, ultrasonography and excretory urography (Edwards et al., 2006) (Yip, Peh, Tam, Li, & Lam, 1998). When designing a diagnostic pathway, first-line diagnostic imaging tests should have high sensitivity to ensure disease positives are included in the test population for further investigation. Second-line investigations should be highly specific, to ensure false positives are minimized. As each diagnostic test incurs cost, increases time from presentation to diagnosis and has inevitably some associated risk, the quest is to replace a series of tests with a single diagnostic test providing information about both the upper and lower urinary tracts. The chosen first-line test should not only be able to accurately diagnose upper tract disease but also be able to determine accurately which patients should be referred for rigid cystoscopy and which should be simply discharged or followed-up, as the diagnosis of bladder cancer ultimately depends on rigid cystoscopy of the bladder and histological evaluation of the resected tissue (Stenzl et al., 2009). It has been proposed the diagnostic accuracy of the investigative pathway and the time to diagnosis may be improved by substituting CT urography for ultrasound and excretory urography for examination of the upper tracts (Van Der Molen et al., 2008). CT urography is emerging as one-stop diagnostic imaging technique that offers a thorough evaluation of the urinary tract for stones, renal masses, and urothelial neoplasms in a single examination (O'Connor, Fitzgerald, & Maher, 2010). The precise role of CT urography for diagnosing bladder cancer is more controversial (Turney et al., 2006) (Cohan, Caoili, Cowan, Weizer, & Ellis, 2009) (Sadow, Silverman, O'Leary, & Signorovitch, 2008).

2 Bladder cancer

An estimated 104,400 incident cases of bladder cancer were diagnosed in Europe in 2006, of which 82,800 were found in men and 21,600 in women. This represents 6.6% of the total cancers in men and 2.1% in women, with an estimated male: female ratio of 3.8:1.0. For men, bladder cancer is the fourth most common cancer resulting in 4.1% of total male cancer deaths and 1.8% of total female cancer deaths. At diagnosis, 70% of bladder cancer are non-muscle invasive and approximately 30% are muscle-invasive disease (Ferlay et al., 2007).

The prevalence of bladder cancer increases with age, the highest incidence occurring in the 70-80 year old group with a peak age of 71 (Cancer Research UK, 2010). Early diagnosis is important as disease progression may be rapid. A delay of more than 12 weeks is a negative prognostic indicator for muscle invasive bladder cancer (Hollenbeck et al., 2010; Sánchez-Oritiz et al., 2003). The most common presentation is visible haematuria and the prevalence of bladder cancer in patients with visible haematuria is between 12-20% (Sutton, 1990) (Khadra et al., 1999) (Edwards et al., 2006).

2 Voided urine cytology

Cytological evaluation of exfoliated cells in the voided urine can be used to detect urothelial cancers. The value of voided urine cytology in evaluating patients with haematuria remains controversial (Rodgers et al., 2006a) (Viswanath, Zelhof, Ho, Sethia, & Mills, 2008) (Hofland & Mariani, 2004).

2 Flexible cystoscopy

The accepted reference standard for examining the bladder in patients with haematuria is flexible or rigid cystoscopy (Rodgers et al., 2006a) (Stenzl et al., 2009) although there are few studies evaluating the diagnostic accuracy of flexible cystoscopy. Flexible cystoscopy is reported to be at least equivalent in diagnostic accuracy to rigid cystoscopy and for some lesions, such as those at the anterior bladder neck, superior (Clayman, Reddy, & Lange, 1984) (Pavone-Macaluso, Lamartina, Pavone, & Vella, 1992). Flexible cystoscopy is a very commonly performed minimally invasive procedure with low morbidity (Burke, Shackley, & O'Reilly, 2002), but is associated with an infection risk of approximately 3% (Johnson et al., 2007) and some patients find it painful (Taghizadeh et al., 2006). In a study evaluating patients experience after flexible cystoscopy, visible

haematuria (19%), urinary frequency (37%), and dysuria (50%) were found more frequently than expected (Burke et al., 2002).

2 CT urography

CT urography is defined as multidetector CT examination of the kidneys, ureters and bladder with at least one imaging series acquired during the excretory-phase following intravenous contrast administration (Van Der Molen et al., 2008). CT urography offers a single imaging test of high diagnostic accuracy with the potential to replace multiple alternative imaging tests in the diagnostic pathway, improve patient experience, improve diagnostic performance and accelerate diagnosis (Nolte-Ernsting & Cowan, 2006). CT urography is rapidly becoming accepted as the preferred test for diagnosing upper tract disease responsible for haematuria, such as calculi, UTUC and renal cell carcinoma (Nolte-Ernsting & Cowan, 2006) (Van Der Molen et al., 2008) (O'Connor et al., 2010). CT urography has been evaluated for evaluation of urinary tract calculi (Smith et al., 1996) (Smith et al., 1995), renal masses (Silverman et al., 1994) (Silverman, Gan, Mortele, Tuncali, & Cibas, 2006) and UTUC (Cowan et al., 2007) (Jinzaki et al., 2011) and is in general clinical use.

CT urography has high diagnostic accuracy for urothelial cancers compared with excretory urography (Cowan et al., 2007) (Albani et al., 2007) (Fritz et al., 2006) (Gray Sears et al., 2003) but has the disadvantage of a higher radiation exposure of 20.1 mSv compared with 11.9 mSv for excretory urography (Vrtiska et al., 2009). The improvement in diagnostic capabilities outweighs the use of increased radiation dose for CT urography in this population group with a prevalence of upper and lower tract cancer of 25% (Vrtiska et al., 2009).

Excretory-phase CT urography opacifies the collecting system, ureter and bladder with excreted contrast medium for assessment of the urothelium. Thin collimation, fast table speed and single breath hold acquisition are important factors which help provide multiplanar reformatted images of high spatial resolution.

Review of multiplanar reformatted images further improves specificity (Van Der Molen et al., 2008) (Dillman et al., 2008).

The principal purpose of CT urography is assessment of the upper urinary tract, and CT protocols are designed to optimise upper tract opacification and hence maximise diagnostic accuracy for upper tract disease. In addition to diagnosing upper tract

urothelial tumours (UTUC) (Caoili et al., 2005), CT urography can also be used to diagnose bladder cancer (Cohan et al., 2009) (Turney et al., 2006) (Cowan & Crew, 2010). A secondary additional role is provision of a non-invasive method of assessing bladder abnormalities (Turney et al., 2006) (Sadow et al., 2008) (Cohan et al., 2009).

If CT urography is performed before flexible cystoscopy, identification of a bladder mass may direct the cystoscopist to the tumour enhancing the sensitivity of cystoscopy. CT urography may also be of value in cases where flexible cystoscopy is a technical failure.

The role of CT urography and flexible cystoscopy for diagnosing bladder cancer is to determine which patients undergo rigid cystoscopy in order to make the final diagnosis of bladder cancer by histological evaluation of biopsied or resected tissue and determine which patients are classified as normal. In this paper, we consider CT urography and flexible cystoscopy within the patient pathway as additional, replacement or triage tests (Bossuyt, Irwig, Craig, & Glasziou, 2006).

2 Summary of introducing new diagnostic imaging strategies

Conventional diagnostic imaging pathways for haematuria, including ultrasonography, intravenous urography, retrograde ureteropyelography and CT urography, are complicated and lengthy. The principal aim of any new diagnostic strategy must be to simplify and shorten the time from presentation to diagnosis. In summary, the ideal new diagnostic strategy should be better, quicker, easier, safer, cheaper and nicer. The diagnostic accuracy of CT urography for urinary tract stones and solid renal masses surpasses that for ultrasonography and intravenous urography as described in the previous section. This means that CT urography has the potential to be a single replacement test for ultrasonography and intravenous urography, if it possesses high diagnostic accuracy for UTUC, the last piece of the jig saw puzzle. New evidence relating to the diagnostic accuracy of CT urography for UTUC and bladder cancer suggests CT urography might also be the technique of choice for imaging the urothelium for both UTUC and suspected bladder cancer (Cowan et al., 2007) (Cowan, Mallett, & Crew, 2011) (Blick et al., 2011) (Jinzaki et al., 2011) (Wang et al., 2010) (Wang et al., 2009).

2.1 Evaluation of a new diagnostic strategy using CT urography as the initial imaging technique for upper urinary tract evaluation in 1005 patients presenting with visible haematuria to a one-stop, purpose-designed, hospital haematuria clinic

2.1 Abstract

2.1 Purpose

To evaluate the diagnostic strategy using CT urography as the initial imaging test in patients with visible haematuria referred directly to a one-stop purpose-designed hospital haematuria clinic.

2.1 Method

The clinical cohort consisted of a consecutive series of patients presenting with visible haematuria over a 57-month period, age ≥ 40 years, urinary tract infection excluded. All underwent same day CT urography and flexible cystoscopy. Reference standard was histopathology following biopsy or surgery, and 1-5 year imaging and histopathology database follow-up.

2.1 Results

Of the 1011 patients, 10 were excluded because of no contrast administration (n = 6), and no histopathological verification (n=4). Upper urinary tracts were classified as 1 = normal, 2 = probably normal, 3 = equivocal, 4 = probably tumour and 5 = definitely tumour. Scores of 1 and 2 were considered negative and patients discharged, scores of 3-5 as positive and patients underwent further diagnostic imaging, biopsy, surgery or follow-up. Disease prevalence for UTUC = 2.2% (n = 22/1001), renal cell carcinoma = 2.4% (n = 24/1001), upper urinary tract stones = 15.1% (n = 151/1001), normal upper urinary tracts = 80.3% (n = 804/1001). For CT urography for diagnosing UTUC and renal cell carcinoma using CIA software 95% CI by Wilson method; sensitivity = 1.0 (95% CI 0.93 to 1.0), specificity = 0.98 (95% CI 0.97 to 0.99), PPV = 0.72 (95% CI 0.60 to 0.81), and NPV = 1.0 (95% CI 0.99 to 1.0).

2.1 Conclusion

High disease prevalence and high sensitivity of CT urography for diagnosing upper urinary tract stones, renal cell carcinoma and UTUC justifies use of CT urography with unenhanced, nephrographic and excretory-phases, as the first line imaging test for investigating haematuria in patients at high risk.

2.1 Method

The proposed new diagnostic strategy constituted a radical change in local hospital practice. It was enabled by the award of a £250,000 pump priming grant from Thames Valley Cancer Network Services. The original application was turned down by the NHS Modernization Agency as the diagnostic strategy was deemed to be too modern.

Patients who attend their general practitioner with visible haematuria and who are over 40 years of age with urinary tract infection excluded are referred via a call centre simultaneously to departments of urology and radiology following a vetting process by the consultant uroradiologist. Patients are given an appointment for CT urography and flexible cystoscopy on the same day. The CT urography examination is performed on a designated list with capacity of 6 patients per week. Patients on arriving at the hospital are first seen by a clinical nurse specialist who takes a detailed history and performs a physical examination. Same day urine cytology, CT urography and flexible cystoscopy are then carried out. Patients are seen again by the clinical nurse specialist after the investigations have been completed provided with a treatment plan before leaving hospital.

The methods were performed according to the hospital haematuria rapid diagnosis clinic protocol with approval granted from the chairman of the hospital institutional review board.

The clinical cohort consisted of a consecutive series of 1011 patients attending a hospital haematuria rapid diagnosis clinic over a 57 month period, between 01-Mar-2004 and 29-Dec-2008. Of the 1011 patients, 6 were excluded because of no contrast administration (n = 6). The final study population consisted of 1005 patients with CT urography and flexible cystoscopy and histopathological correlation.

There were 806 (80.2 %) male patients, 199 (19.8%) female patients, mean age = 67.2 years, (range = 40.3 - 97.6 years). Criteria for referral were at least one episode of visible haematuria, 40 years of age or older, and urinary tract infection excluded.

A Lightspeed QXi, 8 slice CT machine (General Electric, Milwaukee, USA) was used. Patients were given 750 ml-1000 ml of tap water to drink in the waiting room during the 30 minutes before the study and asked to void immediately before the CT examination. The first acquisition series was from the top of the kidneys to 2 cm below the symphysis pubis on expiration. Via and intravenous cannula in the antecubital fossa, using a split-bolus protocol, 100 ml of nonionic contrast medium (Iopamidol 300) given (300 mg I / ml). Between the nephrographic and excretory-phase acquisitions the patient was

exercised by walking around the CT gantry. At 6-8 minutes the patient was replaced on the CT table and rolled twice in anticlockwise and then clockwise directions. New scout views were obtained and at 10 min a further 50 ml of intravenous contrast medium was injected via a pump (3 ml/s) and 100 s after the second bolus, a series acquired from the top of the liver to 2 cm below the pubic symphysis. If there was full opacification of the ureters initial review; the examination was considered completed. Images were viewed on a workstation as axial and multiplanar reformatted images running Advantage Windows (G.E. Healthcare, U.K.) or Voxar3D software version 6.3, (Toshiba Medical Visualization Systems, U.K.). The examinations were reported as soon as they were available on the local workstation by a consultant uroradiologist initially with 3 years experience of reading CT urograms and 11 years uroradiology experience. The CT urography report was available before the patient underwent flexible cystoscopy. The uroradiologist was blinded to the flexible cystoscopy results as CT urograms were reported before the flexible cystoscopy tests were completed.

The CT urography examinations were scored using a 3-point system, where 1 = normal, 2 = equivocal and 3 = positive for UTUC. A score of 1 was considered negative and patients discharged. Scores of 2 and 3 were considered positive and patients underwent further diagnostic imaging, ureteroscopy or retrograde ureteropyelography-guided biopsy, surgery or follow-up.

On the same day, flexible cystoscopy was performed after the CT urogram, by a urologist with experience ranging from over 10 years as a consultant to 2 years specialist urological training. Patients with a CT urography score of 1 for the upper tracts and a negative flexible cystoscopy score of were discharged. Those patients with a CT urography score of 2 and 3 were referred for retrograde ureteropyelogeraphy and biopsy, or ureteroscopy and biopsy or surgery.

For both tests clinical information consisting of age, sex and referral symptoms were available to those reporting index tests, as is standard during clinical practice.

Sensitivity , specificity, PPV and NPV of CT urography for diagnosing UTUC and renal cell carcinoma were calculated.

The reference standard consisted of review of the hospital imaging and histopathology databases in December 2009 for all patients and reports from the medical notes for those referred for rigid cystoscopy. Follow-up was for a minimum of 12 and a maximum

of 69 months. The reference standard for UTUC consisted of ureteroscopic or retrograde pyelography-guided-biopsy and histopathological evaluation of tissue from cystoscopic biopsy or surgical resection. There were four patients who were positive for tumour on CT urography, two cases of renal cell carcinoma and two of UTUC, in whom there was no histopathological verification. According to Rutjes et al this constitutes a 'no gold standard situation'. For these cases a consensus based diagnosis was made, using expert opinion of a uroradiologist, oncologist and urologist from the urology cancer multidisciplinary team to avoid bias from leaving out unverified patients from the calculation (Rutjes, Reitsma, Coomarasamy, Khan, & Bossuyt, 2007).

Standard paired measures of diagnostic accuracy: sensitivity, specificity, PPV and NPV were calculated per patient. 95% Confidence intervals (95% CI) were calculated using CIA software (Altman, Machin, Bryant, & Gardener, 2000) using Newcombe method (Newcombe, 1998) for paired proportions and the Wilson method for single proportions (Wilson, 1927).

Uninterpretable results, for technically inadequate CT urography were carefully examined for each patient to determine whether the cause of the technical inadequacy could have been potentially related to presence of disease. This was not found in any patient, so these patients were excluded from the analysis without risk of introducing bias into the study results.

Indeterminate test results, where test results are equivocal (score 2 for CT urography and flexible cystoscopy) are included in each analysis as specified.

2.1 Results

The results for disease prevalence in 1005 patients analysed with visible haematuria evaluated initially with CT urography are given (Table 12). This patient group has been termed high risk for UTUC, but the prevalence of UTUC is low, 2.2%. Bladder cancer is just over eight times more prevalent in this patient group. Stones are far the most common upper urinary tract disease responsible for haematuria, with a prevalence of 15.1%. Most upper tracts were recorded as normal, 80.0% (n=804/1005).

Table 12. Disease prevalence in patients with visible haematuria evaluated initially with CT urography

Disease	Prevalence (%)
Bladder cancer	18.6
Renal cell cancer	2.4
UTUC	2.2
Prostate cancer	3.5
UUT stones	15.1
Bladder stones	1.2
ADPKD	0.3
Chronic pyelonephritis	0.2
Normal UUT	80.3

Abbreviations: UTUC , upper tract urothelial carcinoma, ADPKD, autosomal dominant polycystic kidney disease.

Patients were ≥ 40 years of age with visible haematuria and UTI excluded.

Reference: Cowan NC Nat Rev Urol 2012; 9 :218 - 226.

Results showing the prevalence of UTUC, RCC and stones according to age and sex are shown (Table 13).

Table 13. Prevalence of disease by age group and gender

Age Group (years)	Number of patients*	UTUC	RCC	Stones
Men				
40-49	75	0	2	18
50-59	137	1	2	26
60-69	203	3	6	36
70-79	267	6	8	42
80-89	114	4	1	12
90-99	10	0	0	0
Totals	806	14	19	134
Women				
40-49	20	0	0	2
50-59	46	0	0	4
60-69	55	0	2	6
70-79	48	1	2	5
80-89	25	5	1	1
90-99	5	2	0	0
Totals	199	8	5	18
Overall total	1005	22	24	152

Abbreviations: UTUC, upper urinary tract urothelial carcinoma; RCC, renal cell carcinoma.
*Patients presenting with visible haematuria, over 40 years of age with urinary tract infection excluded.

The diagnostic accuracy of CT urography for upper urinary tract cancer (UTUC and RCC) using CIA software 95% CI by Wilson method was calculated (Table 14). Sensitivity = 1.0 (95% CI 0.93 to 1.0), specificity = 0.98 (95% CI 0.97 to 0.99), PPV= 0.71 (95% CI 0.60 to 0.81), NPV= 1.0 (95% CI 0.99 to 1.0).

Table 14. Results for the diagnostic accuracy of CT urography for UUT tumour (UTUC and RCC) in 1005 patients presenting with visible haematuria and urinary tract infection excluded

n=1005		**Disease status for UUT tumour (UTUC and RCC)**		
		Positive	Negative	
CT urography	Positive	46	19	PPV = 0.71
	Negative	0	940	NPV = 1.0
		Se = 1.0	Sp = 0.98	

The results for the diagnostic accuracy of CT urography for UTUC patients presenting with visible haematuria and urinary tract infection excluded were calculated (Table 15).

Se = 1.0, Sp = 0.98, PPV = 0.55 and NPV = 1.0 .

Table 15. Results for the diagnostic accuracy of CT urography for UTUC in 1005 patients presenting with visible haematuria and urinary tract infection excluded

n=1005*		Disease status for UTUC		
		Positive	Negative	
CT urography	Positive	22	18	PPV = 0.55
	Negative	0	965	NPV = 1.0
		Se = 1.0	Sp = 0.98	

*4 patients who were CT urography positive for tumour were included in the analysis, without histopathological verification of the radiological diagnosis. There were two cases of presumed UTUC and two cases of presumed RCC. If these cases were excluded from the analysis the only change in the figures would be to lower the PPV from 0.58 to 0.45 as shown in the table of result below.

Table 16. Location of UTUC at presentation

n = 22*	Right	Left	% of UTUCs
Collecting system and renal pelvis	8	9	71%
Abdominal ureter	2	0	8%
Pelvic ureter	2	3	21%
	Patients with UTUC and BCa at presentation		
Bladder cancer	8		36%

*Of the 1005 patients, 22 had histologically confirmed UTUC. Of these, 2 patients had multifocal tumour in the kidney and ureter at initial presentation.

The location and frequency of UTUC at presentation is given (Table 16). Three anatomical sites are defined, 1. the collecting system and renal pelvis, 2. the abdominal ureter and 3. the pelvic ureter.

Finally, the mean time from presentation to CT urography and flexible cystoscopy = 13.2 days (3 - 75 days), median = 12 days, mode = 10 days.

2.1 Discussion

Overall assessment of the new diagnostic pathway requires more than one parameter to give a true reflection of its advantages in clinical practice. Relevant end points used were diagnostic accuracy, time to diagnosis, patients opinions obtained via a patient questionnaire and a short economic analysis.

In December 2005, Mrs Sally-Ann Timperley submitted a dissertation in support of an MSc degree to Oxford Brooke's University. The title of the dissertation was "An evaluative case study of a fast track haematuria service for the diagnosis of urological cancer". She used data from the first 10 months of the clinic to support its continuation.

The specific research questions of her dissertation were:

1) What are the costs of providing a fast track haematuria service?

2) What is the patients experience of the fast track service?

3) Does the fast track service help to meet the cancer waiting times targets?

4) Does the service provide an earlier diagnosis of cancer?

The results from her dissertation are given below and they showed that from an economic evaluation the new pathway had reduced the costs due to fewer hospital visits, fewer outpatient clinic appointments and fewer diagnostic tests. The costs were obtained from the relevant departments, which were set by the National Tariff (this included 25% overhead costs). The old pathway was estimated to cost £309.03 per patient and the new pathway at £183.46 per patient. A more detailed analysis of the real costs involved by looking at a number of individual cases as opposed to the theoretical costs as determined by modelling is suggested for future work.

Patient questionnaires showed a preference for the new pathway due predominantly to the greater convenience and decreased time from presentation to diagnosis.

The new pathway improved the quality of patient care by reducing the number of hospital visits needed to make the diagnosis from ≥ 4 to 1 and alleviating patient uncertainty by receipt of a same day diagnosis and treatment plan.

The waiting times analysis showed a reduction in the number of hospital visits for the patient and a reduction in the time interval between referral and diagnosis. Timperley concluded that The use of CT urography allows other imaging tests to be omitted from the diagnostic pathway without compromising the quality of imaging investigation. Using the new pathway patients were fully investigated within a 2 week period, ensuring that national cancer targets can be met.

2.1 Conclusion

CT urography is a single imaging test of high diagnostic accuracy with the ability to replace multiple alternatives, improve patient experience, improve diagnostic performance and accelerate diagnosis.

High disease prevalence and high sensitivity of CT urography for diagnosing upper urinary tract stones, renal cell carcinoma and UTUC justifies use of CT urography with unenhanced, nephrographic and excretory-phases, as the first-line imaging test for investigating haematuria in patients at high risk.

By using a single high-tech imaging technique as a front line investigation, diagnostic accuracy is maintained and the number of tests reduced. By arranging both imaging and cystoscopy tests on the same day, and by having the results of both available for a same day consultation, the time from presentation to diagnosis is accelerated, with the potential to improve prognosis.

2.2 Evaluation of diagnostic strategies for diagnosing bladder cancer using CT urography, flexible cystoscopy and voided urine cytology: Results for 778 patients from a hospital haematuria clinic

2.2 Abstract

2.2 Purpose

To evaluate and compare the diagnostic accuracy of CT urography with flexible cystoscopy and voided urine cytology for diagnosing bladder cancer.

To evaluate diagnostic strategies using CT urography as (i) an additional test or (ii) a replacement test or (iii) a triage test for diagnosing bladder cancer in patients referred to a hospital haematuria rapid diagnosis clinic.

2.2 Methods

The clinical cohort consisted of a consecutive series of 778 patients referred to a hospital haematuria rapid diagnosis clinic from 01-Mar-2004 to 17-Dec-2007. Criteria for referral were at least one episode of visible haematuria, age over 40 years and urinary tract infection excluded. Of the 778 patients, there were 747 with technically adequate CT urography and flexible cystoscopy examinations for analysis.

On the same day patients underwent examination by a clinical nurse specialist followed by voided urine cytology, CT urography and flexible cystoscopy. Voided urine cytology was scored using a 5 point system. CT urography was reported immediately by a uroradiologist and flexible cystoscopy performed by a urologist, each blinded to the results of the other test. Both examinations were scored using a 3 point system: 1 = normal, 2 = equivocal and 3 = positive for bladder cancer.

The reference standard consisted of review of the hospital imaging and histopathology databases in December 2009 for all patients and reports from the medical notes for those referred for rigid cystoscopy. Follow-up was for a minimum of 21 and a maximum of 66 months.

2.2 Results

The prevalence of bladder cancer in the clinical cohort is 20% (n = 156/778).

For the diagnostic strategy using CT urography as an additional test for diagnosing bladder cancer, when scores of 1 are classified as negative and scores of 2 & 3 as positive, sensitivity = 1.0 (95% CI 0.98 to 1.00), specificity = 0.94 (95% CI 0.91 to 0.95), PPV = 0.80 (95% CI 0.73 to 0.85) and NPV = 1.0 (95% CI 0.99 to 1.00).

For the diagnostic strategy using CT urography as a replacement test for flexible cystoscopy for diagnosing bladder cancer, when scores of 1 are classified as negative and scores of 2 and 3 as positive, sensitivity = 0.95 (95% CI 0.90 to 0.97), specificity = 0.83 (95% CI 0.80 to 0.86), PPV = 0.58 (95% CI 0.52 to 0.64), and NPV = 0.98 (95% CI 0.97 to 0.99). Similarly for flexible cystoscopy for diagnosing bladder cancer, if scores of 1 are classified as negative and scores of 2 and 3 as positive for, sensitivity = 0.98 (95% CI 0.94 to 0.99), specificity = 0.94 (95% CI 0.92 to 0.96), PPV = 0.80 (95% CI 0.73 to 0.85) and NPV = 0.99 (95% CI 0.99 to 1.0).

For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), patients with a positive CT urography score are referred directly for rigid cystoscopy, patients with an equivocal or normal score are referred for flexible cystoscopy. sensitivity = 1.0 (95% CI 0.98 to 1.0), specificity = 0.94 (95% CI 0.91 to 0.95), PPV = 0.80 (95% CI 0.73 to 0.85), NPV = 1.0 (95% CI 0.99 to 1.0).

For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 2), patients with a positive CT urography score are referred directly for rigid cystoscopy, patients with an equivocal score are referred for flexible cystoscopy and patients with a normal score undergo clinical follow-up. sensitivity = 0.95 (95% CI 0.90 to 0.97), specificity = 0.98 (95% CI 0.97 to 0.99), PPV = 0.93 (95% CI 0.87 to 0.96), NPV = 0.99 (95% CI 0.97 to 0.99).

For voided urine cytology, if scores of 0 - 3 are classified as negative and 4 - 5 as positive for bladder cancer, sensitivity = 0.38 (95% CI 0.31 to 0.45), specificity = 0.98 (95% CI 0.97 to 0.99), PPV = 0.82 (95% CI 0.72 to 0.88) and NPV = 0.84 (95% CI 0.81 to 0.87).

2.2 Conclusion

There is a clear advantage for the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), in which

patients with a positive CT urography score for bladder cancer are directly referred to rigid cystoscopy, but all other patients undergo flexible cystoscopy. Diagnostic accuracy is the same as for the additional test strategy with the advantage of a 17% reduction of the number of flexible cystoscopies performed.

The sensitivity of voided urine cytology is too low to justify its continuing use in a hospital haematuria rapid diagnosis clinic utilising CT urography and flexible cystoscopy.

2.2 Purpose

The primary aim of this study is to evaluate and compare the diagnostic accuracy of CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer.

The second aim is to evaluate diagnostic strategies using CT urography as (i) an additional test, (ii) a replacement test or (iii) a triage test for diagnosing bladder cancer in patients referred to a hospital haematuria rapid diagnosis clinic.

2.2 Patients and methods

The study was performed according to the standard hospital haematuria rapid diagnosis clinic protocol with approval from the chairman of the hospital institutional review board.

The clinical cohort consisted of a consecutive series of 778 patients attending a hospital haematuria rapid diagnosis clinic between 01-Mar-2004 and 17-Dec-2007 There were 619 (79.6 %) male patients, 159 (20.4%) female patients, mean age = 67.4 years, (range = 36.7 - 97.5 years). Criteria for referral were at least one episode of visible haematuria, 40 years of age or older, and urinary tract infection excluded.

Five patients of 778 patients were excluded because of technically inadequate CT urography due to lack of contrast administration because of patient refusal (n=1) and needle phobia (n=1), inadequate opacification of the bladder secondary to chronic urinary retention (n=2) and artefact from bilateral metallic hip prostheses obscuring the bladder (n=1). Twenty six patients were excluded because of technically inadequate flexible cystoscopy and all subsequently underwent rigid cystoscopy under general anaesthetic. The reasons for the technically inadequate flexible cystoscopy were inability to pass the flexible cystoscope (n=15), unable to tolerate the procedure (n=2),

poor visibility (n=5), flexible cystoscopy not performed due to an administrative error (n=1), urinary tract infection (n=1), consent refused (n=2).

The final study population consisted of 747 patients with CT urography and flexible cystoscopy correlation.

A Lightspeed QXi, 8 slice CT machine (General Electric, Milwaukee, USA) was used. Patients were given 750 ml-1000 ml of tap water to drink in the waiting room during the 30 minutes before the study and asked to void immediately before the CT examination. The first acquisition series was from the top of the kidneys to 2 cm below the symphysis pubis on expiration. Via and intravenous cannula in the antecubital fossa, using a split-bolus protocol, 100 ml of nonionic contrast medium (Iopamidol 300) given (300 mg I / ml). Between the nephrographic and excretory-phase acquisitions the patient was exercised by walking around the CT gantry. At 6-8 minutes the patient was replaced on the CT table and rolled twice in anticlockwise and then clockwise directions. New scout views were obtained and at 10 min a further 50 ml of intravenous contrast medium was injected via a pump (3 ml/s) and 100 s after the second bolus, a series acquired from the top of the liver to 2 cm below the pubic symphysis. If there was full opacification of the ureters on the first axial reconstruction; the examination was considered completed. Images were viewed on a workstation as axial and multiplanar reformatted images running Advantage Windows (G.E. Healthcare, U.K.) or Voxar3D software version 6.3, (Toshiba Medical Visualization Systems, U.K.). The examinations were reported as soon as they were available on the local workstation by a consultant uroradiologist initially with 3 years experience of reading CT urograms and 11 years uroradiology experience. The CT urography report was available before the patient underwent flexible cystoscopy. The uroradiologist was blinded to the flexible cystoscopy results as CT urograms were reported before the flexible cystoscopy tests were completed. For the last eighteen months of the study, the CT urography images were available to the cystoscopist for review on the hospital web PACS system before the flexible cystoscopy.

Both CT urography and flexible cystoscopy examinations were scored using a 3-point system, where 1 = normal, 2 = equivocal and 3 = positive for bladder cancer. Examples of the CT urography scoring system are provided (Figure 19).

On the same day, flexible cystoscopy was performed after the CT urogram, by a urologist with experience ranging from over 10 years as a consultant to 2 years specialist urological training. Patients with a flexible cystoscopy score of 1 and a negative CT urography of the upper tracts were discharged. Those patients with a cystoscopy score

of 2 and 3 were referred for rigid cystoscopy and biopsy or transurethral resection (TUR) of the bladder tumour (Figure 20).

For both tests clinical information consisting of age, sex and referral symptoms were available to those reporting index tests, as is standard during clinical practice.

Voided urine cytology was scored using a five point system: 0 = inadequate or no specimen, 1 = normal, 2 = atypical probably benign, 3 = atypia of uncertain significance, 4 = atypia suspicious of malignancy and 5 = malignant.

Sensitivity, specificity, PPV and NPV of CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer were calculated.

The reference standard consisted of review of the hospital imaging and histopathology databases in December 2009 for all patients and reports from the medical notes for those referred for rigid cystoscopy. Follow-up was for a minimum of 21 and a maximum of 66 months. The reference standard for bladder cancer consisted of rigid cystoscopy and histopathological evaluation of tissue from cystoscopic biopsy or transurethral resection.

Standard paired measures of diagnostic accuracy: sensitivity, specificity, PPV and NPV were calculated per patient. 95% Confidence intervals (95% CI) were calculated using CIA software (Altman et al., 2000) using Newcombe method (Newcombe, 1998) for paired proportions and the Wilson method for single proportions (Wilson, 1927).

Uninterpretable results, for technically inadequate CT urography or flexible cystoscopy were carefully examined for each patient to determine whether the cause of the technical inadequacy could have been potentially related to presence of disease. This was not found in any patient, so these patients were excluded from the analysis without risk of introducing bias into the study results.

Indeterminate test results, where test results are equivocal (score 2 for CT urography and flexible cystoscopy) are included in each analysis as specified.

Figure 19. CT urography scoring of the bladder for bladder cancer

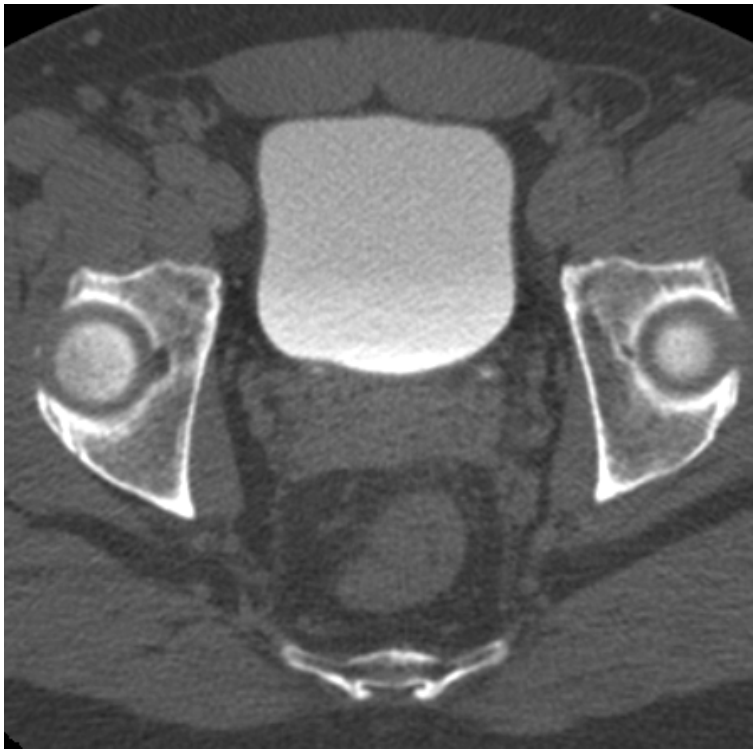


Figure 19a. Score 1 = Normal

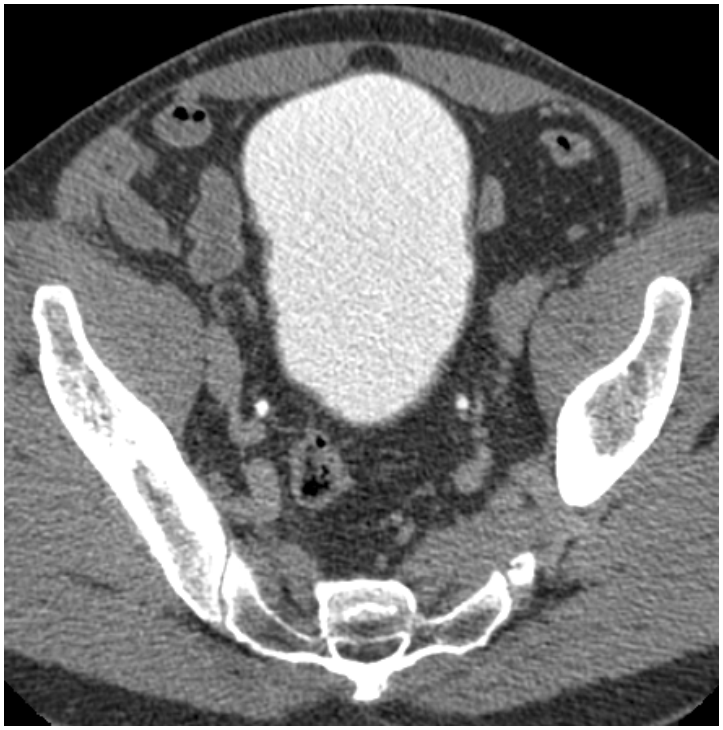


Figure 19b. Score 2 = Equivocal (minor focal wall thickening).

Figure 19. CT urography scoring of the bladder for bladder cancer

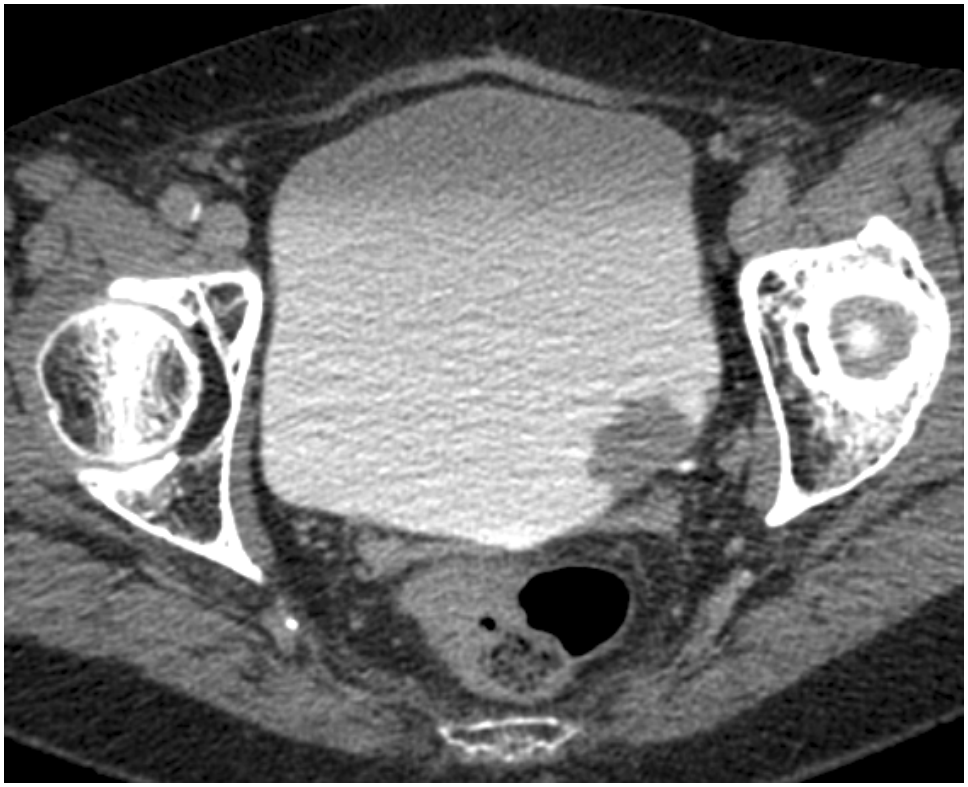
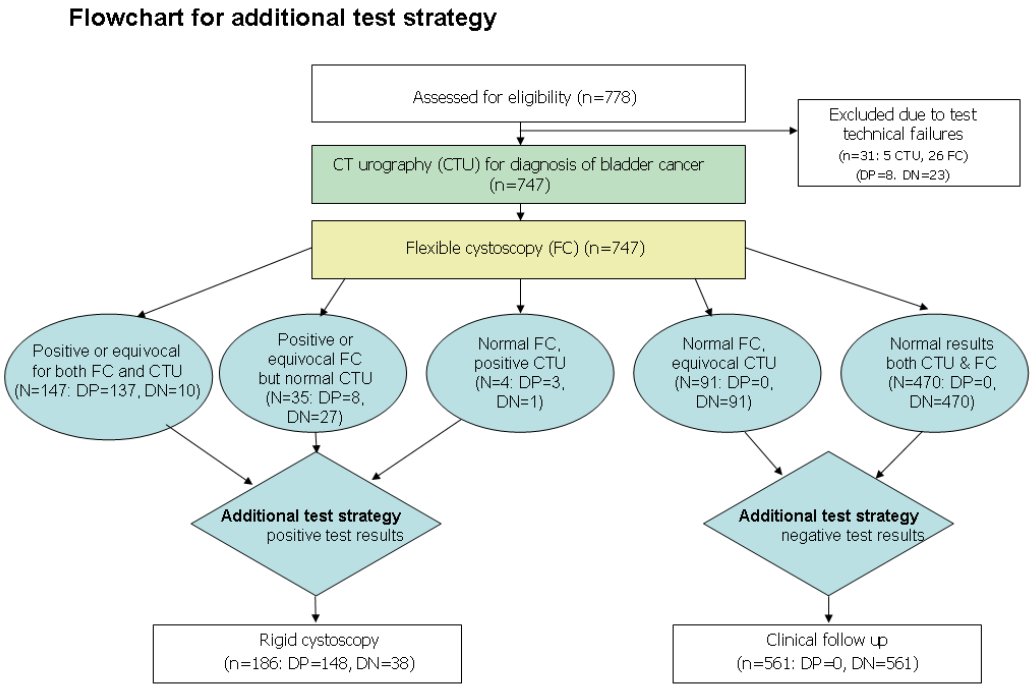


Figure 19c. Score 3 = Bladder cancer

Figure 20. Flow diagram illustrating the diagnostic strategy using CT urography as a additional test for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic.



2.2 Results

This study evaluates and compares CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer in a clinical cohort of 778 patients from a hospital haematuria rapid access clinic.

Of the 778 patients referred for all three tests on the same day, there were 5 technical failures for CT urography (Table 17), 26 technical failures for flexible cystoscopy (Table 18) and 747 patients with technically adequate CT urography and flexible cystoscopy examinations for comparison.

Table 17. Results for patients in whom CT urography was a technical failure and with BCa (three of five patients)

n=3/5	CTU	FC	CYT	G & S	SEX	Reason for technical failure
1	0	3	3	G3, T2	M	Poor opacification due to chronic retention
2	0	3	5	G3, T1	M	Poor opacification due to chronic retention
4	0	3	3	G3, T2	F	Artefact from total hip replacement

Abbreviations: BCa, bladder cancer; CTU, CT urography; FC, flexible cystoscopy; CYT, voided urine cytology; G & S, grade and stage.

Table 18. Results for patients in whom flexible cystoscopy was a technical failure and with BCa (five of twenty six patients)

	CTU	FC	CYT	G & S	SEX	Reason for technical failure
1	3	0	3	G3, T1	M	Unable to pass scope, urethral stricture
2	3	0	5	G3, T2	M	Unable to pass scope, urethral stricture
3	2	0	5	G3, T2	M	Unable to pass scope, urethral stricture
4	1	0	3	G3, T1	F	Unable to pass scope, urethral stricture
5	1	0	3	CIS	M	Poor views

Abbreviations: BCa, bladder cancer; CTU, CT urography; FC, flexible cystoscopy; CYT, voided urine cytology; G & S, grade and stage; CIS, carcinoma in situ.

The test results for CT urography and flexible cystoscopy scores for patients with and without bladder cancer are given in detail (Table 19).

Table 19.

Results for CT urography compared with FC for diagnosing BCa

Results for disease (BCa) positive patients	**CT urography**			
Score	3	2	1	Total
3	126	7	5	138
Flexible cystoscopy 2	1	3	3	7
1	3	0	0	3
Total	130	10	8	148
Results for disease (BCa) negative patients	**CT urography**			
Score	3	2	1	Total
3	0	2	6	8
Flexible cystoscopy 2	0	8	21	9
1	1	91	470	562
Total	1	101	497	599

System of scoring for BCa: Score 3, tumour; Score 2, equivocal; Score 1, normal.

Abbreviations: FC, flexible cystoscopy; BCa, bladder cancer

The prevalence of bladder cancer was 20% (156/778). Of the 131 patients with a definite positive CT urography (Score 3), 130 out of 131 (99%) were histologically proven to have bladder cancer. The patient with a false positive CT urography result was found to have an adherent blood clot at cystoscopy (Figure 21).

Figure 21. The single case for which CT urography was false positive for bladder cancer.

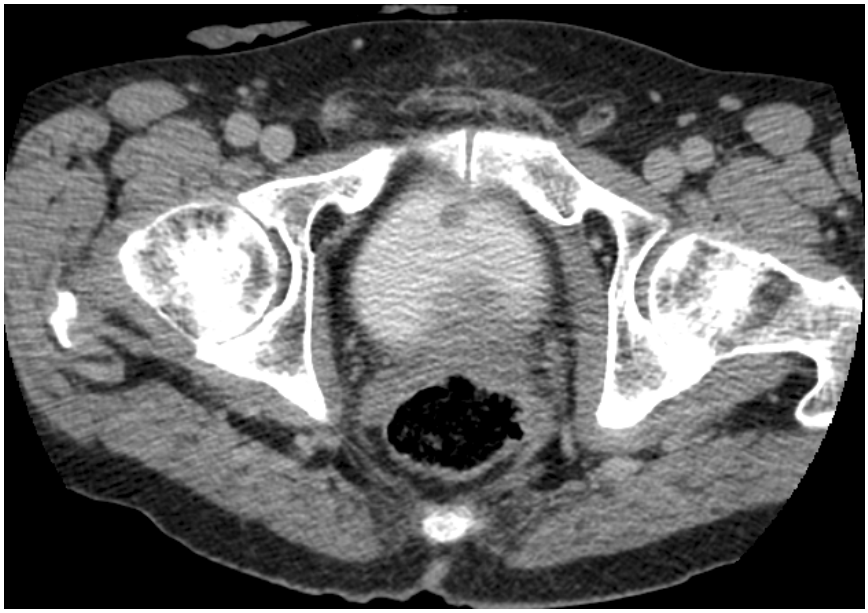


Figure 21. CT urography score of bladder cancer (3) but the mass lesion in the bladder was adherent blood clot.

In 3 patients bladder cancer was missed at flexible cystoscopy (n=3/788, 0.04%) but detected on CT urography (Figure 7 - 8).

Figure 22. CT urography positive, flexible cystoscopy negative for BCa

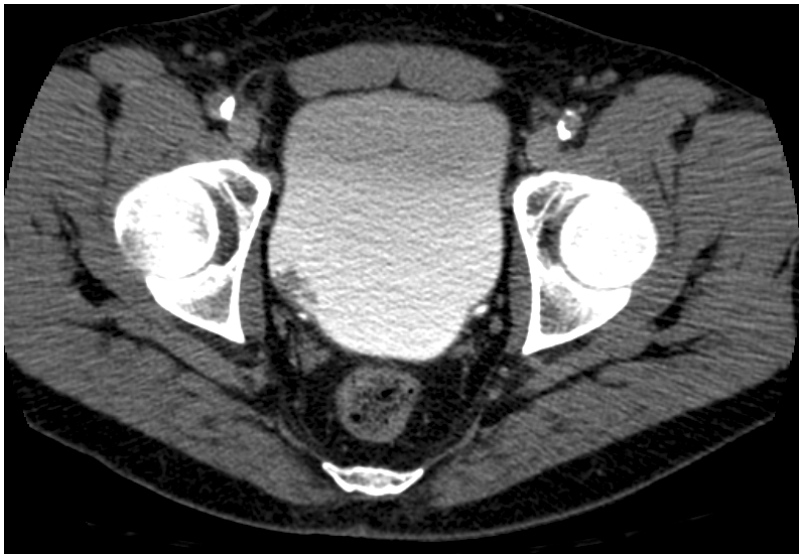


Figure 22. Bladder cancer (G1 Ta) missed on flexible cystoscopy

Figure 23. CT urography positive, flexible cystoscopy negative for BCa

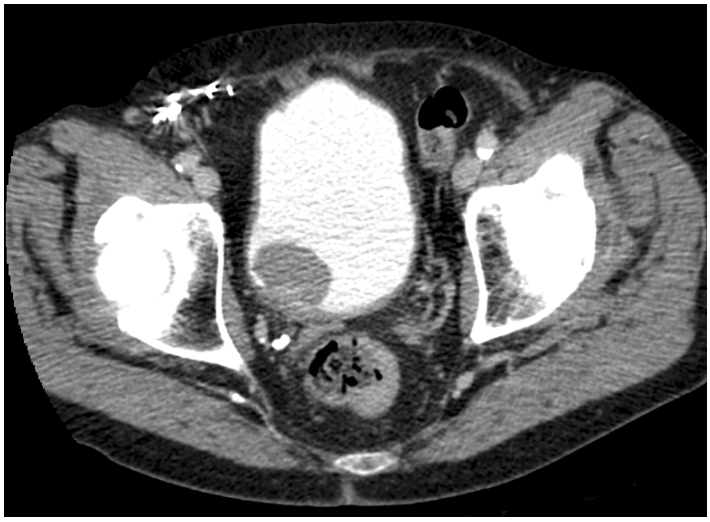


Figure 23. Bladder cancer (G3 T1) missed on flexible cystoscopy

1. Results for the diagnostic strategy using CT urography as an additional test to flexible cystoscopy.

For the diagnostic strategy using CT urography as an additional test for diagnosing bladder cancer (Figure 20), when scores of 1 are classified as negative and scores of 2 and 3 as positive, sensitivity = 1.0 (95% CI 0.98 to 1.00), specificity = 0.94 (95% CI 0.91 to 0.95), PPV = 0.80 (95% CI 0.73 to 0.85) and NPV = 1.0 (95% CI 0.99 to 1.00). This diagnostic strategy was the original strategy used when the rapid diagnosis clinic began. It has the advantage of high diagnostic accuracy but as both CT urography and flexible cystoscopy are performed this strategy is the most expensive of those analysed.

2. Results for the diagnostic strategy using CT urography as a replacement test for flexible cystoscopy

This diagnostic strategy considers CT urography as a potential replacement test for flexible cystoscopy prior to referral for rigid cystoscopy or follow-up (Figure 24). A positive CT urography test result was defined as patients with either an equivocal or positive score (Scores 2 and 3), so all patients with a potentially positive diagnosis are referred for rigid cystoscopy. Similarly, a positive flexible cystoscopy test result was defined as either an equivocal or positive score (Scores 2 and 3).

The sensitivity of CT urography is 0.95 (95% CI 0.90 to 0.97) and the sensitivity of flexible cystoscopy is 0.98 (95% CI 0.94 to 0.99). Comparing the sensitivity of the two tests, flexible cystoscopy has a higher sensitivity by 0.03 (95% -0.013 to 0.085), but this is not significantly different from CT urography. Of the 505 patients scored as 1 or normal on CT urography, 8 patients (1.6 %) were subsequently diagnosed with bladder cancer of which 7 were small non-muscle invasive tumours and 1 was a flat carcinoma-in-situ (CIS). Of these, 3 were related to the bladder base, which is a particularly difficult site for visualisation (Table 20). Three patients with subsequently proven bladder cancer were missed, by flexible cystoscopy (flexible cystoscopy score 1) (Table 21).

Table 20. Information about the eight patients with normal CT urography (Score 1) and histopathological proven BCa (CT urography false negatives)

Bladder cancer grade	Number of patients	Voided urine cytology scores
Low-grade (G1, Ta) non-muscle invasive	4	1, 2, 2, 3
High-grade (G3, T1) non-muscle invasive	2	1, 5
High-grade (G3, T2) non-muscle invasive	1	2
Carcinoma-in-situ (CIS)	1	5

All cases were invisible on CT urography even with retrospective review.

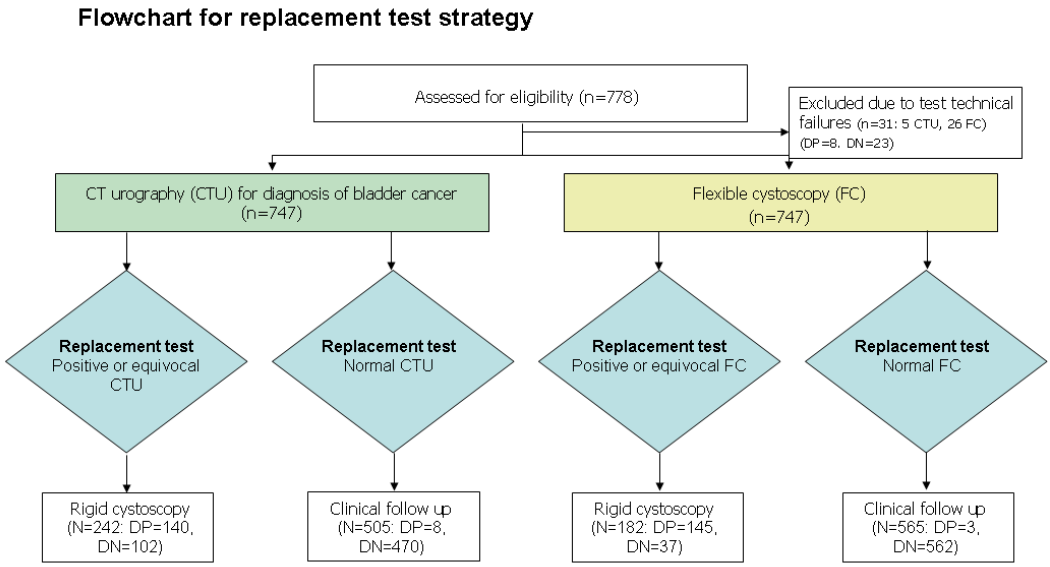
Table 21. Information about the three patients with normal FC (Score 1) and histopathological proven BCa (FC false negatives)

	CTU	FC	CYT	G & S	Site of tumour
1	5	1	1	G1, Ta	Lateral to trigone
2	5	1	5	G3, T1	Lateral to trigone
3	5	1	5	G3, T1	Lateral wall mass, 3 cm

Abbreviations: CTU, CT urography; FC, flexible cystoscopy; CYT, voided urine cytology, G & S, grade and stage.

The specificity of flexible cystoscopy is 0.94 (95% CI 0.92 to 0.96) and CT urography is 0.83 (95% CI 0.80 to 0.86). The specificity of flexible cystoscopy is significantly higher 0.11 (95% CI 0.074 to 0.144). The higher specificity of flexible cystoscopy is important, as using this diagnostic strategy referral of CT urography positive patients results in an extra 9% (65 of 747) of patients being incorrectly referred for rigid cystoscopy (Table 19) (Figure 24).

Figure 24. Flow diagram illustrating the diagnostic strategy using CT urography as a replacement test for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic.



3. Results for the diagnostic strategy using CT urography as a triage test prior to rigid cystoscopy, flexible cystoscopy or follow-up

If CT urography is used as a triage test for diagnosing bladder cancer in the rapid access clinic, two options are presented.

For option 1 where CT urography is used as a triage test to "rule in" bladder cancer (Figure 25), patients identified as positive by CT urography are referred directly for rigid cystoscopy and patients with equivocal and normal results by CT urography are referred for flexible cystoscopy. The flow chart for this diagnostic strategy is shown (Figure 25) and the results for diagnostic accuracy (Tables 22 and 23).

Table 22. Results for triage strategy Option 1 compared with additional test strategy (All CT urography negatives were referred for FC)

Disease positive (BCa) patients		Additional test strategy		
		Positive	Negative	Total
Triage test strategy, Option 1	Positive	148	0	148
	Negative	0	0	0
	Total	148	0	148

Disease negative (BCa) patients		Additional test strategy		
		Positive	Negative	Total
Triage test strategy, Option 1	Positive	38	0	38
	Negative	0	561	561
	Total	38	561	599

Table 23. Results for the diagnostic accuracy of additional, replacement and triage test strategies for diagnosing BCa using CT urography, FC and voided urine cytology

Diagnostic strategy:	Additional test strategy	Replacement test strategy	Replacement test strategy	Triage test strategy Option 1	Triage test strategy Option 2	
	CTU & FC	CTU	FC	CTU and/or FC	CTU and/or FC	Voided urine cytology
	Scores 3 & 2, positive; score 1 , negative	Scores 3 & 2, positive, Score 1, negative	Scores 3 & 2, positive, Score 1, negative	CTU score 3, positive; scores 2 & 1, equivocal; FC scores 3 & 2 positve; score 1, negative	CTU score 3, positive; score 2, equivocal; score 1, negative; FC scores 3 & 2 positive, score 1, negative	Scores 1-3, negative; Scores 4-5, positive
Se (95% CI)	1.00 (0.98-1.00)	0.95 (0.90-0.97)	0.98 (0.94-0.99)	1.0 (0.98-1.00)	0.95 (0.90-0.97)	0.38 (0.31-0.45)
Sp (95% CI)	0.94 (0.91-0.95)	0.83 (0.80-0.86)	0.94 (0.92-0.96)	0.94 (0.91-0.95)	0.98 (0.97-0.99)	0.98 (0.97-0.99)
PPV (95% CI)	0.80 (0.73-0.85)	0.58 (0.52-0.64)	0.80 (0.73-0.85)	0.80 (0.73-0.85)	0.93 (0.87-0.96)	0.82 (0.72-0.88)
NPV (95% CI)	1.00 (0.99-1.00)	0.98 (0.97-0.99)	0.99 (0.99-1.0)	1.0 (0.99-1.0)	0.99 (0.97-0.99)	0.84 (0.81-0.87)
Average number of tests per patient	2.0	1.0	1.0	1.8	1.15	1.0

Abbreviations: Se, sensitivity; Sp, specificitiy; PPV, positive predictive value; NPV, negative predictive value; CTU, CT urography; FC, flexible cystoscopy

For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), sensitivity = 1.0 (95% CI 0.98 to 1.0), specificity = 0.94 (95% CI 0.91 to 0.95), PPV = 0.80 (95% CI 0.73 to 0.85), NPV = 1.00 (95% CI 0.99 to 1.00).

Using this strategy, both sensitivity and specificity are exactly the same as the additional test strategy (Table 23) but the number of flexible cystoscopies is reduced by 17% with considerable cost savings.

In option 2 CT urography is used as a triage test both to "rule in" and "rule out" bladder cancer. In option 2, patients with positive CT urography scores for bladder cancer are referred directly for rigid cystoscopy, patients with equivocal CT urography scores are referred for flexible cystoscopy and patients with negative CT urography results are referred for clinical follow-up (Figure 26). The test results of this alternative strategy are shown (Figure 26) and (Table 23). For the diagnostic strategy triage test option 2, sensitivity = 0.95 (95% CI 0.90 to 0.97), specificity = 0.98 (95% CI 0.97 to 0.99), PPV = 0.93 (95% CI 0.87 to 0.96), NPV = 0.99 (95% CI 0.97 to 0.99). Compared to both the additional test strategy and triage option 1, the triage option 2 strategy has a significantly lower sensitivity by 0.054 (95 % CI 0.017 to 0.103), excluding it from clinical use (Table 23). The triage option 2 however has a significantly higher specificity (0.045: 95% CI 0.029 to 0.065) compared to the additional test and triage option 1 (Table 23).

Figure 25. Flow diagram illustrating the diagnostic strategy using CT urography as a triage test, option 1, for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic.

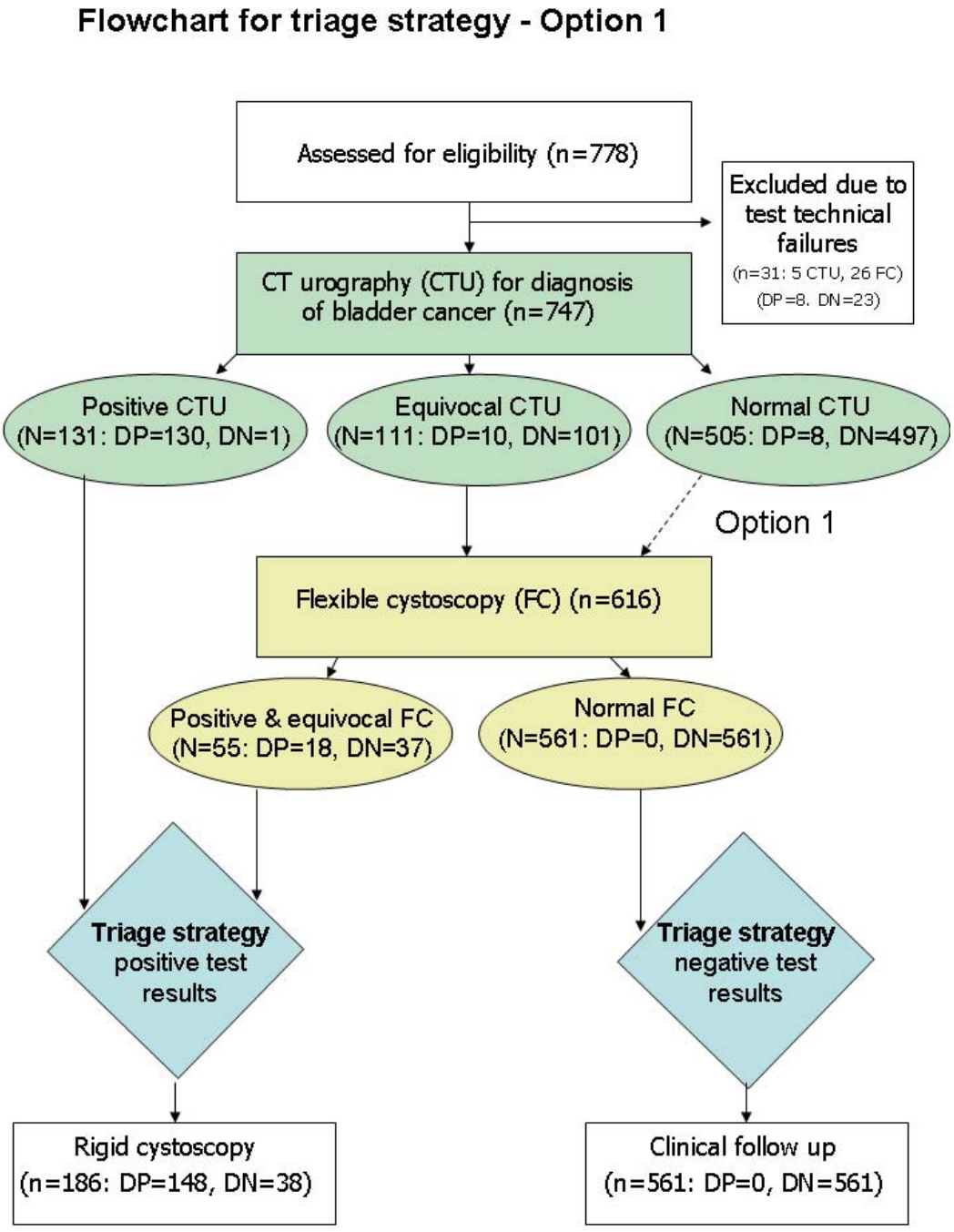
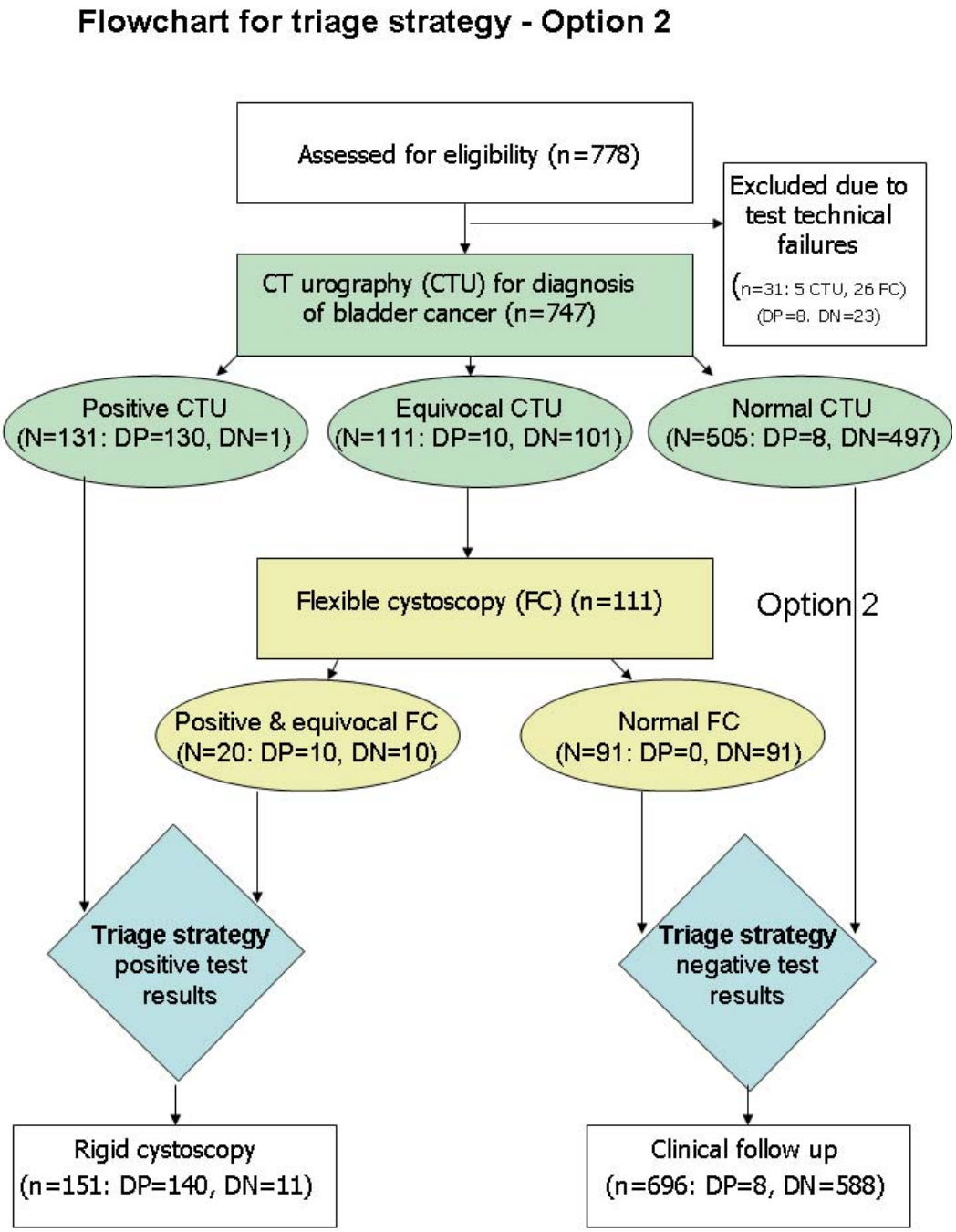


Figure 26. Flow diagram illustrating the diagnostic strategy using CT urography as a triage test, option 2, for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic.



2.2 Role of voided urine

Urine cytology was found to have an unacceptably low sensitivity for diagnosis of any urothelial cancer of 0.38 (95% CI 0.31 to 0.45) even though the specificity is 0.98 (95% CI 0.96 to 0.99), using the clinically relevant threshold where scores of 4 and 5 were classified as positive results (Table 24 and 25). In this clinical cohort, there were no cases of histologically proven bladder cancer in whom voided urine cytology was positive and CT urography and flexible cystoscopy were negative, however there were two patients with bladder cancer, a negative CT urography score and a positive cytology result (Table 24).

Table 24. Results for voided urine cytology for diagnosing BCa

Cytology Score	Patients with BCa	Patients with UTUC	Patients without BCa or UTUC	Total
0	12	1	32	45
1	40	4	467	511
2	12	1	48	61
3	31	9	40	80
4	22	1	8	31
5	39	4	7	50
Total	156	20	602	778

Abbreviations: BCa, bladder cancer; UTUC, upper tract urothelial carcinoma

Table 25. Results for the diagnostic accuracy of voided urine cytology for diagnosing bladder cancer

		Urothelial carcinoma		
		Positive	Negative	Total
Voided urine cytology	Positive	66	15	81
	Negative	110	587	697
	Total	176	602	778

There were five patients with both BCa and UTUC.

2.2 Discussion

The role of CT urography and flexible cystoscopy for diagnosing bladder cancer is to determine which patients undergo rigid cystoscopy in order to make the final diagnosis of bladder cancer by histological evaluation of biopsied or resected tissue and determine which patients are classified as normal.

Exercising the patient before the excretory series by walking around the CT machine and rolling on the CT table to improve bladder opacification (Kim et al., 2008) (Turney et al., 2006) is an important manoeuvre which may improve the diagnostic accuracy of CT urography for diagnosing bladder cancer (Figure 27).

This study examines the role of CT urography for diagnosing bladder cancer with reference to various diagnostic strategies in which CT urography is (i) an additional test, (ii) as a replacement test and (iii) as a triage test (options 1 and 2).

The strategy currently in use is the additional test strategy which shows high diagnostic accuracy but is the most expensive option as both CT urography and flexible cystoscopy are attempted on every patient. It is the standard by which other strategies are compared.

In the replacement strategy CT urography and flexible cystoscopy have similar sensitivities for diagnosing bladder cancer, but CT urography is not a suitable replacement test for flexible cystoscopy because the specificity is significantly lower than flexible cystoscopy which would mean too many patients being referred unnecessarily for rigid cystoscopy.

Two diagnostic strategies using CT urography as a triage test are presented. Option 1 has equal sensitivity to the additional test strategy and allows reduction in the number of flexible cystoscopies by 17%. Option 2, has a slightly less sensitivity compared with the additional test strategy, although not statistically significant, but would have missed 8 bladder cancer. The advantage of option 2 is that it that it allows a reduction in the number of flexible cystoscopies by 43%.

The sensitivity of voided urine cytology is too low to justify its continuing use in a hospital haematuria rapid diagnosis clinic utilising CT urography and flexible cystoscopy. It is a redundant test which could be dropped from the diagnostic pathway without adversely affecting diagnostic accuracy.

From the results of our study comparing different strategies using CT urography (Table 23), the preferred strategy is triage test option 1 (Figure 25). This has identical diagnostic performance to the current strategy which uses CT urography as an additional test, but reduces the number of tests for patients identified with bladder cancer by CT urography. These patients are referred directly to rigid cystoscopy without an additional flexible cystoscopy, with a cost saving at no diagnostic penalty. If the costs of the four strategies at standard private patient charges are calculated and the difference between the additional strategy worked out, there is an overall saving of £142,350 across 747 patients, equivalent to £190 per patient for Triage strategy option 1, (Table 26).

Table 26. Standard 2011 private patient costs and savings for diagnostic strategies compared with the additional test strategy

Strategy:	Additional	Replacement	Triage Option 1	Triage Option 2
Overall Cost:	£ 1,570,026	£ 820,381	£ 1,427,676	£ 839, 906
Savings:	£ 0	£ 749, 645	£ 142,350	£ 739,120

Figure 27. Exercising the patient by rolling on the CT table may improve bladder opacification and diagnostic accuracy of CT urography for bladder cancer

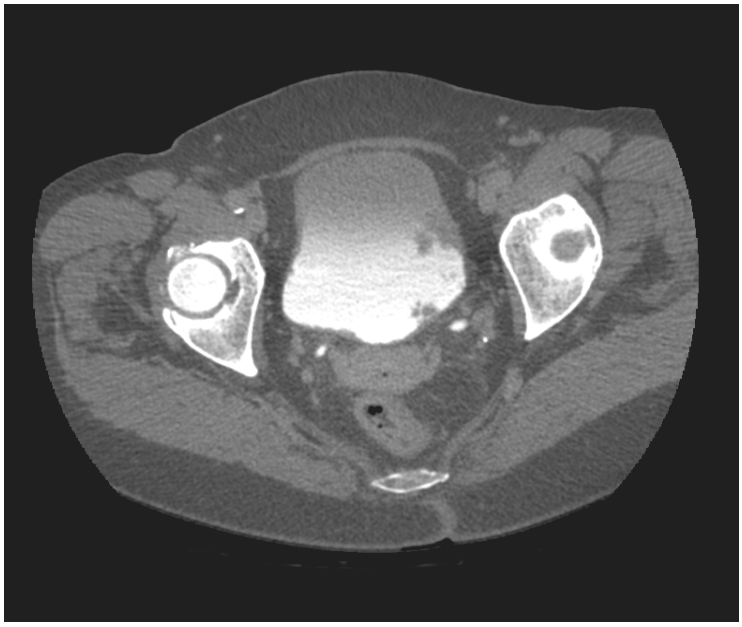


Figure 27a. CT urography showing supine excretory-phase image acquired supine at 12.5 min post without exercising the patient.

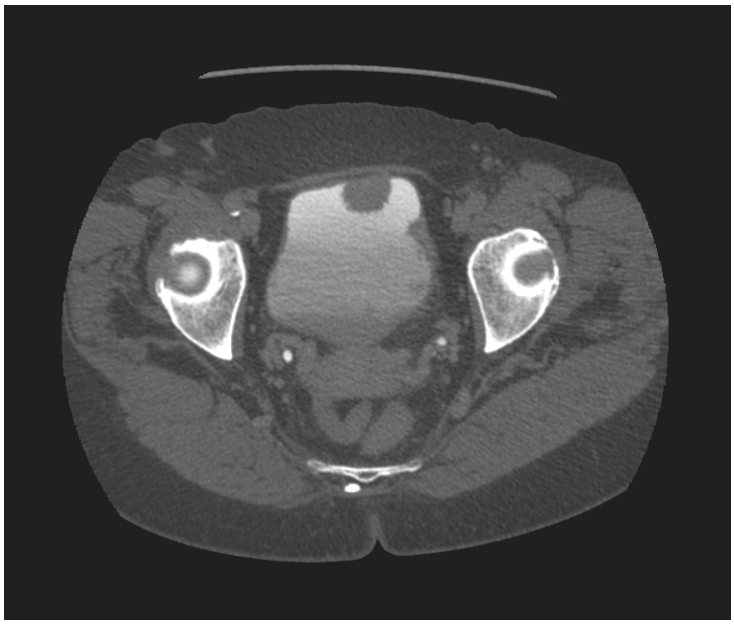


Figure 27b. Following exercising including rolling on the CT table a large anterior wall bladder cancer is now demonstrated.

2.2 Limitations

The reference standard although the best achievable with the study design, is still imperfect as there is the potential for incomplete follow-up. Some patients may move out of the hospital catchment area and be lost to follow-up or patient follow-up details on the hospital databases might be incomplete. The risk of this happening is small but it is noted as a limitation to the study.

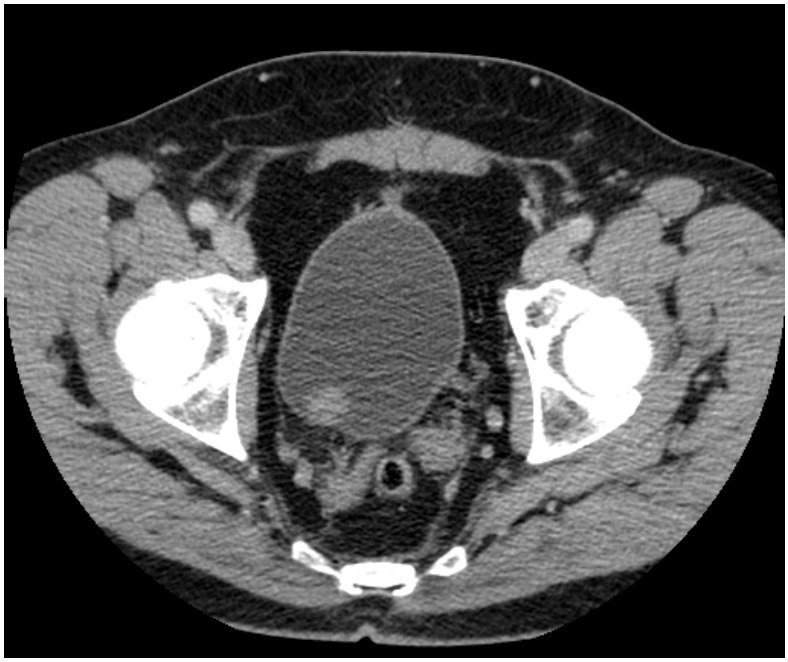
The results of this study are from a specially designed clinic in a single centre. Research on a wider scale in multiple centres would be useful before recommendations for the NHS are made.

Training programmes to teach radiologists how to read CT urography are required on a national basis. Teaching courses similar to those for CT colonography have many advantages for the future (Dachman et al., 2008).

The CT technique described in this paper is optimised for upper tract evaluation rather than for evaluation of the bladder requiring multiple image series acquired at different phases following the administration of intravenous contrast in the presence of a full bladder (Jinzaki et al., 2007) (Kim, Park, Ahn, & et al, 2004) (Cohan et al., 2009) (Figure 9).

To help optimise opacification of the upper tracts by encouraging urine flow, patients void immediately before the CT examination. This manoeuvre inevitably compromises the diagnostic accuracy of CT urography for diagnosing bladder cancer, as the bladder may be partially distended at the time of imaging making identification of small bladder wall lesions more difficult as they may be confused with folds.

Figure 28. To fully optimize CT urography for diagnosing bladder cancer, images are acquired during multiple phases of contrast enhancement



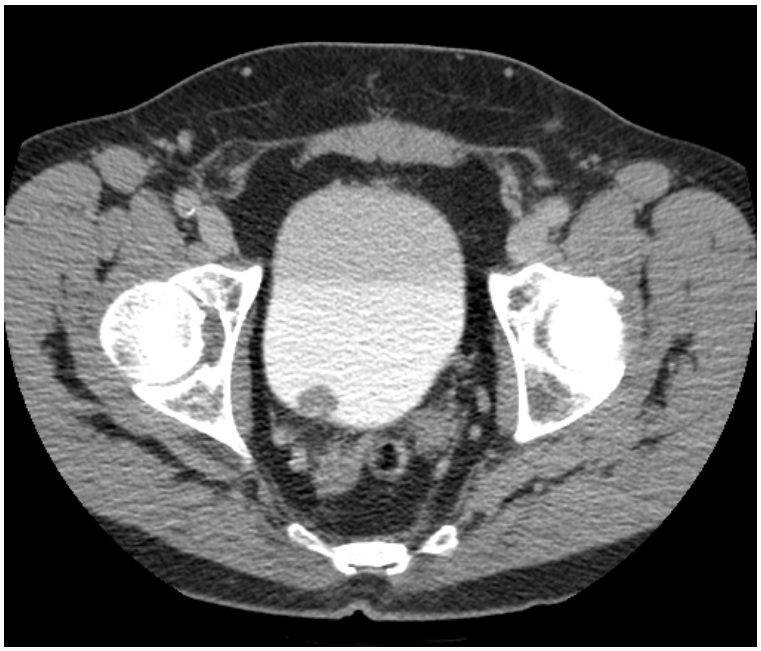


Figure 28. Both the 60 s and 12.5 min post-contrast images clearly demonstrate a small bladder cancer close to the right ureteric orifice.

2.2 Conclusion

In conclusion, we recommend the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), for use in a hospital haematuria rapid diagnosis clinic. Patients with a positive CT urography score for bladder cancer are directly referred to rigid cystoscopy, but all other patients undergo flexible cystoscopy. Diagnostic accuracy is the same as for the additional test strategy with the cost saving advantage of a reduction of the number of flexible cystoscopies performed by 17%.

The sensitivity of voided urine cytology is too low to justify its continued use in a hospital haematuria rapid diagnosis clinic utilising CT urography and flexible cystoscopy.

Discussion

Evaluation of new diagnostic strategies

Whether all patients with haematuria should undergo CT urography, or whether there are subgroups of patients who are more likely to benefit from CT urography than others, remains under investigation. Some notable features of CT urography mean that it should be targeted towards a select patient population. These include the length of time required in the CT suite, the increased radiation dose compared to other CT studies, and the large bolus of intravenous contrast administered.

The ideal initial diagnostic imaging test should have high sensitivity and specificity for diseases at high prevalence in the test population. Deciding what constitutes a high prevalence is not just a clinical decision but also depends on economic and political factors. Some results of disease prevalence in patients evaluated for haematuria using ultrasonography and intravenous urography are shown (Table 1)**.** The prevalence of disease in a series of patients over 40 years of age who presented with visible haematuria and were evaluated using CT urography are given (Table 12) (Cowan et al., 2011). Comparison of the results displayed in Tables 1 and 12 shows there is a 4.4 -22 times greater prevalence for UTUC and a 1.8 - 5.1 greater prevalence for stones in the study using CT urography rather than ultrasonography and / or intravenous urography as the initial imaging investigation. Although the populations cannot be exactly age matched in the three studies, the difference in prevalence is striking and is most likely to reflect that greater diagnostic accuracy of CT urography compared with ultrasonography and intravenous urography for investigating haematuria.

The prevalence of specific underlying diseases responsible for haematuria can be predicted by various risk factors. The two most readily identifiable risk factors that reflect the prevalence of urothelial carcinoma are the presence of visible or nonvisible haematuria and increasing patient age. This knowledge can be used clinically for stratification into groups of patients at low-risk and high-risk for urothelial carcinoma (Table 27).

Table 27.

Summary of diagnostic strategies for investigating haematuria

	Diagnostic strategy			
Risk for UTUC:	**Low risk**			**High risk**
Age:	< 40 y		> 40 y	**> 40 y**
Haematuria:	Nonvisible	Visible	Nonvisible	**Visible**
Initial test:	US KUB	US KUB, if normal then unenhanced CT KUB	Unenhanced CT KUB, if normal then US KUB	**CT urography UE NG EX phases**
Second test:	-	FC	FC	**FC**

Abbreviations: UE, unenhanced; KUB, kidneys, ureters and bladder; US, ultrasonography; CT, computed tomography; FC, flexible cystoscopy; UTUC, upper urinary tract urothelial carcinoma.

The high risk group consists of patients ≥ 40 years with visible haematuria and urinary tract infection excluded. UTUC is most prevalent in this population (Table 27), which justifies initial investigation with excretory-phase CT urography.

The low risk group comprises patients > 40 years with nonvisible haematuria and those under < 40 years old with either nonvisible or visible haematuria. The disease with the greatest prevalence in patients with nonvisible haematuria under the age of 40 years is medical renal disease (Tomson & Porter, 2002), so renal tract ultrasonography is recommended as the initial imaging test in these patients. Ultrasonography can elucidate the presence, position and outline of the kidneys, cortical thickness, and the presence of large stones, large renal masses, and hydronephrosis. Stones are the most common cause of haematuria in patients under the age of 40 years with visible haematuria and those older than 40 years of age with nonvisible haematuria and

urinary tract infection excluded. The prevalence of UTUC is very low in these patients. Given that unenhanced CT has the highest sensitivity for upper urinary tract stones, it is recommended as the initial imaging investigation in these patients. Unenhanced CT can detect small stones, hydronephrosis, hydroureter, and some renal masses, upper tract urothelial cancers and bladder cancers.

A method of triaging patients by incorporating a risk score has been proposed (Table 28) (Cowan et al., 2011).

Table 28. Risk scores for urothelial carcinoma

Risk factor	Risk score
> 40 years of age	1
Haematuria	
Visible	2
Nonvisible, persistent	1
Nonvisible, unspecified	0
Imaging findings	
UTUC	2
Bladder Cancer	2
Renal mass	2
Hydronephrosis, hydroureter	2
Urine cytology	
Normal, atypical probably benign, atypia of uncertain origin	0
Atypia suspicious of malignancy, malignant cells seen	2
Occupational exposure	
Smoking	2
Aromatic amines	2
Benzenes	2
Analgesic abuse, phenacetin	2
Urethral stricture preventing cystoscopy	2

CT urography becomes justified when the sum of the risk scores is ≥ 3.

Abbreviations: UTUC, upper urinary tract urothelial carcinoma.

Patients with a risk score of ≥ 3, should undergo CT urography those with a risk score of <3, should undergo unenhanced CT or the kidney, ureters and bladder. If ultrasonography or unenhanced CT reveal an increased risk for urothelial cancer as defined by the risk score (≥ 3), then CT urography becomes justified. (Stenzl et al., 2009) (Blick et al., 2011).

For patients of any age in the low risk group with persistent nonvisible haematuria and normal imaging investigations, repeat imaging is only justified if there is a significant change in the risk score, for example if urinary tract symptoms or visible haematuria are reported. The optimum diagnostic imaging strategy for patients at high risk for urothelial carcinoma consists of initial CT urography as a replacement for conventional upper tract imaging techniques (Cowan et al., 2011) and as a triage test for bladder assessment. For patients at low risk of UTUC, ultrasonography and unenhanced CT of the kidneys, ureters and bladder should be used instead (Nolte-Ernsting & Cowan, 2006) (Van Der Molen et al., 2008) (Sudakoff et al., 2008) (Wang et al., 2009). A diagrammatic summary of such a diagnostic strategy is given (Table 27 and 29).

Interest has recently increased in the potential role of CT urography for evaluating the bladder.(Cohan et al., 2009) (Turney et al., 2006) (Sadow et al., 2008) Blick *et al*. assessed diagnostic strategies for diagnosing bladder cancer using CT urography as an additional, replacement or triage test in 778 patients. They concluded that patients with a positive CT urography score for bladder cancer should directly undergo rigid cystoscopy, and those with normal or equivocal scores should undergo flexible cystoscopy. The diagnostic accuracy is the same as for the additional test strategy, which dictates that all patients undergo CT urography and flexible cystoscopy but has the advantage of a 17% reduction in the number of flexible cystoscopies performed.

Table 29. Summary of diagnostic strategies for investigating haematuria - latest thinking

	Diagnostic strategy			
Risk for UTUC:	**Low risk**			**High risk**
Age:	**< 50 y**		**> 50 y**	**> 50 y**
Haematuria:	**Nonvisible**	**Visible**	**Nonvisible**	**Visible**
Initial test:	**US KUB? or CT KUB unenhanced**	**CT urography UE & NG phases**	**CT urography UE & NG phases**	**CT urography UE, NG & EX phases**
Second test:	FC?	**FC**	**FC**	**FC**

Abbreviations: US, ultrasonography; KUB, kidneys, ureters and bladder; CT, computed tomography; UE, unenhanced; NG, nephrographic; EX, excretory; FC, flexible cystoscopy; UTUC, upper urinary tract urothelial carcinoma.

Chapter 3. Identifying problems and finding solutions

Once the issues relating to optimising CT urography technique have been overcome, the principal problems associated with CT urography for investigating haematuria are reader error, false positive diagnoses and increased radiation dose. Other problems which are important but are considered secondary issues include the length of time the patient is required to be in the CT room for the complete examination, availability of CT, cost compared with other imaging techniques, the need for special image viewing hardware and software for optimum reporting, the diagnosis of unexpected extra-genitourinary disease, the requirement for a quality assurance program and the over utilization of CT urography for inappropriate indications.

There are many ways to reduce reader error, but perhaps the best method of teaching radiologists to read CT urography is to introduce a formative teaching program designed to simulate clinical reporting. Reader training, interpretation and certification has already been employed for CT colonography (Dachman et al., 2008) (Soto, Barish, & Yee, 2005). Various diagnostic accuracy studies have revealed that the positive predictive value of CT urography for UTUC is low,(Chow et al., 2007) (Sudakoff et al., 2008) (Maheshwari et al., 2010) (Cowan et al., 2007) ranging from 0.50–0.82, which currently precludes the notion of referring patients for curative surgery as soon as they are diagnosed. A list of false positive diagnoses is given (Table 30). Therefore, UTUC diagnosed with CT urography should be biopsied (by ureteroscopy or retrograde ureteropyelography-guided) for histopathological confirmation of the diagnosis before proceeding to surgery (Roupret et al., 2011).

Table 30. False positive diagnoses for UTUC

1	Clot
2	Debris
3	Kink of the ureter (accentuated by inspiration)
4	Fibroepithelial polyp
5	Injury to the ureter (passage of a stone, stent placement or ureteroscopy)
6	Ureteritis cystica
7	Flow artifacts (furosemide administration or layering effects)
8	Unusual looking papilla, a normal variant
9	Nephrogenic adenoma
10	Amyloid
11	Renal cell carcinoma
12	Lymphoma
13	Vascular impression
14	Inflammation, fibrosis

Over utilization of high-tech imaging services such as multidetector CT, MRI and PET-CT is defined as performing imaging procedures that are unlikely to improve patient outcome (Hendee et al., 2010). Health care systems in which there is a fee-for-service payment process, self-referral practices, and defensive medicine might influence the over utilization of imaging, which can be responsible for unnecessary health care costs and frequently exposes patients to unnecessary radiation. CT urography requires a higher dose of radiation than excretory urography, which can only be justified by its increased diagnostic accuracy in the correct clinical setting (Vrtiska et al., 2009). Individual patient radiation doses can be minimized by close attention to optimizing image acquisition parameters and by using CT dose-reducing techniques (Toth & Hsieh, 2009). The use of referral guidelines that incorporate appropriateness criteria based on objective clinical evidence and comparative effectiveness research make an important contribution to reducing over utilization. Further comparative effectiveness research of imaging technology is called for as a deterrent to over utilization of medical imaging (Hendee et al., 2010).

3.1 Retrograde ureteropyelography-guided biopsy of upper tract urothelial carcinoma detected by CT urography to eliminate false positive results and to determine histopathological diagnosis and grade

3.1 Abstract

3.1 Purpose

To evaluate the technical success and diagnostic accuracy of retrograde ureteropyelography-guided biopsy (RGB) for upper tract urothelial cancer (UTUC) initially found by CT urography.

3.1 Methods

The clinical cohort consisted of a selected group of patients, over 40 years of age, with visible haematuria, UTI excluded, presenting between 17/10/2006 - 09/02/2009 and investigated initially with CT urography. CT urography was scored using a five point scale: 1 = normal, 2 = probably normal, 3 = equivocal, 4 = probably positive, 5 = definitely positive for UTUC. retrograde ureteropyelography +/- RGB was attempted on patients with scores of 3, 4 or 5. Procedures were performed by a single uroradiologist using digital C-arm fluoroscopy, using intravenous sedation and analgesia. The reference standard included histopathology from surgery, RGB or ureteroscopic-guided biopsy (UGB), clinical, imaging and histopathology database follow-up.

3.1 Results

140 patients were referred for retrograde ureteropyelography with a view to RGB, following CT urography for haematuria. Of the 140 patients, 7 were cancelled before proceeding to retrograde ureteropyelography. Of 133 patients in which retrograde ureteropyelography was attempted, there were 94 male and 39 females, age range 40.7 years to 90.3 years, average 70.9 years. Retrograde ureteropyelography was positive for UTUC in 89 and negative for UTUC in 38 patients. There were 6 technical failures of retrograde ureteropyelography due to non-visualization of the ureteric orifice and these were classified as retrograde ureteropyelography positive results as clinically the patients were treated as being retrograde ureteropyelography positive in that they required further tests. Of the 89 retrograde ureteropyelography positive patients, excluding the 6 retrograde ureteropyelography technical failures, 87 underwent RGB.

The RGB was not performed on 2 patients who were retrograde ureteropyelography positive and receiving warfarin anticoagulant therapy. RGB was diagnostic and positive in 64, diagnostic and negative in 11 and non-diagnostic in 12.

Of the 64 patients with RGB positive results for UTUC, 52 were confirmed positive by histopathology following radical nephroureterectomy, in the remaining 12 patients treatment was non-operative.

Of the 52 patients positive for UTUC on histopathology from both RGB and radical nephroureterectomy: RGB correctly determined grade in 41 (79%), undergraded in 8 (15%) and overgraded in 3 (6%) of cases.

3.1 Conclusion

RGB may be employed as the initial method for histopathological diagnosis of UTUC.

Undergrading of UTUC by RGB may lead to inappropriate endoscopic treatment in 15% of patients.

3.1 Introduction

Biopsy is an important for patients with UTUC because the results can influence management. False positive diagnoses may be eliminated by biopsy providing by histopathological confirmation of diagnosis as well as information about tumour grade, which is used to determine treatment.

The standard treatment for UTUC has been open nephroureterectomy with excision of a bladder cuff around the ipsilateral distal ureter (ONU). Since the widespread adoption of minimally invasive surgical techniques, laparoscopic nephroureterectomy (LNU) has been increasingly used for UTUC. The superior perioperative outcomes achieved with laparoscopic approaches include less blood loss, decreased perioperative pain, fewer days to convalescence and shorter hospital stays. Emerging data suggests that the oncological outcomes are comparable between ONU and LNU.

Endoscopic management of UTUC has traditionally been reserved for patients with solitary kidneys, bilateral synchronous tumours, baseline renal insufficiency or comorbid diseases that preclude abdominal surgery. Recently for patients with low-volume and low-grade UTUC, endoscopic treatment has been recently proposed.

This chapter evaluates an innovative technique for UTUC biopsy performed under local anaesthetic and sedoanalgesia, using a flexible cystoscope and ureteroscopic biopsy forceps guided by fluoroscopy.

3.1 Materials and methods

The clinical cohort consisted of a selected group of patients, over 40 years of age, with visible haematuria, UTI excluded, presenting between 17/10/2006 - 09/02/2009 and investigated initially with CT urography. CT urography was scored using a five point scale: 1 = normal, 2 = probably normal, 3 = equivocal, 4 = probably positive, 5 = definitely positive for UTUC. retrograde ureteropyelography was attempted on patients with scores of 3, 4 or 5 and retrograde ureteropyelography-guided biopsy (RGB) was attempted if a lesion was thought to be UTUC. Procedures were performed by a single uroradiologist using digital C-arm fluoroscopy, using intravenous sedation and analgesia. Sensitivity and specificity were calculated for retrograde ureteropyelography for diagnosing UTUC. The reference standard included histopathology from surgery, RGB or

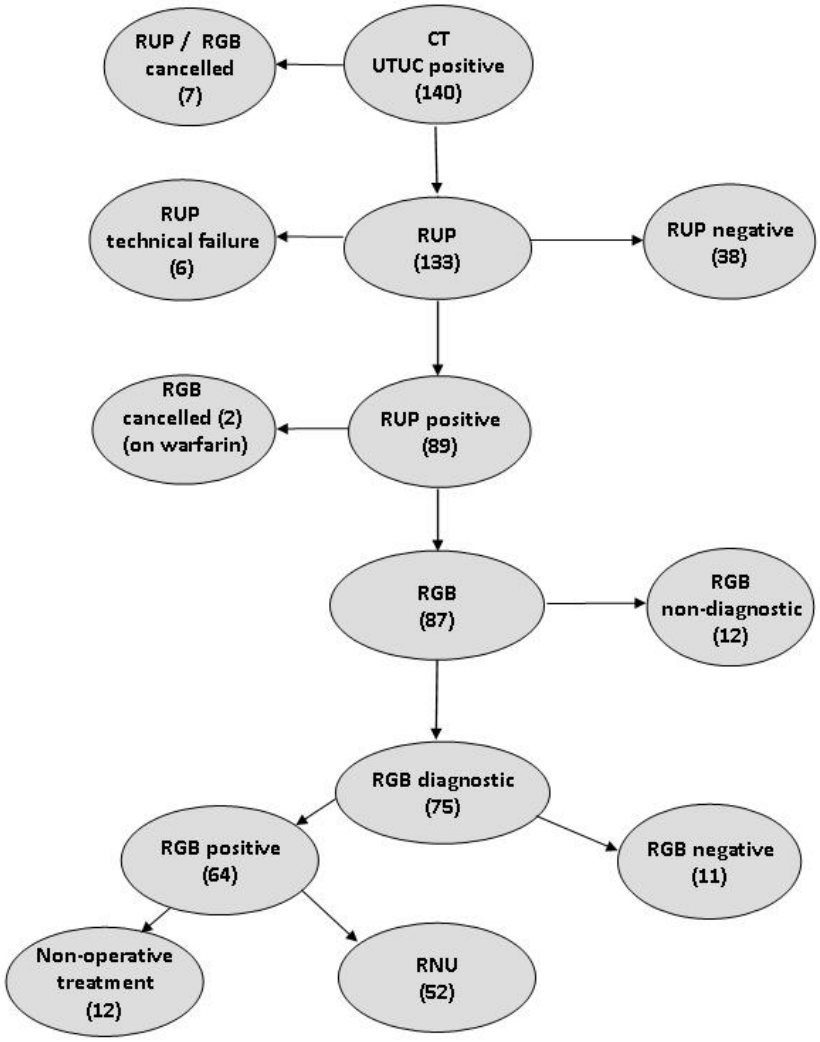
ureteroscopic-guided biopsy (UGB), clinical, imaging and histopathology database follow-up.

All retrograde ureteropyelography and RGB procedures were carried out in the interventional radiology suite. Patients gave informed consent and were given oral antibiotic prophylaxis (ciprofloxacin 250 mg). Lignocaine gel was used as a local anaesthetic and lubricant. Sedoanalgesia, diazemuls (2.5 - 10 mg intravenously) and pethidine (50 - 100 mg intravenously) was given as required. The patient's pulse, blood pressure and oxygen saturation were continuously monitored during the procedure. A flexible cystoscope was passed into the bladder and rotated through 180º to allow greater deviation of the end of the scope and to facilitate identification of the ureteric orifices. A straight tipped hydrophilic guide wire, 0.035", (0.89 mm) 180 cm, flexible 3 cm tip, Terumo Europe NV, 3001 Leuven, Belgium was then passed into the ureteric orifice under direct vision. The guidewire was then manipulated into the renal pelvis using C-arm digital fluoroscopy. The flexible cystoscope was removed and a 4F multipurpose, 80 cm, 0.038", 0.97 mm, angiographic catheter, (Cordis Europa, Roden, The Netherlands) placed over the wire into the renal pelvis. Urine (approximately 5-10 ml) was aspirated to remove air bubbles from the catheter dead space and decompress the intrarenal collecting system before injecting contrast. retrograde ureteropyelography was then performed. The angiographic catheter was exchanged over an Amplatz guide-wire for a 7F Arrow sheath through which a 6F Vista bright tip guiding catheter was placed, (55 cm, 0.070 I.D. (1.8 mm), hockey stick, renal double curve and multipurpose shapes according to the anatomy of the patient), manufactured by Cordis Corporation , Miami, Florida 33102-5700, USA. Piranha ureteroscopic biopsy forceps with smooth edged jaws, working length 115 cm, jaw outside diameter 1.0 mm, required working channel 1.1 mm, Boston Scientific, One Boston Place, Natick, MA 01760-1537, USA, directed by the guiding catheter were used to take biopsies of the UUT lesion. A ureteric stent was not routinely placed at the end of the procedure.

3.1 Results

140 patients were referred for retrograde ureteropyelography with a view to RGB, following CT urography for haematuria (Figure 29).

Figure 29. Flow diagram for RUP-guided biopsy (RGB)



Abbreviations: CT computed tomography; RGB, retrograde ureteropyelography-guided biopsy; RUP, retrograde ureteropyelography, UTUC, upper urinary tract urothelial carcinoma; RNU, radical nephroureterectomy.

Of the 140 patients, 7 were cancelled before proceeding to retrograde ureteropyelography. Of 133 patients in which retrograde ureteropyelography was attempted, there were 94 male and 39 females, age range 40.7 years to 90.3 years, average 70.9 years. Retrograde ureteropyelography was positive for UTUC in 89 and negative for UTUC in 38 patients. There were 6 technical failures of retrograde ureteropyelography due to non visualization of the ureteric orifice and these were classified as retrograde ureteropyelography positive results as clinically the patients were treated as being retrograde ureteropyelography positive in that they required further tests. The reference standard consisted of histopathology results from surgically resected specimens and imaging and histopathology database follow-up.

Of the 89 retrograde ureteropyelography positive patients, excluding the 6 retrograde ureteropyelography technical failures, 87 underwent RGB. The RGB was not performed on 2 patients who were retrograde ureteropyelography positive and receiving warfarin anticoagulant therapy.

Of the 12 patients which were RGB non-diagnostic, 8 were UTUC positive, of which 3 were Grade 3, 5 were Grade 2 and 0 were Grade 1. 2 had no follow-up histopathology, 1 debris, 1 benign stricture.

11 patients were RGB negative, there were two benign strictures, one giant papilla, one stones in a calyceal diverticulum, one chronic obstructive pyelonephritis, one UTUC, one TB, amyloid, renal cell carcinoma, urothelial metastatic renal cell carcinoma, one prostate metastases.

Of the 64 patients with RGB positive results for UTUC, 52 were confirmed positive by histopathology following radical nephroureterectomy, in the remaining 12 patients treatment was non-operative.

Of the 52 patients positive for UTUC on histopathology from both RGB and radical nephroureterectomy: RGB correctly determined grade in 41 (79%), undergraded in 8 (15%) and overgraded in 3 (6%) of cases (Table 31).

One patient required ureteric stent placement later the same day for clot colic. There were no complications requiring further intervention.

Table 31. Correlation between histopathological grade of retrograde ureteropyelography-guided biopsy and surgically resected specimen

n = 52	Grade of surgically resected specimen		
	3	**2**	**1**
Grade of RGB 3	**23**	1	0
2	2	**14**	2
1	1	5	**4**

Abbreviations: RGB, retrograde ureteropyelography-guided biopsy

Key:	**Undergraded**	**Correctly graded**	**Overgraded**

3.1 Discussion

CT urography is the preferred imaging examination for diagnosing UTUC and bladder cancer (Cowan 2012, Blick et al 2011). CT urography was validated for diagnosing UTUC (Cowan et al., 2007) (Wang et al., 2009) (Maheshwari et al., 2010) (Jinzaki et al., 2011).

False positives for UTUC found by CT urography are of concern to the urologist who clearly does not wish to perform a nephroureterectomy for non-malignant disease. False positive diagnoses for UTUC are listed (Table 30) and include benign tumours such as urothelial polyps, nephrogenic adenomas, clot, debris, flow voids, ureteritis cystica, amyloid and vascular indentations.

Biopsy of a ureteral mass using 7F flexible-shaft grasping forceps was first reported by Meranze et al in 1982, (Meranze, Pollack, & Banner, 1982) . They describe a technique in which a guidewire, a 5F ureteral catheter and a piece of 8F catheter tubing placed coaxially over the 5F catheter are placed by the urologist in theatre. The patient was then transferred to the fluoroscopy suite where the 5F ureteral catheter and guidewire are removed and replaced by the 7F biopsy forceps. The technique described involved the patient visiting theatre and the fluoroscopy suite and there was limited directional control of the grasping forceps by the 8F catheter tubing. Since the original report, there have been considerable developments in catheters, guidewires and grasping forceps providing greater control and smaller F sizes allowing easier insertion into the ureter. Also using a flexible cystoscopy and fluoroscopic guidance a technique for retrograde ureteropyelography and stent placement and removal has been described by the authors team. The technique is performed on an outpatient basis under sedoanalgesia (McFarlane et al 2001) which allows interventional ureteric procedures to be performed in an interventional radiology suite without the need for a general anaesthetic, an operating theatre or patient transfer from theatre to a fluoroscopy room.

3.1 Conclusions

If CT urography demonstrates an UTUC then RGB may be performed to provide histological confirmation of the diagnosis prior to radical nephroureterectomy. Using this technique false positive diagnoses for UTUC may be avoided, unnecessary nephrectomy prevented in cases of benign disease mimicking malignancy and information obtained relating to tumour grade which may be of use if nephron sparing treatments are considered.

RGB may be used as the first-choice method for histopathological diagnosis of UTUC.

Conclusion

Recommendations for the NHS

This thesis advocates the use of a one-stop strategy for the haematuria clinic with same day clinical consultation, CT urography and flexible cystoscopy. The main advantage of using high-tech imaging as a first-line test combined with a one-stop service is rapid and accurate diagnosis which has the potential to improve prognosis.

The high diagnostic accuracy of unenhanced-phase CT urography for stones, nephrographic-phase CT urography for renal masses is already established. This thesis provides evidence supporting the use of the excretory-phase CT urography for diagnosing urothelial cancer. The high diagnostic accuracy compared with other techniques, makes CT urography the preferred initial imaging investigation for patients presenting with haematuria.

To ensure optimization of CT urography technique and maximum diagnostic accuracy, attention to detail of the CT urography method is important. By careful scrutiny of the indications and technique, the radiation dose of CT urography may reach an acceptable range for those patients with haematuria who are at high risk of bladder cancer and UTUC.

For patients at high risk for bladder cancer and UTUC, CT urography should be used as a triage test before cystoscopy and as the initial imaging test for examination of the upper urinary tract.

As the positive predictive value of CT urography for UTUC is low, UTUC diagnosed with CT urography should be biopsied by ureteroscopy or retrograde ureteropyelography-guided for histopathological confirmation of the diagnosis before proceeding to surgery.

Future developments

Teaching radiologists to read CT urography

Misdiagnosis due to reader error is an important factor limiting diagnostic accuracy. Participation at courses and lectures and reading papers and articles on the subject is helpful to promote an understanding of the technique, but cannot be a substitute for experience in reading CT urograms in a real clinical situation. A formative teaching program simulating clinical reporting is suggested as the preferred method of teaching radiologists to read CT urograms and to reduce reader error. Such programmes exist for CT colonography (Dachman et al., 2008) and are likely to be an important future development in the field of CT urography as radiologists performance becomes more intensely scrutinised.

Use of a template will also assist in promoting a methodical approach to reporting and recording. An example of such a template is provided on the adjacent page.

Figure 30. An example of a CT urography reporting template

ID:		**DOB:**	
History:		**DOE:**	
		Age:	
		Sex:	
Radiologist:		**Time started:**	
Today's date:		**Time finished:**	

SCORE	**OPACIFICATION**			**DISEASE**	**R 0 1 2**	**L 0 1 2**	**SIGNS**
	ExPh1 0 1 2	**ExPh2 0 1 2**	**Sum 0 1 2**	Kid:			
R-CS				CS:			
R-AbU				AbU:			
R-PelU				PelU:			
R-HN (y/n)				Bladder			
R-HU (y/n)							
L-CS				Lymph-adenopathy			
L-AbU				Bones			
L-PelU				Adrenal			
L-HN (y/n)				Prostate			
L-HU (y/n)							
Bladder				Other Disease			
Diagnosis:							
Notes:							

Abbreviations: ExPh1, excretory-phase 1; ExPh2, excretory-phase 2; Sum, overall score.
Reducing misdiagnosis due to reader error by introduction of an innovative teaching programme designed to simulate clinical reporting and provide formative assessment

MR urography

MR urography has some advantages over CT urography because it does not use ionizing radiation, but currently the spatial resolution of MR urography falls below CT urography which is important when looking for small urothelial lesions in the upper urinary tract (Nolte-Ernsting, Staatz, Tacke, & Gunther, 2003) (Leyendecker, Barnes, & Zagoria, 2008) (Takahashi et al., 2008) (Takahashi et al., 2010b) . MR urography is usually reserved for patients with a contra-indication to iodine based CM or radiation. Occasionally it is used as a problem solving tool (Silverman et al., 2009). New developments in MRI technology which may solve these issues are awaited.

Dual-energy CT

The basic principle of dual-energy CT (DECT) is the acquisition of datasets from the same anatomical location at different kVp values, usually 80 and 140 kVp (Karcaaltincaba & Aktas, 2011) (Hartman et al., 2012) (Coursey et al., 2010) (Kaza et al., 2012) (Kaza, Platt, & Megibow, 2013). The principles of DECT were first described over 30 years ago, but recent developments in hardware design allow simultaneous acquisition, eliminating the problem of misregistration. Applications of the technique are based on the differential x-ray attenuation of different tissues at different photon energies. Clinical applications featured in current research include renal stone characterization, renal mass evaluation, urinary stone detection in iodinated solution and urothelial tumour detection (Hartman et al., 2012).

The ability of DECT to differentiate different types of tissue or material within the body allows datasets to be reconstructed with the removal of various materials. The subtraction of iodine from contrast-enhanced DECT images to produce virtual unenhanced (VUE) images could potentially replace true unenhanced (TUE) images for examinations requiring an unenhanced series of images to make the diagnosis, e.g. the characterization of renal and adrenal masses. The primary advantage is reduction in patient radiation dose by removing the unenhanced-phase from the multiphase examination. In CT urography for haematuria, an unenhanced-phase is needed in this examination to evaluate for fat, calcifications and stones. An unenhanced-phase is also needed for estimation of enhancement of masses of the kidney and collecting system.

Using VUE images instead of a TUE images, the mean dose may be reduced by approximately 35% to (Sahni, Shinagare, & Silverman, 2013) (Ascenti et al., 2013).

The sensitivity for detection of calculi on the VUE images of CT urography, depends on the size of the calculi and the iodine concentration within the collecting system (Takahashi et al., 2010a) (Moon, Park, Kim, & Park, 2012). Takahashi et al. reported an overall sensitivity of 0.63 for detection of urinary tract stones on VUE images generated from pyelographic dual source dual energy CT. If the data is stratified by stone size, 79% of stones greater than 3 mm and 29% of stones less than 3 mm were detected. Others have reported similar results (Moon et al., 2012). The lower sensitivity of VUE images for detection of small calculi is due to higher image noise on the VUE compared with TUE images and "over-subtraction" of the surrounding iodine pixels. A TUE examination may be required if the image quality of VUE images are poor (Takeuchi et al., 2012).

Dual energy CT is currently being evaluated in clinical practice, which may lead to reduction in patient radiation dose (Shinagare, Sahni, Sadow, Erturk, & Silverman, 2011) (Coursey et al., 2010). Single-phase DECT urography with synchronous nephrographic-excretory-phase enhancement represents an "all-in-one" approach, which enables detection of urinary stones, accurate distinction of enhancing from non-enhancing renal masses and identification of urothelial neoplasms, with a radiation dose saving of up to 45% (Ascenti et al., 2013). Results from further work are awaited.

Diffusion-weighted MRI for diagnosing bladder cancer and upper urinary tract urothelial cancer

MRI has the potential to offer functional information through pulse sequences such as diffusion-weighted MRI (DW MRI) and dynamic contrast enhanced MRI (DCE MRI).

Diffusion-weighted MRI is a noninvasive imaging technique that showing promise for early diagnosis and localisation of tumours by detection of early microstructural changes. It also has potential for predicting and monitoring early evaluation of treatment response (Thoeny & Ross, 2010). It is a topic of considerable current interest and there have been a number of recent reviews (Thoeny, Forstner, & De Keyzer, 2012).

Attempts have been made to correlate quantitative DW MRI parameters with histological grades of prostate and bladder tumours (Takeuchi et al., 2009).

DW MRI has a short acquisition time which allows it to be added to routine imaging protocols without significant time penalty. It is particularly useful in patients with contraindications to intravenous gadolinium-based contrast agents.

Technical aspects of diffusion-weighted MRI

DWI is a low spatial resolution MRI sequence that depicts molecular diffusion, which is Brownian motion of free water molecules (protons) in biological tissues (Le et al., 1988). Nearly all clinically available MRI systems have the capability of performing DWI examinations in addition to standard MRI.

Image interpretation

Image analysis is performed qualitatively by means of visual assessment and quantitatively by means of Apparent Diffusion Coefficient (ADC) measurements. First line image interpretation is usually performed with visual assessment of the SI on images acquired at high b values and their corresponding ADC maps. Typical malignant lesions display hyperintensity on images acquired at b values of 800 – 1000 s/mm^2 and corresponding low ADC values on the ADC maps, due to impaired diffusion caused by hypercellularity of the lesion. These solid lesions usually can be distinguished from cystic and necrotic components, which display intermediate or low SI on images acquired at high b values but show high ADC values on the corresponding ADC maps. Because oedema or inflammation can sometimes be mistaken for tumour tissue and manifest as high SI on high b value images due to the T2 shine-through effect, the distinction between tumour and inflammation or oedema is only possible based on assessment of the ADC map, where a high ADC is present in both oedema and inflammation but not in tumours.

An abscess can also manifest as high SI lesion on high b value image with low ADC on the corresponding ADC map probably due to the high viscosity of the abscess. Clinical correlation is therefore important to correctly interpret DWI.

Diffusion-weighted MRI for bladder cancer

Several studies have investigated the use of DW MRI for diagnosis, staging, prediction of histological differentiation (grade), and assessment of treatment response.

Using DWI, bladder cancer can be detected by visual assessment as high SI lesions on high b value images (e.g. 800 – 1000 s/mm^2) with a distinct contrast to the low SI of urine in the filled bladder and the low SI of the surrounding fat, where as the bladder wall usually shows intermediate SI on high b value images and ADC maps.

On corresponding ADC maps, BCa displays low SI in contrast to the high SI of urine, allowing delineation of the tumour and quantification by means of ADC value.

Several studies have demonstrated the potential of DW MRI for staging bladder cancer, but more work needs to be done to determine if DWI can replace DCE MRI in this clinical setting as the results are conflicting (El-Assmy et al., 2009) (Takeuchi et al., 2009) (Watanabe et al., 2009).

In a prospective study comparing T2-weighted images and DW images for diagnosing bladder cancer, DWI was shown to have slightly higher diagnostic accuracy (Abou-El-Ghar, El-Assmy, Refaie, & El-Diasty, 2009).

The aggressiveness of urothelial cancer is defined according to the histopathological grade of the tumour. Attempts have been made to define the tumour grade by using DWI. The mean ADC (b values 0 and 1000 sec/mm^2) of G3 bladder tumours has been reported to be significantly lower ($P < 0.01$) than that of G1 and G2 tumours (Takeuchi et al., 2009).

These initial results are promising, though currently the use of DW MRI for bladder cancer detection and staging is limited to the research setting (Bouchelouche, Turkbey, & Choyke, 2012).

Diffusion-weighted MRI for detection and characterization of UTUC

Yoshida et al report on a selected series of 76 patients suspected of having UTUC, of which 16 had previously positive CT imaging findings. They suggest that T1 and T2 weighted imaging and DW MRI are sufficient to diagnose UTUC and that DCE MRI does not significantly improve diagnostic accuracy over and above the other three sequences. They conclude that DW MRI provides accurate information for the diagnosis of UTUC in a noninvasive manner. The addition of DW MRI to T1 and T2 weighted imaging increases

the sensitivity of MRI in identifying UTUC. Lastly they suggest that DW MRI could be a useful adjunct to preoperative assessment of biological aggressiveness.

Sufana Iancu et al performed a retrospective study on a selected series of patients with visible haematuria and suspected UTUC from previous CT urography. They confirmed that the mean ADC value of UTUCs was significantly lower than normal renal parenchyma as found by other authors (Yoshida et al., 2008) (Takeuchi, Matsuzaki, Kubo, & Nishitani, 2008) (Akita et al., 2011) (Sufana Iancu et al., 2013). The study also demonstrated the limitation of the DW MRI technique in depicting carcinoma in situ and small lesions less than or equal to 5 mm in diameter, a feature also reported by Nishizawa et al. (Nishizawa et al., 2010). Due to a lack of specificity they recommended DW MRI to be used in addition to standard MR urography sequences. They found no significant differences in the ADC values between muscle invasive versus non-muscle invasive tumours, locally advanced versus organ confined and between G1, G2 or G3 tumours. The authors recommended that the association between ADC value and tumour grade and stage need to be further investigated in a large prospective multi-institutional study (Sufana Iancu et al., 2013). As the pathological stage of UTUC, needed to differentiate between non-muscle invasive and muscle-invasive disease, cannot be predicted accurately using endoscopic biopsy, DW MRI potentially might be able to achieve improved pre-operative staging in future.

Diffusion-weighted MRI for detection of pelvic lymph node metastases

CT is not able to detect micrometastases in normal sized nodes. Recent MRI studies involving superparamagnetic particles of iron oxide or DW MRI sequences show promising results. A significant difference in ADC values for metastatic and non-metastatic lymph nodes has been demonstrated (Papalia et al., 2012). Results from further work are awaited.

Potential of high-Z contrast agents for CT

In clinical CT, conventional iodine-based CM are widely used to amplify the x-ray attenuation of vascular structures or the urinary tract, leading to an increased contrast in the reconstructed image, assisting diagnosis. Tube voltages normally range from 80 to 140 kV depending on patient size and scan protocol. Depending on the filtration used

with the x-ray tube, the mean energies of the resulting x-ray spectra, range from around 55 keV to over 110 keV for 140 kV spectra with strong added filtration, e.g. the additional tin filter commonly used for better spectral separation in dual-source dual-energy CT. Among the reasons for the common use of iodine-based substances are their good body-tolerance, water solubility and the relatively high mass attenuation coefficient of iodine in the energy range used in clinical contrast enhanced CT. Elements with higher atomic number and a higher K-edge may provide greater attenuation of the x-ray spectra used in clinical CT. Heavy metals such as ytterbium, tungsten or gold may surpass iodine in terms of x-ray attenuation for photon energies in the respective spectra. A list is given (Table 32).

Table 32. List of simulated pure high-Z materials

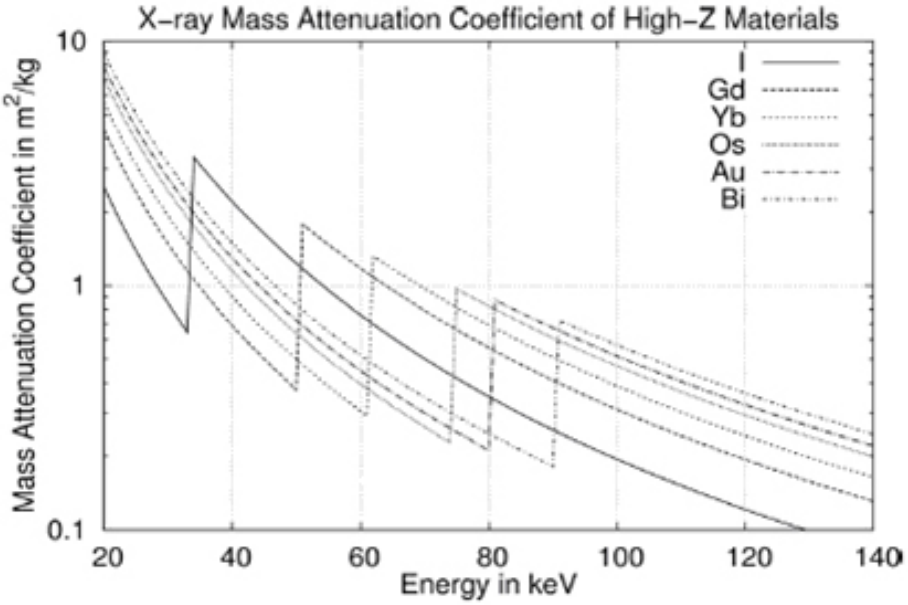
Material	Symbol	Atomic number	Concentration (mg/ml)	K-edge energy (keV)
Iodine	**I**	53	10	33.2
Gadolinium	**Gd**	64	10	50.2
Holmium	**Ho**	67	10	55.6
Ytterbium	**Yb**	70	10	61.3
Hafnium	**Hf**	72	10	65.3
Tungsten	**W**	74	10	69.5
Osmium	**Os**	76	10	73.9
Gold	**Au**	79	10	80.7
Bismuth	**Bi**	83	10	90.5

Figure 31 shows a plot of the mass attenuation coefficient versus energy of various materials. For energies above the K-edge energy of a given high-Z element, these elements exhibit a mass attenuation coefficient much higher than iodine.

For most filtrations and scan protocols used in clinical CT, CM based on high-Z materials may yield an increased contrast-to-noise ratio at equal dose which would allow for significant dose reduction when aiming for equal constant contrast-to-noise ratio.

As many of these elements are toxic or difficult to include in biocompatible chemical complexes, there are currently no approved CM available for clinical CT that are primarily based on high-Z materials. Recent research in atomic nanostructures such as carbon nanotubes, fullerenes and nanoparticles is opening up new possibilities, e.g. biocompatible container structures that are able to hold relatively large amounts of heavy elements. This approach has already been successfully used in the field of contrast agents for MRI to contain gadolinium atoms inside carbon nanotubes. Further examples are the use of gold nanoparticles for visualisation of atherosclerotic lesions and other diagnostic applications are proposed. The use of tungsten and bismuth nanoparticles is also proposed. In future wide-spread use of high-Z elements for CT contrast agents should be possible provided the limitations mentioned above are overcome (Nowak, Hupfer, Brauweiler, Eisa, & Kalender, 2011).

Figure 31. Mass attenuation coefficients of iodine and a selection of high-Z materials



Positron emission tomography / computed tomography (FDG PET / CT)

PET/CT with 18F-fluorodoxyglucose (18F-FDG) is an established imaging technique for pre-operative cancer staging. 18F-FDG is a marker of increased glucose uptake. Many malignant neoplasms and metastases have enhanced glucose utilisation and hence increased glucose uptake. 18F-FDG is taken up within tumour cells but not fully metabolized resulting in intracellular accumulation. PET imaging in combination with CT offers high sensitivity examination for metabolic activity with precise anatomical localization. There have been very few reports on the use of 18F-FDG PET/CT to image bladder cancer, mainly because the urinary excretion of 18F-FDG interferes with the ability to distinguish wall activity from luminal activity. Other tracers like 11C-choline, 11C-acetate and 11C-methionine, all have minimal urinary excretion, have been used for PET/CT in bladder cancer.

In a meta-analysis by Lu et al. (Lu et al., 2012) the pooled sensitivity and specificity of 18F-FDG PET or PET/CT for staging or restaging metastatic lesions of bladder cancer were 0.82 (95%CI:0.72-0.89) and 0.89 (95%CI:0.81-0.95) respectively. The authors conclude, that the results suggest the diagnostic accuracy of 18F-FDG PET or PET/CT is sufficient to warrant its use in staging or restaging (metastatic) lesions of urinary BCa. Due to the small number of patients and limited number of studies analysed, the diagnostic capability of 18F-FDG PET or PET/CT in detection of primary bladder cancer wall lesions could not be assessed. Due to urinary excretion of 18F-FDG it is difficult to evaluate lesions in the bladder and involvement of the detrusor muscle. 18F-FDG PET/CT is not likely to play an important role in diagnosing and T-staging of bladder cancer in the future. 18F-FDG PET/CT may be used for staging and restaging of metastatic disease.

11C-choline PET/CT is reported to have no advantage compared with 18F-FDG PET/CT in the detection of metastatic bladder cancer (Golan, Sopov, Baniel, & Groshar, 2011) and no advantage compared with CT alone (Maurer et al., 2012). The use of other tracers such as 11C-methionine and 11C-acetate have been reported (Ahlstrom et al., 1996)(Schoder et al., 2012). The role of both 11C-methionine and 11C-acetate in bladder cancer needs to be elucidated further in larger prospective trials (Bouchelouche et al., 2012).

Cost-effective analysis

Medical imaging continues to be one of the fastest growing fields in medicine. High-tech modalities such as multidetector CT, combined positron emission tomography and CT (PET / CT) and MRI are undergoing rapid developments and increasing demand. Increased imaging costs, now exceed $100 billion dollars per year in the USA (Iglehart, 2006). This has led to the recognition of the need to consider cost in the medical decision making process and to apply new technologies in a cost-effective manner.

Cost-effective analysis (CEA) is a method of economic evaluation in which costs and outcomes of a program and at least one alternative are compared (Otero, Rybicki, Greenberg, & Neumann, 2008).

Without economic analyses, finite health care resources are likely to be allocated inefficiently (Kielar, El-Maraghi, & Carlos, 2007).

For many technology assessments the randomized controlled trial (RCT) is the tool of choice. RCTs have traditionally been used to evaluate the clinical effects of new technologies or procedures (Gazelle, McMahon, Siebert, & Beinfeld, 2005).

When properly designed and conducted, RCTs can provide useful data for decision makers. RCTs will always be a critically important component of technology assessment activities because, if conducted appropriately, they are less prone to systematic bias. However, RCTs may be inappropriate or impractical for answering many of the questions now faced by health care decision makers. In addition to the long-appreciated difficulty of translating the observed efficacy of a technology from an RCT into real world effectiveness, evaluating the costs of therapies may also be difficult in the context of an RCT. For example, the technologies being evaluated may be new enough that pricing does not reflect the costs that might be seen in a competitive marketplace. Clinical trials are best suited for detection of differences in treatment effect, as reflected in variables such as objective response rates or survival. In addition, the trials are generally performed with ideal circumstances by expert clinicians who practice in the best hospitals. This means that prospective cost assessments, if performed, may not be able to be directly applicable to routine health care and may be even less applicable to other physicians, clinical settings, countries, or health care systems. Learning curve effects may also falsely increase the apparent cost of the new technologies (Gazelle et al., 2005).

Conducting RCTs is also expensive and time-consuming: The average phase III trial is estimated to cost $86 million (DiMasi, Hansen, & Grabowski, 2003). As a result, the trials are generally limited to fairly short time horizons and limited sample sizes. It may be impossible to draw conclusions about narrowly defined groups of patients and include all conditions for which the procedures might be performed. Randomized trials are not particularly well suited for use in the evaluation of diagnostic imaging tests. Withholding a noninvasive imaging test that might provide useful diagnostic information creates difficult ethical dilemmas. RCTs also cannot be used to examine the myriad of possible combinations of tests or threshold values that might be performed in a given clinical situation, nor can they be used to predict the usefulness of a test, should treatments for the condition improve. Diagnostic technologies differ in many ways from therapeutic medical technologies. Most important, diagnostic technologies do not generally directly affect long-term patient outcomes. Instead, the results of diagnostic tests can influence the care of patients, and in that way, they may affect long-term outcomes. Because of this, the benefits associated with the use of a specific diagnostic technology will depend on the performance characteristics (e.g. sensitivity and specificity) of the test and on other factors, such as the prevalence of disease and the effectiveness of available treatments for the disease in question. The fact that diagnostic tests affect short-term, or "surrogate," outcomes rather than long-term patient outcomes makes the evaluation of these tests more complicated than the evaluation of therapeutic technologies (Gazelle et al., 2005).

In 2006, Rodgers et al published a health technology assessment: Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation (Rodgers et al., 2006b). The purpose of which was to determine the most effective diagnostic strategy for the investigation of nonvisible and visible haematuria in adults. The authors concluded that there was insufficient data currently available to derive an evidence-based algorithm of the diagnostic pathway for haematuria.

A number of different imaging modalities were evaluated as tests to detect different or general underlying causes of haematuria. There was overlap between conditions targeted by the different imaging modalities. The evidence from studies included in the review was insufficient to draw any firm conclusions regarding the diagnostic accuracy of imaging studies in determining the cause of haematuria. Economic evaluations suggested that ultrasound followed by CT for patients with a negative test, but found to have persistent haematuria during follow-up screening, may be a cost-effective

approach. In the absence of firm supporting evidence, the decision on whether or not to conduct imaging investigations should be made on an individual patient basis. Research into the cumulative diagnostic value of imaging investigations as well as their effects on long-term patient outcome is urgently required.

The review did not include a radiologist as one of the authors nor did it focus on CT urography to any great extent. Although published in 2006, only a very limited number of references having CT urography as their subject were cited. Much work relating to CT urography has since been published, after the review was completed.

From a clinical imaging perspective the results of the review were of little help in suggesting which diagnostic imaging strategies should be used, as it was recommended that imaging investigations should be conducted on an individual basis.

In future, economic analyses for diagnostic imaging technologies should be performed in a timely way, so that the results are available before diagnostic tests are adopted into routine clinical practice. Exactly how this is done is an unsolved challenge, but one that is important to address so diagnostic imaging techniques are used for maximum patient benefit.

CT urography with image acquisition at 60-70 s post-injection of contrast media

A small number of studies have looked at the diagnostic accuracy CT urography, with images acquired at 60–70 s following administration of intravenous contrast media, for diagnosing UTUC (Metser et al., 2012) (Kupershmidt, Margolis, Jang, Massey, & Metser, 2011) and bladder cancer (Park, Kim, Lee, Choi, & Cho, 2007) (Jinzaki et al., 2007) (Kim et al., 2004).

The purpose of the prospective study by Metser et al. was to compare contrast material – enhanced CT urography 60 seconds after injection of contrast material (urothelial-phase) after intravenous administration of a diuretic with the standard 5 minute delayed excretory-phase in a high risk population for upper tract tumours.

Patients were given 750 ml of water orally, 30-45 minutes before the contrast media injection and 10 mg of furosemide intravenously, 8 minutes beforehand. Images were acquired in the supine position. The patients were not exercised or rolled. Results from the study showed that more than 20% of ureteric segments above the iliac crest and 25% - 30% of ureteric segments below the iliac crest were less than 50% opacified at the time of the excretory-phase imaging. Such poor opacification of the ureter may impair

detection of UTUC and shows the technique used here to be suboptimal. Other results from the study show that tumour detection was as good or better using the 60 s-phase compared with the excretory-phase for diagnosing UTUC. The authors concluded that a single phase protocol may be sufficient for initial upper tract examination and also for surveillance. Also they found that adoption of a single CT urography 60 s-phase protocol has a higher detection rate for both UTUC and bladder cancer than excretory-phase CT urography and results in decreased examination time and decreased radiation exposure compared with multiphase techniques.

The fundamental problem with the study is that an optimised 60 s-phase examination was compared with a suboptimal excretory-phase study, as patients were not exercised or rolled and the time delay of 5 minutes was too short to provide optimal upper tract opacification.

Acquiring CT urography images at 60 s has advantages over 750 s in terms of increased patient throughput but compromises on diagnostic accuracy, because of decreased opacification (Caoili, Inampudi, Cohan, & Ellis, 2005).

More work needs to be done comparing fully optimised 60 – 70 s-phases with fully optimised CT excretory-phase imaging at 750 – 900 s in patients with a high prevalence of UTUC.

Final conclusion

CT urography, including unenhanced, nephrographic and excretory-phases, is recommended as the initial diagnostic imaging test before cystoscopy for adult patients presenting with visible haematuria at high risk for stones, renal cell carcinoma, UTUC and bladder cancer. A same day, one stop clinic minimizes the time from presentation to diagnosis. The development of CT urography for investigating haematuria originally began with hypotheses, then pilot study presentations followed by published papers. Some of this work has been incorporated into guidelines of the European Society of Urogenital Radiology (Van Der Molen et al., 2008) and the European Association of Urology (Stenzl et al., 2009) (Roupret et al., 2013) (Ljungberg et al., 2010). Ultimately a sea change in clinical practice is hoped for in order to improve the quality of the service available to patients and improve patient outcomes (Berwick, 2013) (Seddon, 2010).

References

Abou-El-Ghar, M. E., El-Assmy, A., Refaie, H. F., & El-Diasty, T. (2009). Bladder cancer: diagnosis with diffusion-weighted MR imaging in patients with gross hematuria. *Radiology, 251,* 415-421.

Ahlstrom, H., Malmstrom, P. U., Letocha, H., Andersson, J., Langstrom, B., & Nilsson, S. (1996). Positron emission tomography in the diagnosis and staging of urinary bladder cancer. *Acta Radiol, 37,* 180-185.

Akita, H., Jinzaki, M., Kikuchi, E., Sugiura, H., Akita, A., Mikami, S. et al. (2011). Preoperative T Categorization and Prediction of Histopathologic Grading of Urothelial Carcinoma in Renal Pelvis Using Diffusion-Weighted MRI. *American Journal of Roentgenology, 197,* 1130-1136.

Albani, J. M., Ciaschini, M. W., Streem, S. B., Herts, B. R., & Angermeier, K. W. (2007). The Role of Computerized Tomographic Urography in the Initial Evaluation of Hematuria. *Journal of Urology,* 644-648.

Altman, D. G., Machin, D., Bryant, T. N., & Gardener, M. J. (2000). *Statistics with Confidence*. (2 nd ed.) London: BMJ Books.

Anderson, E. M., Murphy, R. M., Rennie, A. T. M., & Cowan, N. C. (2006). Multidetector computed tomography urography (MDCTU) for diagnosing urothelial malignancy. *Clinical Radiology, 62,* 324-332.

Ascenti, G., Mileto, A., Gaeta, M., Blandino, A., Mazziotti, S., & Scribano, E. (2013). Single-phase dual-energy CT urography in the evaluation of haematuria. *Clin Radiol, 68,* e87-e94.

Bae, K. T. (2010). Intravenous Contrast Medium Administration and Scan Timing at CT: Considerations and Approaches1. *Radiology, 256,* 32-61.

References

Berwick, D. M. (2013). *Improving the safety of patients in England.* National advisory group on the safety of patients in England.

Blick, C. G., Nazir, S. A., Mallett, S., Turney, B. W., Onwu, N. N., Roberts, I. S. et al. (2011). Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. *BJU Int.,* 84-94.

Bosniak, M. A. (1991). The small (less than or equal to 3.0 cm) renal parenchymal tumor: detection, diagnosis, and controversies. *Radiology, 179,* 307-317.

Bossuyt, P. M., Irwig, L., Craig, J., & Glasziou, P. (2006). Comparative accuracy: assessing new tests against existing diagnostic pathways. *British Medical Journal, 332,* 1089-1092.

Botteman, M. F., Pashos, C. L., Redaelli, A., Laskin, B., & Hauser, R. (2003). The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics., 21,* 1315-1330.

Bouchelouche, K., Turkbey, B., & Choyke, P. L. (2012). PET/CT and MRI in Bladder Cancer. *J Cancer Sci.Ther., S14*.

Brenner, D. J. & Hall, E. J. (2007). Computed tomography--an increasing source of radiation exposure. *N.Engl J Med., 357,* 2277-2284.

Brenner, D. J., Shuryak, I., & Einstein, A. J. (2011). Impact of Reduced Patient Life Expectancy on Potential Cancer Risks from Radiologic Imaging. *Radiology, 261,* 193-198.

Brien, J. C., Shariat, S. F., Herman, M. P., Ng, C. K., Scherr, D. S., Scoll, B. et al. (2010). Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. *J Urol, 184,* 69-73.

Bromage, S. J., Liew, M. P. C., Moore, K. C., Raju, B., & Shackley, D. C. (2012). The economic implications of unsuspected findings from CT urography performed for haematuria. *British Journal of Radiology*.

Burke, D. M., Shackley, D. C., & O'Reilly, P. H. (2002). The community-based morbidity of flexible cystoscopy. *BJU Int., 89,* 347-349.

Cancer Research UK. (15-3-2010). UK Bladder Cancer Statistics.
Ref Type: Online Source

Caoili, E. M., Cohan, R. H., Inampudi, P., Ellis, J. H., Shah, R. B., Faerber, G. J. et al. (2005). MDCT Urography of Upper Tract Urothelial Neoplasms. *AJR Am.J.Roentgenol., 184,* 1873-1881.

Caoili, E. M., Cohan, R. H., Korobkin, M., Platt, J. F., Francis, I. R., Faerber, G. J. et al. (2002). Urinary tract abnormalities: initial experience with multi-detector row CT urography. *Radiology, 222,* 353-360.

Caoili, E. M., Inampudi, P., Cohan, R. H., & Ellis, J. H. (2005). Optimization of Multi-Detector Row CT Urography: Effect of Compression, Saline Administration, and Prolongation of Acquisition Delay. *Radiology, 235,* 116-123.

Cha, E. K., Shariat, S. F., Kormaksson, M., Novara, G., Chromecki, T. F., Scherr, D. S. et al. (2012). Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. *Eur.Urol, 61,* 818-825.

Chen, G. L., El-Gabry, E. A., & Bagley, D. H. (2000). Surveillance of upper urinary tract transitional cell carcinoma: the role of ureteroscopy, retrograde pyelography, cytology and urinalysis. *J Urol, 164,* 1901-1904.

Chow, L. C., Kwan, S. W., Olcott, E. W., & Sommer, G. (2007). Split-Bolus MDCT Urography with Synchronous Nephrographic and Excretory Phase Enhancement. *AJR Am.J.Roentgenol., 189,* 314-322.

Chow, L. C. & Sommer, F. G. (2001). Multidetector CT Urography with Abdominal Compression and Three-Dimensional Reconstruction. *AJR Am.J.Roentgenol., 177,* 849-855.

Chow, W. H., Dong, L. M., & Devesa, S. S. (2010). Epidemiology and risk factors for kidney cancer. *Nat Rev Urol, 7,* 245-257.

Clark, J. Y., Thompson, I. M., & Optenberg, S. A. (1995). Economic Impact of Urolithiasis in the United States. *The Journal of Urology, 154,* 2020-2024.

Clayman, R. V., Reddy, P., & Lange, P. H. (1984). Flexible fiberoptic and rigid-rod lens endoscopy of the lower urinary tract: a prospective controlled comparison. *J Urol, 131,* 715-716.

Cohan, R. H., Caoili, E. M., Cowan, N. C., Weizer, A. Z., & Ellis, J. H. (2009). MDCT Urography: Exploring a New Paradigm for Imaging of Bladder Cancer. *AJR Am.J.Roentgenol., 192,* 1501-1508.

Coursey, C., Nelson, R. C., Boll, D. T., Paulson, E. K., Ho, L. M., Neville, A. M. et al. (2010). Dual-Energy Multidetector CT: How Does It Work, What Can It Tell Us, and When Can We Use It in Abdominopelvic Imaging?1. *RadioGraphics, 30,* 1037-1055.

Cowan, N. C. (2012). CT urography for hematuria. *Nat Rev Urol, 9,* 218-226.

Cowan, N. C. & Crew, J. P. (2010). Imaging bladder cancer. *Curr.Opin.Urol, 20,* 409-413.

Cowan, N. C., Mallett, S., & Crew, J. P. (2011). Justification for using CT urography as the first-line diagnostic imaging test for investigating hematuria in patiets at high risk of upper urinary tract cancer. The Thirty-Sixth Scientific Assembly of the Society of Uroradiology, Carlsbad, Calfornia, U.S.A. -, 50. 20-3-2011.
Ref Type: Abstract

Cowan, N. C., Turney, B. W., Taylor, N. J., McCarthy, C. L., & Crew, J. P. (2007). Multidetector computed tomography urography (MDCTU) for diagnosing upper urinary tract tumour. *BJU International, 99,* 1363-1370.

Dachman, A. H., Kelly, K. B., Zintsmaster, M. P., Rana, R., Khankari, S., Novak, J. D. et al. (2008). Formative Evaluation of Standardized Training for CT Colonographic Image Interpretation by Novice Readers. *Radiology, 249,* 167-177.

Dillman, J. R., Caoili, E. M., & Cohan, R. H. (2007). Multi-detector CT urography: a one-stop renal and urinary tract imaging modality. *Abdominal Imaging, 32,* 519-529.

Dillman, J. R., Caoili, E. M., Cohan, R. H., Ellis, J. H., Francis, I. R., & Schipper, M. J. (2008). Detection of upper tract urothelial neoplasms: sensitivity of axial, coronal reformatted, and curved-planar reformatted image-types utilizing 16-row multi-detector CT urography. *Abdom.Imaging, 33,* 707-716.

DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics, 22,* 151-185.

Edwards, T. J., Dickinson, A. J., Natale, S., Gosling, J., & McGrath, J. S. (2006). A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU International, 97,* 301-305.

El-Assmy, A., Abou-El-Ghar, M. E., Mosbah, A., El-Nahas, A. R., Refaie, H. F., Hekal, I. A. et al. (2009). Bladder tumour staging: comparison of diffusion- and T2-weighted MR imaging. *Eur Radiol, 19,* 1575-1581.

Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M., & Boyle, P. (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol, 18,* 581-592.

Fielding, J. R., Silverman, S. G., Samuel, S., Zou, K. H., & Loughlin, K. R. (1998). Unenhanced helical CT of ureteral stones: a replacement for excretory urography in planning treatment. *American Journal of Roentgenology, 171,* 1051-1053.

Fowler, K. A., Locken, J. A., Duchesne, J. H., & Williamson, M. R. (2002). US for detecting renal calculi with nonenhanced CT as a reference standard. *Radiology, 222,* 109-113.

Fritz, G. A., Schoellnast, H., Deutschmann, H. A., Quehenberger, F., & Tillich, M. (2006). Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. *European Radiology, 16,* 1244-1252.

Gazelle, G. S., McMahon, P. M., Siebert, U., & Beinfeld, M. T. (2005). Cost-effectiveness Analysis in the Assessment of Diagnostic Imaging Technologies. *Radiology, 235,* 361-370.

Golan, S., Sopov, V., Baniel, J., & Groshar, D. (2011). Comparison of 11C-choline with 18F-FDG in positron emission tomography/computerized tomography for staging urothelial carcinoma: a prospective study. *J Urol, 186,* 436-441.

Gray Sears, C., Ward, J. F., Sears, S. T., Puckett, M. F., Kane, C. J., & Amling, C. L. (2003). Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. *Journal of Urology, 168,* 2457-2460.

Grossfeld, G. D., Litwin, M. S., Wolf, S. J., Hricak, H., Shuler, C. L., Agerter, D. C. et al. (2001a). Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association Best Practice Policy-Part 11: Patient evaluation, cytology, voided markers, imaging, cystscopy, nephrology evaluation, and follow-up. *Urology, 57,* 604-610.

Grossfeld, G. D., Litwin, M. S., Wolf, S. J., Hricak, H., Shuler, C. L., Agerter, D. C. et al. (2001b). Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association best practice policy-Part 1: definition, detection, prevelence, and etiology. *Urology, 57,* 599-603.

Grossfeld, G. D., Wolf, S. J., Litwin, M. S., Hricak, H., H, Schuer, C. L. et al. (2001c). Asymptomatic microscopic hematuria in adults: Summary of the AUA best practice policy recommendations. *American Family Physician, 63,* 1145-1154.

Hall, M. C., Womack, S., Sagalowsky, A. I., Carmody, T., Erickstad, M. D., & Roehrborn, C. G. (1998). Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology, 52,* 594-601.

Hartman, R., Kawashima, A., Takahashi, N., Silva, A., Vrtiska, T., Leng, S. et al. (2012). Applications of dual-energy CT in urologic imaging: an update. *Radiol Clin North Am, 50,* 191-205, v.

Hellawell, G. O., Cowan, N. C., Holt, S. J., & Mutch, S. J. (2002). A radiation perspective for treating loin pain in pregnancy by double-pigtail stents. *BJU International, 90,* 801-808.

Hendee, W. R., Becker, G. J., Borgstede, J. P., Bosma, J., Casarella, W. J., Erickson, B. A. et al. (2010). Addressing overutilization in medical imaging. *Radiology, 257,* 240-245.

Hofland, C. A. & Mariani, A. J. (2004). Is cytology required for a hematuria evaluation? *J Urol, 171,* 324-326.

Hollenbeck, B. K., Dunn, R. L., Ye, Z., Hollingsworth, J. M., Skolarus, T. A., Kim, S. P. et al. (2010). Delays in diagnosis and bladder cancer mortality. *Cancer, 116,* 5235-5242.

Iglehart, J. K. (2006). The new era of medical imaging--progress and pitfalls. *N Engl.J Med., 354,* 2822-2828.

Israel, G. M. & Bosniak, M. A. (2005). How I Do It: Evaluating Renal Masses. *Radiology, 236,* 441-450.

Jamis-Dow, C. A., Choyke, P. L., Jennings, S. B., Linehan, W. M., Thakore, K. N., & Walther, M. M. (1996). Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. *Radiology, 198,* 785-788.

Jinzaki, M., Matsumoto, K., Kikuchi, E., Sato, K., Horiguchi, Y., Nishiwaki, Y. et al. (2011). Comparison of CT Urography and Excretory Urography in the Detection and Localization of Urothelial Carcinoma of the Upper Urinary Tract. *AJR Am.J.Roentgenol., 196,* 1102-1109.

Jinzaki, M., Tanimoto, A., Shinmoto, H., Horiguchi, Y., Sato, K., Kuribayashi, S. et al. (2007). Detection of bladder tumors with dynamic contrast-enhanced MDCT. *AJR Am.J.Roentgenol., 188,* 913-918.

Johnson, M. I., Merrilees, D., Robson, W. A., Lennon, T., Masters, J., Orr, K. E. et al. (2007). Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. *BJU Int., 100,* 826-829.

Kalra, M. K., Maher, M. M., Toth, T. L., Hamberg, L. M., Blake, M. A., Shepard, J. A. et al. (2004). Strategies for CT Radiation Dose Optimization. *Radiology, 230,* 619-628.

Karcaaltincaba, M. & Aktas, A. (2011). Dual-energy CT revisited with multidetector CT: review of principles and clinical applications. *Diagn.Interv.Radiol, 17,* 181-194.

Katzberg, R. W. (1997). Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. *Radiology, 204,* 297-312.

Kawamoto, S., Horton, K. M., & Fishman, E. K. (2006). Opacification of the Collecting System and Ureters on Excretory-Phase CT Using Oral Water as Contrast Medium. *American Journal of Roentgenology, 186,* 136-140.

Kawashima, A., Vrtiska, T. J., LeRoy, A. J., Hartman, R. P., McCollough, C. H., & King, B. F. Jr. (2004). CT Urography. *RadioGraphics, 24,* 235-254.

Kaza, R. K., Platt, J. F., & Megibow, A. J. (2013). Dual-energy CT of the urinary tract. *Abdom.Imaging, 38,* 167-179.

Kaza, R. K., Platt, J. F., Cohan, R. H., Caoili, E. M., Al-Hawary, M. M., & Wasnik, A. (2012). Dual-Energy CT with Single- and Dual-Source Scanners: Current Applications in Evaluating the Genitourinary Tract. *RadioGraphics, 32,* 353-369.

Kekelidze, M., Dwarkasing, R. S., Dijkshoorn, M. L., Sikorska, K., Verhagen, P. C., & Krestin, G. P. (2010). Kidney and urinary tract imaging: triple-bolus multidetector CT urography as a one-stop shop--protocol design, opacification, and image quality analysis. *Radiology, 255,* 508-516.

Kelly, J. D., Fawcett, D. P., & Goldberg, L. C. (2009). Assessment and management of non-visible haematuria in primary care. *British Medical Journal, 338,* a3021.

Kemper, J., Regier, M., Stork, A., Adam, G., & Nolte-Ernsting, C. (2006). Multislice CT Urography (MSCTU): Evaluation of a Modified Scan Protocol for Optimized Opacification of the Collecting System. *Fortschr Röntgenstr, 178,* 531-537.

Khadra, M. H., Pickard, R. S., Charlton, M., Powell, P. H., & Neal, D. E. (1999). A prospective analysis of 1,939 patients with hematuria to evaluate current diagnostic practice. *Journal of Urology, 163,* 524-527.

Kielar, A. Z., El-Maraghi, R. H., & Carlos, R. C. (2007). Health-related quality of life and cost-effectiveness analysis in radiology. *Acad.Radiol, 14,* 411-419.

Kim, J. K., Park, S.-Y., Ahn, H. J., & et al (2004). Bladder cancer: analysis of multidetector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. *Radiology, 231,* 725-731.

Kim, S., Wang, L. L., Heiken, J. P., Siegel, C. L., Hildebolt, C. F., & Bae, K. T. (2008). Opacification of urinary bladder and ureter at CT urography: effect of a log-rolling procedure and postvoiding residual bladder urine volume. *Radiology, 247,* 747-753.

Knox, M. K., Cowan, N. C., Rivers-Bowerman, M. D., & Turney, B. W. (2008). Evaluation of multidetector computed tomography urography and ultrasonography for diagnosing bladder cancer. *Clinical Radiology, 63,* 1317-1325.

Knox, M. K., Rivers-Bowerman, M. D., Bardgett, H. P., & Cowan, N. C. (2010). Multidetector computed tomography with triple-bolus contrast medium administration protocol for preoperative anatomical and functional assessment of potential living renal donors. *European Radiology, 20,* 2590-2599.

Konety, B. R., Joyce, G. F., & Wise, M. (2007). Bladder and upper tract urothelial cancer. *J Urol, 177,* 1636-1645.

Kupershmidt, M., Margolis, M., Jang, H. J., Massey, C., & Metser, U. (2011). Evaluation of Upper Urinary Tract Tumors With Portal Venous Phase MDCT: A Case-Control Study. *American Journal of Roentgenology, 197,* 424-428.

Lang, E. K., Macchia, R. J., Thomas, R., Ruiz-Deya, G., Watson, R. A., Richter, F. et al. (2002). Computerized tomography tailored for the assessment of microscopic hematuria. *Journal of Urology, 167,* 547-554.

Le, B. D., Breton, E., Lallemand, D., Aubin, M. L., Vignaud, J., & Laval-Jeantet, M. (1988). Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology, 168,* 497-505.

Lee, S., Jung, S. E., Rha, S. E., & Byun, J. Y. (2012). Reducing radiation in CT urography for hematuria: Effect of using 100 kilovoltage protocol. *Eur.J Radiol, 81,* e830-e834.

Leyendecker, J. R., Barnes, C. E., & Zagoria, R. J. (2008). MR urography: techniques and clinical applications. *RadioGraphics, 28,* 23-46.

Liu, W., Mortele, K. J., & Silverman, S. G. (2005). Incidental Extraurinary Findings at MDCT Urography in Patients with Hematuria: Prevalence and Impact on Imaging Costs. *American Journal of Roentgenology, 185,* 1051-1056.

Ljungberg, B., Cowan, N. C., Hanbury, D. C., Hora, M., Kuczyk, M. A., Merseburger, A. S. et al. (2010). EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol, 58,* 398-406.

Lopez-Beltran, A. & Montironi, R. (2004). Non-Invasive Urothelial Neoplasms: According to the Most Recent WHO Classification. *European Urology, 46,* 170-176.

Lu, Y. Y., Chen, J. H., Liang, J. A., Wang, H. Y., Lin, C. C., Lin, W. Y. et al. (2012). Clinical value of FDG PET or PET/CT in urinary bladder cancer: A systemic review and meta-analysis. *European Journal of Radiology, 81,* 2411-2416.

Mahesh, M. (2009a). Conventional, Spiral, and Electron Beam CT: Background. In *MDCT Physics: The Basics - Technology, Image Quality and Radiation Dose* (1 ed., pp. 5-16). Wolters Kluwer / Lippincott Williams & Wilkins.

Mahesh, M. (2009b). Multiple-Row Detector Computed Tomography. In *MDCT Physics: The Basics - Technology, Image Quality and Radiation Dose* (1 ed., pp. 17-35). Wolters Kluwer / Lippincott Williams & Wilkins.

Maheshwari, E., O'Malley, M. E., Ghai, S., Staunton, M., & Massey, C. (2010). Split-Bolus MDCT Urography: Upper Tract Opacification and Performance for Upper Tract Tumors in Patients With Hematuria. *American Journal of Roentgenology, 194,* 453-458.

Malmström, P.-U. (2003). Time to abandon testing for microscopic haematuria in adults? *British Medical Journal, 326,* 813-815.

Margulis, V., McDonald, M., Tamboli, P., Swanson, D. A., & Wood, C. G. (2009). Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol, 181,* 2044-2051.

Margulis, V., Youssef, R. F., Karakiewicz, P. I., Lotan, Y., Wood, C. G., Zigeuner, R. et al. (2010). Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. *J Urol, 184,* 453-458.

Mariani, A. J., Mariani, M. C., Macchioni, C., Stams, U. K., Hariharan, A., & Moriera, A. (1989). The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. *J.Urol, 141,* 350-355.

Maurer, T., Souvatzoglou, M., Kubler, H., Opercan, K., Schmidt, S., Herrmann, K. et al. (2012). Diagnostic efficacy of [11C]choline positron emission tomography/computed tomography compared with conventional computed tomography in lymph node staging of patients with bladder cancer prior to radical cystectomy. *Eur Urol, 61,* 1031-1038.

McFarlane, J. P., Cowan, N. C., Holt, S. J., & Cowan, M. J. (2001). Outpatient ureteric procedures: a new method for retrograde ureteropyelography and ureteric stent placement. *British Journal of Urology, 87,* 172-176.

McTavish, J. D., Jinzaki, M., Zou, K. H., Nawfel, R. D., & Silverman, S. G. (2002). Multi-detector row CT urography: comparison of strategies for depicting the normal urinary collecting system. *Radiology, 225,* 783-790.

Meindl, T., Coppenrath, E., Kahlil, R., Muller-Lisse, U., Reiser, M., & Muller-Lisse, U. (2006). MDCT urography: retrospective determination of optimal delay time after intravenous contrast administration. *European Radiology,* 1-8.

Memarsadeghi, M., Heinz-Peer, G., Helbich, T. H., Schaefer-Prokop, C., Kramer, G., Scharitzer, M. et al. (2005). Unenhanced Multi-Detector Row CT in Patients Suspected of Having Urinary Stone Disease: Effect of Section Width on Diagnosis. *Radiology, 235,* 530-536.

Meranze, S. G., Pollack, H. M., & Banner, M. P. (1982). The use of grasping forceps in the upper urinary tract: Technique and radiologic implications. *American Journal of Roentgenology, 144,* 171-173.

Metser, U., Goldstein, M. A., Chawla, T. P., Fleshner, N. E., Jacks, L. M., & Malley, M. E. (2012). Detection of Urothelial Tumors: Comparison of Urothelial Phase with Excretory Phase CT Urography - A Prospective Study. *Radiology, 264,* 110-118.

Moon, J. W., Park, B. K., Kim, C. K., & Park, S. Y. (2012). Evaluation of virtual unenhanced CT obtained from dual-energy CT urography for detecting urinary stones. *Br.J Radiol, 85,* e176-e181.

Morcos, S. K. (2007). Computed tomography urography technique, indications and limitations. *Curr.Opin.Urol, 17,* 56-64.

Nawfel, R. D., Judy, P. F., Schleipman, A. R., & Silverman, S. G. (2004). Patient radiation dose at CT urography and conventional urography. *Radiology, 232,* 126-132.

Newcombe, R. G. (1998). Improved confidence intervals for the difference between binomial proportions based on paired data. *Stat.Med., 17,* 2635-2650.

Nilsson, A. (2004). Contrast-enhanced ultrasound of the kidneys. *Eur.Radiol., 14 Suppl 8,* 104-109.

Nishizawa, S., Imai, S., Okaneya, T., Nakayama, T., Kamigaito, T., & Minagawa, T. (2010). Diffusion weighted imaging in the detection of upper urinary tract urothelial tumors. *Int.Braz.J Urol, 36,* 18-28.

Nolte-Ernsting, C. & Cowan, N. (2006). Understanding multi-slice CT urography techniques: Many roads lead to Rome. *European Radiology, 16,* 2670-2686.

Nolte-Ernsting, C. C., Staatz, G., Tacke, J., & Gunther, R. W. (2003). MR urography today. *Abdom.Imaging, 28,* 191-209.

Noroozian, M., Cohan, R. H., Caoili, E. M., Cowan, N. C., & Ellis, J. H. (2004). Multislice CT urography: state of the art. *The British Journal of Radiology, 77,* S74-S86.

Nowak, T., Hupfer, M., Brauweiler, R., Eisa, F., & Kalender, W. A. (2011). Potential of high-Z contrast agents in clinical contrast-enhanced computed tomography. *Med.Phys., 38,* 6469-6482.

O'Connor, O. J., Fitzgerald, E., & Maher, M. M. (2010). Imaging of Hematuria. *American Journal of Roentgenology, 195,* W263-W267.

O'Malley, M. E., Hahn, P. F., Yoder, I. C., Gazelle, G. S., McGovern, F. J., & Mueller, P. R. (2003). Comparision of excretory phase, helical computed tomography with intravenous urography in patients with painless haematuria. *Clinical Radiology, 58,* 294-300.

Otero, H. J., Rybicki, F. J., Greenberg, D., & Neumann, P. J. (2008). Twenty years of cost-effectiveness analysis in medical imaging: are we improving? *Radiology, 249,* 917-925.

Papalia, R., Simone, G., Grasso, R., Augelli, R., Faiella, E., Guaglianone, S. et al. (2012). Diffusion-weighted magnetic resonance imaging in patients selected for radical cystectomy: detection rate of pelvic lymph node metastases. *BJU Int., 109,* 1031-1036.

Park, S. B., Kim, J. K., Lee, H. J., Choi, H. J., & Cho, K. S. (2007). Hematuria: portal venous phase multi detector row CT of the bladder--a prospective study. *Radiology, 245,* 798-805.

Pavone-Macaluso, M., Lamartina, M., Pavone, C., & Vella, M. (1992). The flexible cystoscope. *Int Urol Nephrol, 24,* 239-242.

Plail, R. (1990). Detecting bladder cancer. *British Medical Journal, 301,* 567-568.

Remzi, M., Haitel, A., Margulis, V., Karakiewicz, P., Montorsi, F., Kikuchi, E. et al. (2009). Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int., 103,* 307-311.

Ripolles, T., Agramunt, M., Errando, J., Martįnez, M. J., Coronel, B., & Morales, M. (2004). Suspected ureteral colic: plain film and sonography vs unenhanced helical CT. A prospective study in 66 patients. *European Radiology, 14,* 129-136.

Rodgers, M., Nixon, J., Hempel, S., Aho, T., Kelly, J., Neal, D. et al. (2006a). Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technology Assessment, 10*.

Rodgers, M., Nixon, J., Hempel, S., Aho, T., Kelly, J., Neal, D. et al. (2006b). Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technol.Assess., 10,* iii-259.

Roupret, M., Babjuk, M., Comperat, E., Zigeuner, R., Sylvester, R., Burger, M. et al. (2013). European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol, 63,* 1059-1071.

Roupret, M., Zigeuner, R., Palou, J., Boehle, A., Kaasinen, E., Sylvester, R. et al. (2011). European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. *Eur.Urol, 59,* 584-594.

Rutjes, A., Reitsma, J., Coomarasamy, A., Khan, K., & Bossuyt, P. (2007). *Evaluation of diagnostic tests when there is no gold standard. A review of methods.* (Rep. No. 11).

Sadow, C. A., Silverman, S. G., O'Leary, M. P., & Signorovitch, J. E. (2008). Bladder Cancer Detection with CT Urography in an Academic Medical Center. *Radiology, 249,* 195-202.

Sahni, V. A., Shinagare, A. B., & Silverman, S. G. (2013). Virtual unenhanced CT images acquired from dual-energy CT urography: accuracy of attenuation values and variation with contrast material phase. *Clin Radiol, 68,* 264-271.

Sánchez-Oritiz, R. F., Huang, W. C., MICK, R., Van Arsdalen, K. N., Wein, A. J., & Malkowicz, S. B. (2003). An Interval Longer than 12 Weeks Between the Diagnosis of Muscle Invasion and Cystectomy is Associated with Worse Outcome in Bladder Carcinoma. *J Urol, 169,* 110-115.

Schoder, H., Ong, S. C., Reuter, V. E., Cai, S., Burnazi, E., Dalbagni, G. et al. (2012). Initial results with (11)C-acetate positron emission tomography/computed tomography (PET/CT) in the staging of urinary bladder cancer. *Mol.Imaging Biol., 14,* 245-251.

Seddon, J. (2010). *Systems thinking in the public sector*. Axminster, U.K.: Triarchy Press.

Shih, Y. C., Chien, C. R., Xu, Y., Pan, I. W., Smith, G., & Buchholz, T. (2011). Economic Burden of Renal Cell Carcinoma in the US. *Pharmacoeconomics, 29,* 331-341.

Shinagare, A. B., Sahni, V. A., Sadow, C. A., Erturk, S. M., & Silverman, S. G. (2011). Feasibility of Low-Tube-Voltage Excretory Phase Images During CT Urography: Assessment Using a Dual-Energy CT Scanner. *American Journal of Roentgenology, 197,* 1146-1151.

Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians, 62,* 10-29.

Silverman, S. G., Gan, Y. U., Mortele, K. J., Tuncali, K., & Cibas, E. S. (2006). Renal Masses in the Adult Patient: The Role of Percutaneous Biopsy. *Radiology, 240,* 6-22.

Silverman, S. G., Lee, B. Y., Seltzer, S. E., Bloom, D. A., Corless, C. L., & Adams, D. F. (1994). Small (< or = 3 cm) renal masses: correlation of spiral CT features and pathologic findings. *AJR Am.J.Roentgenol., 163,* 597-605.

Silverman, S. G., Lyendecker, J. R., & Amis, E. S. (2009). What is the current role of CT urography and MR urography in the evaluation of the urinary tract? *Radiology, 250,* 309-323.

Smith, R. C., Rosenfield, A. T., Choe, K. A., & et al (1995). Acute flank pain: comparison of noncontrast enhanced CT and intravenous urography. *Radiology, 194,* 789-794.

Smith, R. C., Verga, M., McCarthy, S., & Rosenfield, A. T. (1996). Diagnosis of acute flank pain: value of unenhanced helical CT. *AJR Am.J.Roentgenol., 166,* 97-101.

Sodickson, A. (2012). Strategies for reducing radiation exposure in multi-detector row CT. *Radiol Clin N Am, 50,* 1-14.

Song, J. H., Beland, M. D., & Mayo-Smith, W. W. (2012). Incidental clinically important extraurinary findings at MDCT urography for hematuria evaluation: prevalence in 1209 consecutive examinations. *AJR Am J Roentgenol., 199,* 616-622.

Soto, J. A., Barish, M. A., & Yee, J. (2005). Reader training in CT colonography: how much is enough? *Radiology, 237,* 26-27.

Sourtzis, S., Thibeau, J. F., Damry, N., Raslan, A., Vandendris, M., & Bellemans, M. (1999). Radiologic investigation of renal colic: unenhanced helical CT compared with excretory urography. *American Journal of Roentgenology, 172,* 1491-1494.

Spencer, J., Lindsell, D., & Mastorakou, I. (1990). Ultrasonography compared with intravenous urography in the investigation of adults with haematuria. *British Medical Journal, 301,* 1074-1076.

Stacul, F., Van Der Molen, A., Reimer, P., Webb, J., Thomsen, H., Morcos, S. et al. (2011). Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *European Radiology, 21,* 2527-2541.

Stenzl, A., Cowan, N. C., De Santis, M., Jakse, G., Kuczyk, M. A., Merseburger, A. S. et al. (2009). The Updated EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer. *European Urology, 55,* 815-819.

Sudakoff, G. S., Dunn, D. P., Guralnick, M. L., Hellman, R. S., Eastwood, D., & See, W. A. (2008). Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J Urol, 179,* 862-867.

Sufana Iancu, A., Colin, P., Puech, P., Villers, A., Ouzzane, A., Fantoni, J. C. et al. (2013). Significance of ADC value for detection and characterization of urothelial carcinoma of upper urinary tract using diffusion-weighted MRI. *World J Urol, 31,* 13-19.

Sutton, J. M. (1990). Evaluation of Haematuria in Adults. *Journal of the American Medical Association, 263,* 2475-2480.

Taghizadeh, A. K., El Madani A., Gard, P. R., Li, C. Y., Thomas, P. J., & Denyer, S. P. (2006). When does it hurt? Pain during flexible cystoscopy in men. *Urology International, 76,* 301-303.

Takahashi, N., Vrtiska, T. J., Kawashima, A., Hartman, R. P., Primak, A. N., Fletcher, J. G. et al. (2010a). Detectability of urinary stones on virtual nonenhanced images generated at pyelographic-phase dual-energy CT. *Radiology, 256,* 184-190.

Takahashi, N., Glockner, J. F., Hartman, R. P., King, B. F., Leibovich, B. C., Stanley, D. W. et al. (2010b). Gadolinium Enhanced Magnetic Resonance Urography for Upper Urinary Tract Malignancy. *The Journal of Urology, 183,* 1330-1336.

Takahashi, N., Kawashima, A., Glockner, J. F., Hartman, R. P., Leibovich, B. C., Brau, A. C. S. et al. (2008). Small (<2-cm) Upper-Tract Urothelial Carcinoma: Evaluation with Gadolinium-enhanced Three-dimensional Spoiled Gradient-Recalled Echo MR Urography. *Radiology, 247,* 451-457.

Takeuchi, M., Kawai, T., Ito, M., Ogawa, M., Ohashi, K., Hara, M. et al. (2012). Split-bolus CT-urography using dual-energy CT: feasibility, image quality and dose reduction. *Eur J Radiol, 81,* 3160-3165.

Takeuchi, M., Matsuzaki, K., Kubo, H., & Nishitani, H. (2008). Diffusion-weighted magnetic resonance imaging of urinary epithelial cancer with upper urinary tract obstruction: preliminary results. *Acta Radiol, 49,* 1195-1199.

Takeuchi, M., Sasaki, S., Ito, M., Okada, S., Takahashi, S., Kawai, T. et al. (2009). Urinary bladder cancer: diffusion-weighted MR imaging--accuracy for diagnosing T stage and estimating histologic grade. *Radiology, 251,* 112-121.

Tamai, H., Takiguchi, Y., Oka, M., Shingaki, N., Enomoto, S., Shiraki, T. et al. (2005). Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. *J.Ultrasound Med., 24,* 1635-1640.

Thoeny, H. C. & Ross, B. D. (2010). Predicting and monitoring cancer treatment response with diffusion-weighted MRI. *J Magn Reson.Imaging, 32,* 2-16.

Thoeny, H. C., Forstner, R., & De Keyzer, F. (2012). Genitourinary Applications of Diffusion-weighted MR Imaging in the Pelvis. *Radiology, 263,* 326-342.

Tomson, C. & Porter, T. (2002). Asymptomatic microscopic or dipstick haematuria in adults: which investigations for which patients? A review of the evidence. *BJU International, 90,* 185-198.

Toth, T. & Hsieh, J. (2009). Strategies ot reduce radiation dose in CT. In M.Mahesh (Ed.), *MDCT Physics The Basics - Technology, Image Quality and Radiation Dose* (1 ed., pp. 115-143). Philadelphia: Lippincott Williams & Wilkins.

Turney, B. W., Willatt, J. M. C., Nixon, D., Crew, J. P., & Cowan, N. C. (2006). Computed tomography urography for diagnosing bladder cancer. *BJU International, 98,* 345-348.

Van Der Molen, A., Cowan, N., Mueller-Lisse, U., Nolte-Ernsting, C., Takahashi, S., Cohan, R. et al. (2008). CT urography: definition, indications and techniques. A guideline for clinical practice. *European Radiology, 18,* 4-17.

Viswanath, S., Zelhof, B., Ho, E., Sethia, K., & Mills, R. (2008). Is routine urine cytology useful in the haematuria clinic? *Ann R Coll Surg Engl, 90,* 153-155.

Vrtiska, T. J., Hartman, R. P., Kofler, J. M., Bruesewitz, M. R., King, B. F., & McCollough, C. H. (2009). Spatial Resolution and Radiation Dose of a 64-MDCT Scanner Compared with Published CT Urography Protocols. *AJR Am.J.Roentgenol., 192,* 941-948.

Waldert, M., Karakiewicz, P. I., Raman, J. D., Remzi, M., Isbarn, H., Lotan, Y. et al. (2010). A delay in radical nephroureterectomy can lead to upstaging. *BJU International, 105,* 812-817.

Wang, L. J., Wong, Y. C., Huang, C. C., Wu, C. H., Hung, S. C., & Chen, H. W. (2010). Multidetector computerized tomography urography is more accurate than excretory

urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J Urol., 183,* 48-55.

Wang, L. J., Wong, Y. C., Chuang, C. K., Huang, C. C., & Pang, S. T. (2009). Diagnostic Accuracy of Transitional Cell Carcinoma on Multidetector Computerized Tomography Urography in Patients With Gross Hematuria. *The Journal of Urology, 181,* 524-531.

Warshauer, D. M., McCarthy, S. M., Street, L., Bookbinder, M. J., Glickman, M. G., Richter, J. et al. (1988). Detection of renal masses: sensitivities and specificities of excretory urography / linear tomography, US, and CT. *Radiology, 169,* 363-365.

Watanabe, H., Kanematsu, M., Kondo, H., Goshima, S., Tsuge, Y., Onozuka, M. et al. (2009). Preoperative T staging of urinary bladder cancer: does diffusion-weighted MRI have supplementary value? *AJR Am J Roentgenol., 192,* 1361-1366.

Webb, J. A. W. (1997). Imaging in Haematuria. *Clinical Radiology, 52,* 167-171.

Webb, J. A. W. (1994). Intravenous Urography. In L.Dalla Palma & H. S. Thomsen (Eds.), *European Uroradiology '94* (pp. 36-39). Copenhagen: FADL.

Weinstein, S., Obuchowski, N. A., & Lieber, M. L. (2005). Clinical evaluation of diagnostic tests. *AJR Am J Roentgenol., 184,* 14-19.

Wilson, E. B. (1927). Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc, 22,* 209-212.

Yip, S. K. H., Peh, W. C. G., Tam, P. C., Li, J. H. C., & Lam, C. H. C. (1998). Day case hematuria diagnostic service: use of ultrasonography and flexible cystoscopy. *Urology, 52,* 762-766.

Yoshida, S., Masuda, H., Ishii, C., Saito, K., Kawakami, S., & Kihara, K. (2008). Initial experience of functional imaging of upper urinary tract neoplasm by diffusion-weighted magnetic resonance imaging. *Int.J Urol, 15,* 140-143.

Zagoria, R. J. (2000). Imaging of Small Renal Masses. *American Journal of Roentgenology, 175,* 945-955.

Appendix

1. Certificate awarded for a Best Members Day Presentation at the European Society of Urogenital Radiology Annual Scientific Meeting 2012, Edinburgh. CT urography for hematuria: 10 years work in 10 minutes. Nigel C Cowan and Sue Mallett.

2. Scientific abstract of CT urography for haematuria: 10 years work in 10 minutes. Nigel C Cowan and Sue Mallett. Presented at the members day of the European Society of Urogenital Radiology Annual Scientific Meeting 2012. Edinburgh, Thursday 13th September.

Scientific papers originating and published from this thesis

3. CT urography for hematuria. Cowan, N. C. Nat. Rev. Urol. 2012;9: 218 - 226.

4. Multidetector CT urography for diagnosing upper urinary tract urothelial tumour. Cowan, N.C.; Turney, B.W.; Taylor, N.J.; McCarthy, C.L. & Crew, J.P. BJU Int 2007;99:1363-1370. From Chapter 1.1 .

5. Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. Blick, C.G.; Nazir, S.A.; Mallett, S.; Turney, B.W.; Onwu, N.N.; Roberts, I.S.; Crew, J.P.; Cowan, N.C. BJU Int 2011;110:84-94. From Chapter 2.2 .

6. Example of a CT urography single bolus protocol for haematuria including acquisition and reconstruction parameters.

BSUR
British Society of
Urogenital Radiology

ESUR 2012

European Society of Urogenital Radiology

19th European Symposium on Urogenital Radiology and 7th BSUR Annual Scientific Meeting
13-16 September, Edinburgh UK

ESUR 2012 Best Members' Day Presentation

This is to certify that
Nigel Cowan

was awarded 2nd prize in the category best Members' Day presentation at ESUR 2012 with the presentation entitled

CT Urography for Hematuria: 10 Years Work in 10 minutes

Presentation of which took place at ESUR 2012, September 13-16 2012, Royal College of Surgeons of Edinburgh UK

Sami Moussa
Chair
Scientific Programme Committee

Gertraud Heinz-Peer
President
ESUR

Phil Cook
Chairman
BSUR

CT urography for hematuria: 10 years work in 10 minutes

Presented at the European Society of Urogenital Radiology, Edinburgh, Thursday 13th September 2012

Nigel C Cowan and Sue Mallett

Purpose

Evaluation of a diagnostic strategy using CT urography as the initial imaging technique in patients with visible hematuria (VH) at high risk for urothelial carcinoma.

Materials and methods

The clinical cohort consisted of a consecutive series of 1001 patients, age ≥ 40-years of age, presenting with VH, over a 57-month period, UTI excluded. Same day CT urography and flexible cystoscopy (FC) were performed. Reference standard was histopathology from biopsy or surgery, and 1-5 year imaging and histopathology database follow-up.

Results

Disease prevalence for upper urinary tract urothelial carcinoma (UTUC) = 2.2% (n=22/1001), renal cell carcinoma (RCC) = 2.4% (n=24/1001), UUT stones = 15.1% (n=151/1001), normal UUT's = 80.3% (n=804/1001). For CT urography for diagnosing UTUC; Se = 1.0, Sp = 0.98, PPV = 0.72, and NPV = 1.0.

The prevalence of BCa in the clinical cohort was 20% (n=156/778). For the diagnostic strategy using CT urography for diagnosing BCa as an additional test to FC, Se = 1.0, Sp = 0.94, PPV = 0.80 and NPV = 1.0, as a replacement test for FC, Se = 0.95, Sp = 0.83, PPV = 0.58, and NPV = 0.98 and for CT urography and FC as a triage test for rigid cystoscopy and follow-up (Option 1), Se = 1.0, Sp = 0.94, PPV = 0.80, NPV = 0.99, and for (Option 2), Se = 0.95, Sp = 0.98, PPV = 0.93 , NPV = 0.99.

Conclusions

High disease prevalence and high sensitivity of CT urography for diagnosing UTUC can justify use of CT urography as a first-line imaging test for hematuria in patients at high risk. For diagnosing BCa, there is a clear advantage for the diagnostic strategy triage test Option 1, where patients with a positive CT urography score are directly referred to rigid cystoscopy, but all other patients undergo flexible cystoscopy.

CT urography for hematuria

Nigel C. Cowan

Abstract | Hematuria can signify serious disease such as bladder cancer, upper urinary tract urothelial cell carcinoma (UUT-UCC), renal cell cancer or urinary tract stones. CT urography is a rapidly evolving technique made possible by recent advances in CT technology. CT urography is defined as CT examination of the kidneys, ureters and bladder with at least one series of images acquired during the excretory phase after intravenous contrast administration. The reasoning for using CT urography to investigate hematuria is based on its high diagnostic accuracy for urothelial cell carcinoma (UCC) and favorable comparison with other imaging techniques. The optimum diagnostic imaging strategy for patients with hematuria at high-risk for UCC involves the use of CT urography as a replacement for other imaging tests (ultrasonography, intravenous urography, or retrograde ureteropyelography) and as a triage test for cystoscopy, resulting in earlier diagnosis and improved prognosis of bladder cancer, UUT-UCC, renal cell cancer and stones. Current problems with CT urography for investigating hematuria might be solved with a formative educational program simulating clinical reporting to reduce reader error, and a new technique for image-guided biopsy of UUT-UCC detected by CT urography for histopathological confirmation of diagnosis and elimination of false-positive results. CT urography is recommended as the initial imaging test for hematuria in patients at high-risk for UCC.

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Introduction

Hematuria is defined as the presence of red blood cells in urine, and can signify serious disease such as bladder cancer, upper urinary tract urothelial cell carcinoma (UUT-UCC), renal cell cancer or urinary tract stones.[1–3] If the blood is visible it is considered a symptom; nonvisible hematuria is considered a sign.

The criteria used to diagnose nonvisible hematuria and for referral to a nephrologist or urologist vary widely.[4,5] Nonvisible hematuria can be detected on a chemical dipstick or microscopy. Hemoglobin, either free in the urine or within urinary red blood cells, catalyzes the oxidation of substances on a chemical dipstick, resulting in a color change that indicates hematuria. Urinary dipsticks are useful for detecting nonvisible hematuria, with a sensitivity of 91–100%, but they have a low specificity, ranging from 65% to 99%.[1] Myoglobin, free hemoglobin and oxidizing contaminants in the urine, such as povidone-iodine, can provide false-positive results on dipstick analysis.

Dipstick alone is the most common method of diagnosing hematuria in UK primary care.[6] The American Urological Association Best Practice guidelines recommend confirmation of a positive dipstick test with microscopy, and define nonvisible hematuria as three or more red blood cells per high-power field on microscopic evaluation of the urinary sediment from two of three properly collected midstream urine specimens.[7] For patients at high-risk of urothelial cell carcinoma (UCC) of the bladder or upper urinary tract (those with a history of smoking; occupational exposure to chemicals, dyes, benzenes or aromatic amines; history of visible hematuria; age >40 years; history of urological disorder or disease; history of irritative voiding symptoms; history of UTI resistant to antibiotic treatment; analgesic [for example, phenacetin] abuse; or history of pelvic irradiation or cyclophosphamide therapy) the current UK guidelines suggest that after one positive urinalysis, patients should be referred to a urologist for full evaluation of the upper and lower urinary tracts, principally to exclude life-threatening malignancy.[6–8]

Current standard of care for patients with asymptomatic nonvisible hematuria is to undergo urinalysis on at least two separate occasions, whereas those with symptomatic nonvisible hematuria or visible hematuria are referred immediately after one positive urinalysis and exclusion of transient causes of hematuria and UTI. The next step is to determine whether referral to a urologist or nephrologist is most appropriate based on the results of renal function tests, and to determine if the hematuria originates in the nephron (glomerular or tubular) or from the epithelium. A nephrological referral is recommended in the presence of proteinuria, red blood cell casts on microscopy, elevated serum creatinine, or elevated blood pressure.

Imaging investigations for patients with hematuria are usually performed to diagnose any serious underlying upper urinary tract disease, such as stones, renal cell cancer or UUT-UCC. Traditionally, intravenous urography (IVU) and ultrasonography were the imaging techniques of choice for the initial investigation. In 1990, Khadra *et al.*[2] reported one of the few large observational

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Competing interests
The author declares no competing interests.

series on the subject comprising 1,930 patients. They concluded that all patients with hematuria should undergo cystoscopy and if an upper tract tumor is suspected then a combination of ultrasonography and IVU.[2] In another large series reported by Edwards *et al.*[3] in 2006, the recommendation was the ubiquitous use of ultrasonography with selective IVU for men aged >50 years, with visible hematuria or a positive repeat dipstick urinalysis when initial tests were negative.[3] The relative merits of ultrasonography or IVU as the initial imaging investigation for hematuria have been the subject of much debate.[9] Traditionally, further imaging was considered if no cause for hematuria was found initially, using a combination of ultrasonography, IVU and flexible cystoscopy, CT or renal angiography.[10] In 2006, a Health Technology Assessment review concluded that there was insufficient evidence available to draw any firm conclusions regarding the diagnostic accuracy of imaging studies in determining the cause of hematuria, and that there was insufficient data available to derive an evidence-based algorithm of the diagnostic pathway for hematuria.[6] Since then, data have been steadily accumulating supporting the use of CT urography as an initial one-step imaging modality for the investigation of hematuria.

In this Review, I will first provide an overview of the CT urography technique before describing the reasoning behind using CT urography to investigate hematuria. I will address the optimum diagnostic strategy, identify potential problems associated with the use of CT urography to investigate hematuria and suggest some innovative solutions. Finally, recommendations are given as to how CT urography may be used in every day clinical practice.

Key points

- Hematuria can signify serious disease such as bladder cancer, upper urinary tract urothelial cell cancer (UUT-UCC), renal cell cancer or urinary tract stones
- Patients with hematuria can be divided into low-risk and high-risk groups for UUT-UCC based on risk factors such as patient age, visible hematuria, occupational exposure to toxins and other factors
- CT urography is defined as CT examination of the kidneys, ureters and bladder with at least one series of images acquired during the excretory phase following intravenous contrast administration
- Reasoning for the use of CT urography to investigate hematuria is based on its high diagnostic accuracy for UUT-UCC and favorable comparisons with other imaging techniques
- CT urography is recommended as the initial imaging investigation for patients over 40 years old presenting with hematuria (UTI excluded), specifically those at high risk of urothelial cell carcinoma (UCC)
- The optimum diagnostic imaging strategy for patients at high risk of UCC is to use CT urography as a replacement test for conventional upper tract imaging techniques and as a triage test for cystoscopy

CT urography technique

The development of CT technology

CT urography is a developing diagnostic imaging technique made possible by recent advances in CT technology. It is defined as CT examination of the kidneys, ureters and bladder with at least one series of images acquired during the excretory phase, after administration of intravenous contrast.[11]

CT is a logical conceptual progression from conventional radiography, translating the 2D information of radiographic images into three dimensions. The first CT machine—an invention credited to Godfrey Hounsfield—was introduced into clinical practice in 1973. The subsequent development of multidetector CT represents a major landmark in the evolution of CT. By late 1998, all major CT manufacturers were marketing multidetector CT machines capable of acquiring at least four body sections per gantry rotation. By 2007, CT machines capable of acquiring 320 body sections per gantry rotation were available for clinical use. By increasing the number of detector rows, the data acquisition capability of the machine and the efficiency of the X-ray tube was greatly improved, producing image quality far surpassing that of Hounsfield's original invention.

The two principal clinical advantages of multidetector technology are increased speed of imaging and increased spatial resolution. Increased speed is particularly useful for studies in which patient motion is a limiting factor. Increased spatial resolution makes true isotropic imaging—sometimes described as the holy grail of medical imaging—possible. Isotropic imaging is achieved when the reconstructed image is equally sharp in any plane of the examined volume and requires careful attention to image acquisition and reconstruction parameters. The truly isotropic 3D radiograph has perfect cubic voxels of less than 1 mm in diameter, acquired over large volumes with very short acquisition times, within a single breath hold.

When reconstructing an image for isotropic resolution, the reconstructed slice thickness must equal the pixel size. The image matrix is the number of pixels found across the display field of view and is usually fixed at 512 for most CT machines. It follows, by simple algebra, that the display field of view required to provide isotropic imaging can be calculated by multiplying the reconstructed slice thickness by the matrix. For example, if the reconstructed slice thickness is 0.625 mm and the matrix is 512, then the display field of view required to give isotropic voxels is 320 mm.[12,13] Isotropic resolution with multiplanar viewing is integral to the high diagnostic accuracy of CT urography for UUT-UCC, small stones and renal masses, allowing images to be reviewed without the step reconstruction artifact that can simulate disease. With only axial review it is easy to overlook small tumors of the upper urinary tract or bladder, especially those with their long axis in the axial plane. Many CT applications using isotropic resolution (CT angiography, CT colonography and CT urography) are developing rapidly in clinical practice.[12,13]

Early reports of CT urography for detecting urinary tract abnormalities including stones,[14–17] renal masses[18–21] and UUT-UCC have been very encouraging.[22–28] The first set of guidelines from the Upper Urinary Tract Imaging Group of the European Society of Urogenital Radiology were published in 2008.[11]

Indications and contraindications for CT urography

The indications for CT urography are controversial and consensus has not been reached on the subject.[26] The

Box 1 | Indications for CT urography

- Hematuria (excluding UTI)
- Staging and follow-up of urothelial tumors
- Iatrogenic ureter and bladder injury
- Trauma to the genitourinary tract
- Investigation of fistulae
- Unexplained hydronephrosis
- Planning for percutaneous nephrolithotomy
- Living related kidney donor assessment
- Recurrent UTI

Table 1 | CT urography contrast bolus protocols

Protocol	Indication
Single bolus	Visible hematuria, patients at high risk of upper urinary tract urothelial cell carcinoma
Double bolus	Bladder cancer follow-up
Triple bolus	Assessment of living related kidney donors and patients undergoing percutaneous nephrolithotomy

principal indication is the investigation of hematuria, the subject of this Review. Other indications will not be discussed further here (Box 1). A working knowledge of the indications for a particular diagnostic test is essential before requesting the said test, but there are three other key pieces of information that should be understood in order to avoid requesting redundant diagnostic tests. Firstly, the clinician should use existing clinical knowledge of the patient to estimate the probability that the patient has the disease in question (the pretest probability). Secondly, the clinician should be aware of the sensitivity and specificity of the diagnostic test, and finally the physician must consider whether the results of the test will affect the patient's management.[29] Contraindications for CT urography are few, but center around whether iodine-based contrast or radiation should be avoided.[30]

Optimization of CT urography technique

It is helpful to primarily classify CT urography protocols according to the method used for intravenous contrast administration. There are three main contrast administration protocols, which depend on the number of boluses of contrast used (Table 1). The single bolus protocol is optimized for patients with hematuria at high risk of UUT-UCC, renal masses and stones, and is described in detail in the Supplementary Text file and Supplementary Tables 1–3. This protocol consists of three series of image acquisition: an unenhanced series optimized for detecting stones, a nephrographic series optimized for detecting renal masses and an excretory series optimized for detecting UUT-UCC (Figure 1).

The double bolus protocol makes less contrast media available for the nephrographic and excretory phases than the single bolus protocol and therefore may not demonstrate renal cell carcinoma and UUT-UCC so clearly. For this reason, it is not recommended as an initial diagnostic test for patients at risk of UUT-UCC. If the precontrast series is excluded, and the postcontrast nephrographic and excretory phases are acquired in one series, a low radiation dose is achieved, which is recommended for the follow-up of patients with known bladder cancer or UUT-UCC.[25,31,32]

The triple bolus protocol is used for the assessment of living related kidney donors and patients undergoing percutaneous nephrolithotomy.[33] Although use of a triple bolus protocol for investigating hematuria has been described,[34] it is currently not recommended for routine use because the volume of contrast available for the excretory phase is reduced by bolus splitting, which is likely to compromise diagnostic accuracy.

Many studies have evaluated techniques aimed at promoting complete opacification of the urinary tract during CT urography, in order to optimize the contrast between urine and urothelial disease. Currently there is no consensus regarding the optimum technique. A number of maneuvers have been suggested that are often interrelated in a complex fashion so that adjustment of one will impact on the others. Such maneuvers include oral administration of water, intravenous furosemide or saline to encourage urine flow, abdominal compression, varying the timing of image acquisition, acquiring a second series of images in the excretory phase, increasing the volume of contrast injected, and encouraging patient movement (walking around or log rolling on the CT table) to promote mixing of contrast and urine.

Continuous audit of opacification is required to maintain the standard of CT urography from day to day. All users of CT urography should employ comparable scoring systems. In one such scoring system, the urinary tract is divided into four anatomical components (collecting system and renal pelvis; abdominal ureter; pelvic ureter; and bladder), and each is given a score of 0 (no opacification), 1 (partial opacification) or 2 (complete opacification). The bladder is scored slightly differently, with 0 representing no opacification, 1 indicating regions of interest within the bladder at less than 100 HU, and 2 corresponding to all regions of interest in the bladder over 100 HU. Only by using a similar scoring system across different centers will it be possible to accurately compare different CT urography techniques.

CT urography for hematuria

Diagnostic accuracy of CT urography

The reasoning for using CT urography for the investigation of hematuria ultimately depends on the high diagnostic accuracy of the excretory phase series for urothelial imaging, especially for UUT-UCC. Other component image series (unenhanced and nephrographic) have high diagnostic accuracy for stones and renal masses, but by definition they are not CT urography. To justify its use in patients with hematuria, CT urography must be as good if not better in terms of diagnostic accuracy and patient acceptability than the alternative techniques for imaging UUT-UCC. A number of studies have evaluated the accuracy of CT urography for hematuria (Table 2). In 2002, Lang *et al.* reported a multicenter series of 350 consecutive patients with nonvisible hematuria and negative results on ultrasonography, IVU, abdominal radiography and flexible cystoscopy, who subsequently underwent

excretory phase CT urography. A positive diagnosis rate of 45% was reported for all causes of hematuria, suggesting that excretory phase CT urography was effective for diagnosing refractory cases of hematuria.[35]

A number of studies have compared the diagnostic accuracy of IVU and CT urography.[36–40] Gray Sears *et al.*[36] performed both IVU and CT urography in 115 patients with asymptomatic hematuria. CT urography was found to be more accurate than IVU for diagnosing the cause of nonvisible hematuria. A significant difference between the two imaging techniques was found for the detection of urinary calculi. Unenhanced CT is far superior to IVU in terms of diagnostic accuracy for stones. So far, this is the only study to directly compare CT urography and IVU prospectively in the same patients. The principal limitation of the study was the very small number of patients with UUT-UCC in the sample population ($n = 1$). Although it is conceptually simple to design a study that compares two imaging techniques in the same patients, in practice it is very difficult to justify the increased radiation dose that such patients would receive. Studies using surrogate comparisons are now commonly reported, which require careful scrutiny to ensure that optimum CT urography is compared with optimum IVU to mimic genuine clinical practice. It is also important to ensure that there are a sufficient number of patients with UUT-UCC in each clinical cohort for an assessment of diagnostic accuracy for UUT-UCC to be meaningful.[37]

Albani *et al.*[38] determined the usefulness of CT urography as an alternative to IVU for the initial evaluation of patients with hematuria. Analysis of two separate unmatched groups of patients ($n = 259$ for CT urography; $n = 253$ for IVU) revealed that CT urography was significantly more sensitive than IVU for detecting upper tract disease (94.1% versus 50%). The cohort included an insufficient number of patients with UUT-UCC for a meaningful comparison. The authors also reported low sensitivities (≤40%) for diagnosing lower tract lesions, which is most probably a reflection on the technique used for CT urography and reporting methods. Patient exercise and log rolling were not used.[38]

In 2010, Wang *et al.*[39] performed a retrospective study of adult patients with hematuria who underwent both CT urography and IVU over a 2.5-year period. 19 of 60 patients had UUT-UCC. The sensitivity, specificity and accuracy of IVU for UUT-UCC were 0.750, 0.860 and 0.849, respectively, compared with 0.958, 1.000 and 0.996 for CT urography. The authors concluded that CT urography should be the first choice noninvasive imaging technique for diagnosing UUT-UCC in patients with hematuria. A similar study was reported by Jinzaki *et al.*[40] in 104 patients with hematuria, 46 of whom had UUT-UCC. Per-patient sensitivity, specificity, and overall accuracy for the detection of UUT-UCC with CT urography (93.5%, 94.8%, and 94.2%, respectively) were significantly greater than the corresponding values for IVU (80.4%, 81.0%, and 80.8%; $P = 0.041$, 0.027, and 0.001, respectively).[40] Although the designs of these studies are theoretically imperfect, the results suggest that the diagnostic accuracy of CT urography is greater than IVU for upper urinary tract disease, especially UUT-UCC.

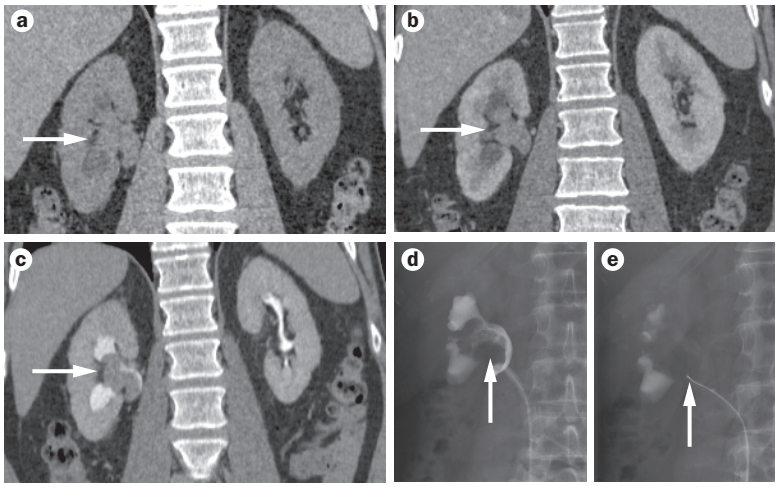

Figure 1 | Imaging and biopsy of a large renal pelvic UUT-UCC. **a** | A large mass in the right collecting system (arrow) is difficult to visualize on unenhanced CT. **b** | The same mass is visible with contrast enhancement in the nephrographic phase. **c** | The mass is most clearly identified on excretory phase imaging. **d** | Retrograde ureteropyelography shows the large right renal pelvic mass with irregularity and destruction of the epithelium. **e** | Fluoroscopically-guided biopsy of the right renal pelvic mass, using ureteroscopic biopsy forceps.

Several retrospective studies report on the diagnostic accuracy of CT urography for UUT-UCC[41–45] against the reference standard of histopathology, cytology and clinical follow-up. Despite the variation in CT urography technique, most report high sensitivities and specificities for UUT-UCC. Many studies using a double bolus protocol give the majority of the contrast volume in the second bolus (Table 2), a move that is likely to reduce the opacification scoring of the upper tract in the excretory phase because most of the contrast will not have been excreted into the collecting systems and ureter at the time of image acquisition.

In 2007, Cowan *et al.*[31] compared the diagnostic accuracy of CT urography and retrograde ureteropyelography for diagnosing UUT-UCC (Figure 2). The clinical cohort consisted of a selected group of 106 patients who presented with hematuria and initially underwent IVU and flexible cystoscopy. Patients with equivocal or positive IVU results and those with negative IVU and flexible cystoscopy results but with persistent hematuria were investigated with CT urography and retrograde ureteropyelography. The reference standard was histopathology from biopsy or resected specimens and 3–5 year clinical follow-up. The sensitivity, specificity, positive predictive value and negative predictive value of CT urography for diagnosing UUT-UCC were 0.97, 0.93, 0.79 and 0.99, respectively. For retrograde ureteropyelography, the sensitivity, specificity, positive predictive value and negative predictive value were 0.96, 0.97, 0.87 and 0.97, respectively. Thus, the diagnostic accuracy was similar for CT urography and retrograde ureteropyelography, which is an important result given that retrograde ureteropyelography is often regarded as the gold standard for imaging UUT-UCC.[31] The authors concluded that the

Table 2 | CT urography for diagnosing UUT-UCC and bladder cancer

Study	*n*	Site	Se	Sp	PPV	NPV	Indications	Bolus	Maneuvers
Fritz *et al.* (2006)[41]	41	UUT	1.00	NR	NR	NR	Histologically verified UUT-UCC	Single (1.5 ml/kg)	None
Chow *et al.* (2007)[42]	8	UUT	1.00	0.99	0.80	1.00	Painless hematuria	Double (40 ml; 80 ml)	900 ml oral water; compression
Sudakoff *et al.* (2008)[43]	11	UUT	0.82	0.98	0.50	1.00	Unspecified hematuria	Double (40 ml; 110 ml)	None
Wang *et al.* (2009)[44]	39	Renal pelvis	0.94	0.99	NR	NR	Visible hematuria	Single (120 ml)	None
Wang *et al.* (2009)[44]	39	Ureter	0.67	0.98	NR	NR	Visible hematuria	Single (120 ml)	None
Maheshwari *et al.* (2010)[45]	9	UUT	1.00	0.99	0.82	1.00	Hematuria (all types)	Double (50 ml; 80 ml)	1,000 ml oral water; log roll on table; partially empty bladder
Jinzaki *et al.* (2011)[40]	46	UUT	0.94	0.95	NR	NR	Hematuria (all types)	Single (2 ml/kg)	400–500 ml oral water
Cowan *et al.* (2007)[31]	32	UUT (CTU)	0.97	0.93	0.79	0.99	Hematuria, equivocal or positive IVU, or persistent hematuria and negative IVU	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination; walk and log roll
Cowan *et al.* (2007)[31]	32	UUT (RUP)	0.96	0.97	0.87	0.97	Hematuria, equivocal or positive IVU, or persistent hematuria and negative IVU	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination; walk and log roll
Blick *et al.* (2011)[47]	156	Bladder (CTU)	0.95	0.83	0.58	0.98	Visible hematuria, ≥40 years; no infection	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination, walk and log roll
Blick *et al.* (2011)[47]	156	Bladder (FC)	0.98	0.94	0.80	0.99	Visible hematuria, ≥40 years; no infection	Double (100 ml; 50 ml)	750–1,000 ml oral water; void before CT examination, walk and log roll
Sadow *et al.* (2008)[51]	54	Bladder (CTU)	0.83	0.94	0.71	0.97	Visible hematuria	Single (100 ml)	900 ml oral water, void before CT examination; 250 ml intravenous saline
Sadow *et al.* (2008)[51]	54	Bladder (FC)	0.94	0.93	0.69	0.99	Visible hematuria	Single (100 ml)	900 ml oral water, void before CT examination; 250 ml intravenous saline

Abbreviations: CTU, CT urography; FC, flexible cystoscopy; IVU, intravenous urography; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; RUP, retrograde ureteropyelography; Se, sensitivity; Sp, specificity; UUT, upper urinary tract; UUT-UCC, upper urinary tract urothelial cell carcinoma.

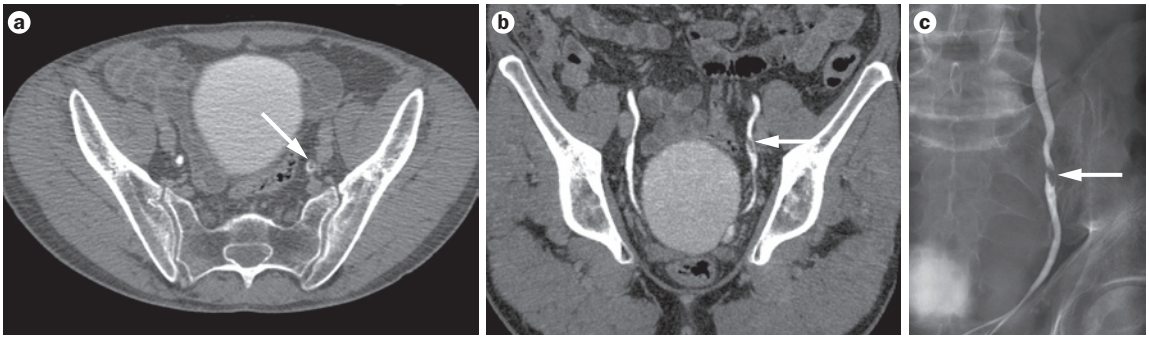

Figure 2 | Imaging and biopsy of urothelial cell carcinoma. **a** | Axial CT urogram during the excretory phase reveals a filling defect in the left pelvic ureter. **b** | Coronal reconstruction of the same examination, again demonstrating a mass in the left pelvic ureter. **c** | Retrograde ureteropyelography immediately before biopsy shows a small urothelial cell carcinoma of the left pelvic ureter.

quantitative evidence provided by the study validated the use of CT urography for diagnosing UUT-UCC.

New diagnostic imaging strategies

Conventional diagnostic imaging pathways for hematuria—including ultrasonography, IVU and CT urography—are complicated and lengthy. The principal aim of any new diagnostic strategy must be to simplify and shorten the time from presentation to diagnosis. The diagnostic accuracy of CT urography for urinary tract stones and solid renal masses surpasses that for ultrasonography and IVU, as described in the previous section. This means that CT urography has the potential to be a single replacement test for ultrasonography and IVU. New evidence relating to the diagnostic accuracy of CT urography for UCC suggests CT urography might also be the technique of choice for imaging the urothelium for suspected UCC.[31,39,40,44,46,47]

Whether all patients with hematuria should undergo CT urography, or whether there are subgoups of patients

who are more likely to benefit from CT urography than others, remains under investigation. Some notable features of CT urography mean that it should be targeted towards a select patient population—these include the length of time required in the CT suite, the increased radiation dose compared to other CT studies, and the large bolus of intravenous contrast administered.

The ideal initial diagnostic imaging test should have high sensitivity and specificity for diseases at high prevalence in the test population. Deciding what constitutes a high prevalence is not just a clinical decision but also depends on economic and political factors. Disease prevalence in patients evaluated for hematuria using ultrasonography and IVU from two studies are shown in Table 3.[2,3] Table 4 shows the prevalence of disease in a series of patients over 40 years of age who presented with visible hematuria and were evaluated using CT urography.[46] Comparison of the data from these studies shows there is a 4.4–22 times greater prevalence of UUT-UCC and a 1.8–5.1 greater prevalence of stones in the cohort who underwent CT urography than those who received ultrasonography or IVU as the initial imaging investigation. Although the study populations cannot be exactly age matched, the difference in prevalence is striking and is most likely to reflect the greater diagnostic accuracy of CT urography for investigating hematuria compared with ultrasonography and IVU.

The prevalence of specific underlying diseases responsible for hematuria can be predicted by the presence of various risk factors. The two most readily identifiable risk factors that reflect the prevalence of UCC are visible hematuria and increasing patient age. This knowledge can be used clinically for stratification into groups of patients at low-risk and high-risk for UCC (Table 5).[46] The high-risk group consists of patients >40 years old with visible hematuria and urinary tract infection excluded. Only in the high-risk group is the prevalence of UUT-UCC sufficient to justify initial investigation with CT urography. The low-risk group comprises patients >40 years old with nonvisible hematuria and those <40 years old with either nonvisible or visible hematuria. The disease with the greatest prevalence in patients aged <40 years with nonvisible hematuria is medical renal disease,[48] so renal tract ultrasonography is recommended as the initial imaging test in these patients. Ultrasonography can elucidate the presence, position and outline of the kidneys, cortical thickness, and the presence of large stones, large renal masses, and hydronephrosis. Stones are the most common cause of hematuria in patients <40 years with visible hematuria and those >40 years of age with nonvisible hematuria with UTI excluded. The prevalence of UUT-UCC is very low in these patients. Given that unenhanced CT has the highest sensitivity for upper urinary tract stones, it is recommended as the initial imaging investigation in these patients. Unenhanced CT can detect small stones, hydronephrosis, hydroureter, and some renal masses, upper tract urothelial cancers and bladder cancers.

Table 3 | Disease prevalence in patients evaluated initially with US and IVU

Disease	Prevalence (%)	
	Visible hematuria	Nonvisible hematuria
Bladder cancer	16.5–19.3	3.7–4.8
Renal cell cancer	0.9–2.0	0.3–1.0
Prostate cancer	0.6	0.2
UUT-UCC	0.1–0.5	0.1–0.2
Stones	3.2–8.8	4.0–7.8
UTI	13.0	13.0
Nephrological disease	10.3	9.4
No disease found	52.5–72.2	68.2–87.3

Data combined from 2 studies.[2,3] Abbreviations: IVU, intravenous urography; US, ultrasonography; UUT-UCC, upper urinary tract urothelial cell carcinoma.

Table 4 | Disease prevalence according to CT urography

Disease	Prevalence (%)
Bladder cancer	18.6
Renal cell cancer	2.4
UUT-UCC	2.2
Prostate cancer	3.5
Upper tract stones	15.1
Bladder stones	1.2
ADPKD	0.3
Chronic pyelonephritis	0.2
Normal upper tracts	80.3

Patients were ≥40 years of age with visible hematuria.[46] Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; UUT-UCC, upper urinary tract urothelial cell carcinoma.

A method of triaging patients by incorporating the risk score has been proposed (Table 5),[46] whereby patients with a risk score of ≥3 undergo CT urography while those with a risk score of <3 undergo unenhanced CT of the kidney, ureters and bladder or ultrasonography. If ultrasonography or unenhanced CT reveal an increased risk for UCC as defined by the risk score (≥3), then CT urography becomes justified.[47,49] For patients of any age in the low-risk group with persistent nonvisible hematuria and normal imaging investigations, repeat imaging is only justified if there is a significant change in the risk score, for example if urinary tract symptoms or visible hematuria are reported. The optimum diagnostic imaging strategy for patients at high-risk for UCC consists of initial CT urography as a replacement for conventional upper tract imaging techniques[46] and as a triage test for bladder assessment. For patients at low-risk of UCC, ultrasonography and unenhanced CT of the kidneys, ureters and bladder should be used instead.[11,26,43,44] A summary of such a diagnostic strategy is given in Figure 3.

Interest has recently increased in the potential role of CT urography for evaluating the bladder.[32,50,51] Blick *et al.*[47] assessed diagnostic strategies for diagnosing bladder cancer using CT urography as an additional, replacement or triage test in 778 patients. They

Table 5 | Risk factors and risk scores for UCC

Risk factor	Risk score
≥40 years of age	1
Hematuria	
Visible	2
Nonvisible, persistent	1
Nonvisible, unspecified	0
Imaging findings	
UUT-UCC	2
Bladder cancer	2
Renal mass	2
Hydronephrosis, hydroureter	2
Stone, large, for planning percutaneous nephrolithotomy	2
Urine cytology	
Normal, atypical probably benign, atypia of uncertain signficance	0
Atypia suspicious of malignancy and malignant	2
Occupational exposure to aromatic amines or benzenes, smoking, analgesic abuse, phenacetin	2
Urethral stricture preventing cystoscopy	2

Abbreviation: UCC, urothelial cell carcinoma; UUT-UCC, upper urinary tract urothelial cell carcinoma.

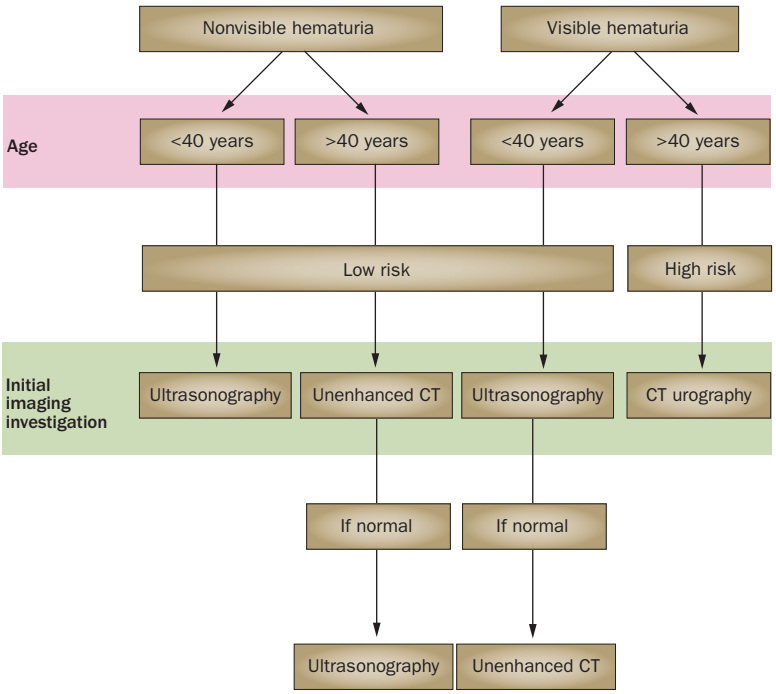

Figure 3 | A summary of diagnostic strategies for investigating hematuria. Patients should undergo imaging investigations according to their risk of urothelial cell carcinoma, which depends on age and whether hematuria is visible.

concluded that patients with a positive CT urography score for bladder cancer should directly undergo rigid cystoscopy, and those with normal or equivocal scores should undergo flexible cystoscopy. The diagnostic accuracy of this triage strategy is the same as for the additional test strategy, which dictates that all patients undergo both CT urography and flexible cystoscopy but has the advantage of a 17% reduction in the number of flexible cystoscopies performed.

Problems and solutions

The principal problems associated with CT urography for investigating hematuria are reader error, false-positive diagnoses and increased radiation dose. Other problems that are also important, but are considered secondary issues, include the length of time the patient is required to be in the CT room for the complete examination, availability of CT, cost compared with other imaging techniques, the need for special image viewing hardware and software for optimum reporting, the diagnosis of unexpected extragenitourinary disease, the requirement for a quality assurance program and the overutilization of CT urography for inappropriate indications.

There are many ways to reduce reader error, but perhaps the best method of teaching radiologists to read CT urography is to introduce a formative teaching program designed to simulate clinical reporting. Reader training, interpretation and certification has already been employed for CT colonography.[52,53]

Various diagnostic accuracy studies have revealed that the positive predictive value of CT urography for UUT-UCC is low,[31,42,43,45] ranging from 0.50 to 0.82, which currently precludes the notion of referring patients for curative surgery as soon as they are diagnosed. A list of false-positive diagnoses is given in Box 2. Therefore, UUT-UCC diagnosed with CT urography should be biopsied (guided by ureteroscopy or retrograde ureteropyelography) for histopathological confirmation of the diagnosis before proceeding to surgery.[54]

Overutilization of high-tech imaging services such as multidetector CT, MR imaging and PET-CT is defined as performing imaging procedures that are unlikely to improve patient outcome.[55] Health-care systems in which there is a fee-for-service payment process, self-referral practices, and defensive medicine might influence the overutilization of imaging, which can be responsible for unnecessary health-care costs and frequently exposes patients to unnecessary radiation. CT urography requires a higher dose of radiation than IVU, which can only be justified by its increased diagnostic accuracy in the correct clinical setting.[56] Individual patient radiation doses can be minimized by close attention to optimizing image acquisition parameters and by using CT dose-reducing techniques.[57] The use of referral guidelines that incorporate appropriateness criteria based on objective clinical evidence and comparative effectiveness research make an important contribution to reducing overutilization. Further comparative effectiveness research of imaging technology is called for as a deterrent to overutilization of medical imaging.[55]

Conclusions

The principal indication for CT urography is the investigation of hematuria. Rapid developments in multidetector CT technology make multiplanar review of isotropic datasets possible providing high-resolution CT urography studies. The high diagnostic accuracy of unenhanced CT

for stones, nephrographic phase CT for renal masses and excretory phase CT for UUT-UCC (compared to other techniques) makes CT urography the preferred initial imaging investigation for patients presenting with hematuria. To ensure the maximum diagnostic accuracy of CT urography, attention to detail is important. For patients at high risk of bladder cancer and UUT-UCC, CT urography should be used as a triage test before cystoscopy and as the initial imaging test for examination of the upper urinary tract. By paying careful attention to indications and technique, the radiation dose of CT urography may reach an acceptable range for those patients with hematuria who are at high risk of bladder cancer and UUT-UCC. Formative teaching programs simulating clinical reporting are suggested as the preferred method of teaching radiologists to read CT urograms and to reduce reader error. As the positive predictive value of CT urography for UUT-UCC is low, patients who are diagnosed with UUT-UCC by CT urography should undergo biopsy (guided by ureteroscopy or retrograde ureteropyelography) for histopathological confirmation of the diagnosis before proceeding to surgery.

CT urography is a uroradiology imaging technique that befits great expectations. In future MR imaging and dual-energy CT may have important roles in imaging hematuria. MR urography has some advantages over CT urography in that it does not use ionizing radiation, but currently the spatial resolution of MR urography falls below CT urography, which is important when looking for small urothelial lesions in the upper urinary tract.[58–60] Dual-energy CT is currently being evaluated in clinical practice, which may lead to reduction in patient radiation dose.[61]

Currently CT urography is the preferred test and is recommended for imaging adult patients over 40 years of age presenting with visible hematuria, once UTI is excluded. In conclusion, CT urography is recommended as an initial imaging test for patients presenting with hematuria who are at high risk of UCC.

Box 2 | False-positive diagnoses for UUT-UCC

- Clot
- Debris
- Kink of the ureter (accentuated by inspiration)
- Fibroepithelial polyp
- Injury to the ureter following passage of a stone, stent placement or ureteroscopy, inflammation, fibrosis
- Ureteritis cystica
- Flow artifacts following furosemide administration or layering effects
- Unusual looking papilla, a normal variant
- Amyloid
- Nephrogenic adenoma
- Renal cell carcinoma
- Lymphoma
- Vascular impressions

Review criteria

The PubMed database was searched using the terms "CT urography", "hematuria", and "urothelial cell carcinoma" for papers published in the last 15 years. Only papers written in English were included.

1. Sutton, J. M. Evaluation of haematuria in adults. *JAMA* **263**, 2475–2480 (1990).
2. Khadra, M. H., Pickard, R. S., Charlton, M., Powell, P. H. & Neal, D. E. A prospective analysis of 1,939 patients with hematuria to evaluate current diagnostic practice. *J. Urol.* **163**, 524–527 (1999).
3. Edwards, T. J., Dickinson, A. J., Natale, S., Gosling, J. & McGrath, J. S. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU Int.* **97**, 301–305 (2006).
4. Kelly, J. D., Fawcett, D. P. & Goldberg, L. C. Assessment and management of non-visible haematuria in primary care. *Br. Med. J.* **338**, a3021 (2009).
5. Malmström, P.-U. Time to abandon testing for microscopic haematuria in adults? *Br. Med. J.* **326**, 813–815 (2003).
6. Rodgers, M. *et al.* Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technol. Assess.* **10**, iii–iv, xi–259 (2006).
7. Grossfeld, G. D. *et al.* Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association best practice policy-Part 1: definition, detection, prevalence, and etiology. *Urology* **57**, 599–603 (2001).
8. Grossfeld, G. D. *et al.* Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association Best Practice Policy-Part 11: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. *Urology* **57**, 604–610 (2001).
9. Webb, J. A. W. in *European Uroradiology '94* (eds Dalla Palma, L. & Thomsen, H. S.) 36–39 (FADL, Copenhagen, 1994).
10. Webb, J. A. W. Imaging in haematuria. *Clin. Radiol.* **52**, 167–171 (1997).
11. Van Der Molen, A. *et al.* CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur. Radiol.* **18**, 4–17 (2008).
12. Mahesh, M. *MDCT Physics: The Basics—Technology, Image Quality and Radiation Dose* 5–16 (Lippincott Williams & Wilkins, Philadelphia, 2009).
13. Mahesh, M. *MDCT Physics: The Basics—Technology, Image Quality and Radiation Dose* 17–35 (Lippincott Williams & Wilkins, Philadelphia, 2009).
14. Smith, R. C. *et al.* Acute flank pain: comparison of noncontrast enhanced CT and intravenous urography. *Radiology* **194**, 789–794 (1995).
15. Smith, R. C., Verga, M., McCarthy, S. & Rosenfield, A. T. Diagnosis of acute flank pain: value of unenhanced helical CT. *AJR Am. J. Roentgenol.* **166**, 97–101 (1996).
16. Sourtzis, S. *et al.* Radiologic investigation of renal colic: unenhanced helical CT compared with excretory urography. *AJR Am. J. Roentgenol.* **172**, 1491–1494 (1999).
17. Fielding, J. R., Silverman, S. G., Samuel, S., Zou, K. H. & Loughlin, K. R. Unenhanced helical CT of ureteral stones: a replacement for excretory urography in planning treatment. *AJR Am. J. Roentgenol.* **171**, 1051–1053 (1998).
18. Bosniak, M. A. The small (less than or equal to 3.0 cm) renal parenchymal tumor: detection, diagnosis, and controversies. *Radiology* **179**, 307–317 (1991).
19. Silverman, S. G. *et al.* Small (< or = 3 cm) renal masses: correlation of spiral CT features and pathologic findings. *AJR Am. J. Roentgenol.* **163**, 597–605 (1994).
20. Zagoria, R. J. Imaging of small renal masses. *AJR Am. J. Roentgenol.* **175**, 945–955 (2000).
21. Warshauer, D. M. *et al.* Detection of renal masses: sensitivities and specificities of excretory urography / linear tomography, US, and CT. *Radiology* **169**, 363–365 (1988).
22. Caoili, E. M. *et al.* Urinary tract abnormalities: initial experience with multi-detector row CT urography. *Radiology* **222**, 353–360 (2002).
23. Chow, L. C. & Sommer, F. G. Multidetector CT urography with abdominal compression and three-dimensional reconstruction. *AJR Am. J. Roentgenol.* **177**, 849–855 (2001).
24. Kawashima, A. *et al.* CT urography. *RadioGraphics* **24**, 235–254 (2004).
25. Anderson, E. M., Murphy, R. M., Rennie, A. T. M. & Cowan, N. C. Multidetector computed tomography urography (MDCTU) for diagnosing urothelial malignancy. *Clin. Radiol.* **62**, 324–332 (2006).
26. Nolte-Ernsting, C. & Cowan, N. Understanding multi-slice CT urography techniques: many roads lead to Rome. *Eur. Radiol.* **16**, 2670–2686 (2006).
27. Dillman, J. R., Caoili, E. M. & Cohan, R. H. Multi-detector CT urography: a one-stop renal and urinary tract imaging modality. *Abdom. Imaging* **32**, 519–529 (2007).
28. Silverman, S. G., Lyendecker, J. R. & Amis, E. S. What is the current role of CT urography and MR

urography in the evaluation of the urinary tract? *Radiology* **250**, 309–323 (2009).
29. Weinstein, S., Obuchowski, N. A. & Lieber, M. L. Clinical evaluation of diagnostic tests. *AJR Am. J. Roentgenol.* **184**, 14–19 (2005).
30. Stacul, F. *et al.* Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur. Radiol.* **21**, 2527–2541 (2011).
31. Cowan, N. C., Turney, B. W., Taylor, N. J., McCarthy, C. L. & Crew, J. P. Multidetector computed tomography urography (MDCTU) for diagnosing upper urinary tract tumour. *BJU Int.* **99**, 1363–1370 (2007).
32. Turney, B. W., Willatt, J. M. C., Nixon, D., Crew, J. P. & Cowan, N. C. Computed tomography urography for diagnosing bladder cancer. *BJU Int.* **98**, 345–348 (2006).
33. Knox, M. K., Rivers-Bowerman, M. D., Bardgett, H. P. & Cowan, N. C. Multidetector computed tomography with triple-bolus contrast medium administration protocol for preoperative anatomical and functional assessment of potential living renal donors. *Eur. Radiol.* **20**, 2590–2599 (2010).
34. Kekelidze, M. *et al.* Kidney and urinary tract imaging: triple-bolus multidetector CT urography as a one-stop shop–protocol design, opacification, and image quality analysis. *Radiology* **255**, 508–516 (2010).
35. Lang, E. K. *et al.* Computerized tomography tailored for the assessment of microscopic hematuria. *J. Urol.* **167**, 547–554 (2002).
36. Gray Sears, C. *et al.* Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. *J. Urol.* **168**, 2457–2460 (2003).
37. O'Malley, M. E. *et al.* Comparision of excretory phase, helical computed tomography with intravenous urography in patients with painless haematuria. *Clin. Radiol.* **58**, 294–300 (2003).
38. Albani, J. M., Ciaschini, M. W., Streem, S. B., Herts, B. R. & Angermeier, K. W. The role of computerized tomographic urography in the initial evaluation of hematuria. *J. Urol.* **177**, 644–648 (2007).
39. Wang, L. J. *et al.* Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J. Urol.* **183**, 48–55 (2010).
40. Jinzaki, M. *et al.* Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am. J. Roentgenol.* **196**, 1102–1109 (2011).
41. Fritz, G. A., Schoellnast, H., Deutschmann, H. A., Quehenberger, F. & Tillich, M. Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. *Eur. Radiol.* **16**, 1244–1252 (2006).
42. Chow, L. C., Kwan, S. W., Olcott, E. W. & Sommer, G. Split-bolus MDCT urography with synchronous nephrographic and excretory phase enhancement. *AJR Am. J. Roentgenol.* **189**, 314–322 (2007).
43. Sudakoff, G. S. *et al.* Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J. Urol.* **179**, 862–867 (2008).
44. Wang, L. J., Wong, Y. C., Chuang, C. K., Huang, C. C. & Pang, S. T. Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. *J. Urol.* **181**, 524–531 (2009).
45. Maheshwari, E., O'Malley, M. E., Ghai, S., Staunton, M. & Massey, C. Split-bolus MDCT urography: upper tract opacification and performance for upper tract tumors in patients with hematuria. *AJR Am. J. Roentgenol.* **194**, 453–458 (2010).
46. Cowan, N. C., Mallett, S. & Crew, J. P. Justification for using CT urography as the first-line diagnostic imaging test for investigating hematuria in patiets at high risk of upper urinary tract cancer. Presented at the 36th Scientific Assembly of the Society of Uroradiology.
47. Blick, C. G. *et al.* Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic. *BJU Int.* http://dx.doi.org/10.1111/j.1464-410X.2011.10664.x.
48. Tomson, C. & Porter, T. Asymptomatic microscopic or dipstick haematuria in adults: which investigations for which patients? A review of the evidence. *BJU Int.* **90**, 185–198 (2002).
49. Stenzl, A. *et al.* The Updated EAU Guidelines on muscle-invasive and metastatic bladder cancer. *Eur. Urol.* **55**, 815–819 (2009).
50. Cohan, R. H., Caoili, E. M., Cowan, N. C., Weizer, A. Z. & Ellis, J. H. MDCT urography: exploring a new paradigm for imaging of bladder cancer. *AJR Am. J. Roentgenol.* **192**, 1501–1508 (2009).
51. Sadow, C. A., Silverman, S. G., O'Leary, M. P. & Signorovitch, J. E. Bladder cancer detection with CT urography in an academic medical center. *Radiology* **249**, 195–202 (2008).
52. Dachman, A. H. *et al.* Formative evaluation of standardized training for CT colonographic image interpretation by novice readers. *Radiology* **249**, 167–177 (2008).
53. Soto, J. A., Barish, M. A. & Yee, J. Reader training in CT colonography: how much is enough? *Radiology* **237**, 26–27 (2005).
54. Roupret, M. *et al.* European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. *Eur. Urol.* **59**, 584–594 (2011).
55. Hendee, W. R. *et al.* Addressing overutilization in medical imaging. *Radiology* **257**, 240–245 (2010).
56. Vrtiska, T. J. *et al.* Spatial resolution and radiation dose of a 64-MDCT scanner compared with published CT urography protocols. *AJR Am. J. Roentgenol.* **192**, 941–948 (2009).
57. Toth, T. & Hsieh, J. in *MDCT Physics The Basics—Technology, Image Quality and Radiation Dose* (ed. Mahesh, M.) 115–143 (Lippincott Williams & Wilkins, Philadelphia, 2009).
58. Nolte-Ernsting, C. C., Staatz, G., Tacke, J. & Gunther, R. W. MR urography today. *Abdom. Imaging* **28**, 191–209 (2003).
59. Leyendecker, J. R., Barnes, C. E. & Zagoria, R. J. MR urography: techniques and clinical applications. *RadioGraphics* **28**, 23–46 (2008).
60. Takahashi, N. *et al.* Small (<2-cm) upper-tract urothelial carcinoma: evaluation with gadolinium-enhanced three-dimensional spoiled gradient-recalled echo MR urography. *Radiology* **247**, 451–457 (2008).
61. Coursey, C. *et al.* Dual-energy multidetector CT: how does it work, what can it tell us, and when can we use it in abdominopelvic imaging? *RadioGraphics* **30**, 1037–1055 (2010).

Supplementary information
Supplementary information is linked to the online version of the paper at www.nature.com/nrurol.

Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour

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OBJECTIVE

To evaluate multidetector computed tomography urography (MDCTU) for diagnosing upper urinary tract (UUT) urothelial tumour by comparison with retrograde ureteropyelography (RUP).

PATIENTS AND METHODS

MDCTU and RUP were used in a selected series of adult patients presenting with haematuria. Entry criteria were based on findings on intravenous urography and were chosen to ensure a high prevalence of UUT urothelial tumour to allow a valid retrospective comparison of the diagnostic techniques. MDCTU and RUP studies were scored for the presence and absence of UUT urothelial tumour by two radiologists, retrospectively and independently, and while unaware of the demographic and clinical information. The reference standards were the histopathology and clinical follow-up.

RESULTS

MDCTU and RUP were used in 106 patients over a 24-month period. RUP was attempted in 151 of 212 UUTs; the corresponding MDCTU for each UUT was reviewed. MDCTU was a true-positive (TP) for urothelial tumour in 31, true-negative (TN) in 111, false-positive (FP) in eight and false-negative (FN) in one UUT, giving a sensitivity of 0.97, a specificity of 0.93, a positive predictive value (PPV) of 0.79 and a negative PV (NPV) of 0.99. RUP was technically successful and diagnostic in 96% of the UUTs (143/151). For diagnosing urothelial tumour, RUP was TP in 26, TN in 112, FP in four and FN in one UUT, giving a sensitivity of 0.97, specificity of 0.93, a PPV of 0.79 and NPV of 0.99.

CONCLUSION

This study validates quantitatively the use of MDCTU for diagnosing UUT urothelial tumour.

KEYWORDS

urography, multidetector-row computed tomography urography, haematuria, kidney, ureter, retrograde ureteropyelography.

INTRODUCTION

Multidetector CT (MDCT) is an established imaging method for detecting and characterizing renal masses, and identifying urinary tract calculi [1,2]. MDCT urography (MDCTU) is a more recent technique developed primarily for investigating urothelial lesions, renal masses and urinary tract stones [3]. MDCTU can also detect significant extra-genitourinary pathology [4]. Multiplanar image analysis is possible with MDCTU, as the thin slices make isotropic or near-isotropic imaging feasible. The concept of MDCTU is attractive as both the renal parenchyma and urothelium can be evaluated with one relatively noninvasive comprehensive examination. Initial experience indicates that MDCTU is a promising method for investigating benign and malignant lesions in the upper urinary tract (UUT) [3].

The most recent AUA guidelines (2001) on the evaluation of asymptomatic haematuria in adults [5], state that although high detection rates of TCC were reported for contrast-enhanced CT images [6,7] the data were considered anecdotal because the studies offered no statistical analysis. The AUA guidelines also indicate that retrograde ureteropyelography (RUP) is commonly considered by many to be the best imaging approach for detecting TCC, but again this opinion is not based on evidence [5].

The latest European Association of Urology (EAU) guidelines on the diagnosis and treatment of UUT TCC (2004) [8] state that IVU is still the first choice of examination for investigating haematuria and that RUP might be useful in cases where IVU is equivocal, with a sensitivity of >75% [9,10]. The EAU guidelines suggest that CT might be useful in the diagnosis and staging of renal parenchymal tumours, but suggest that with CT it is difficult to accurately diagnose small-volume tumours of the renal pelvis and ureter [11,12]. The EAU guidelines recognize that CT can determine the local extent of the primary tumour, invasion in renal parenchyma, and presence of lymph nodes or liver metastasis better than any other imaging technique [11,12], and therefore only advocate CT when an invasive tumour must be excluded. However, the EAU guidelines refer to single-slice CTU and should be updated to be truly relevant to current clinical practice which uses MDCT.

Thus the purpose of the present study was to evaluate quantitatively the use of MDCTU for the diagnosis of UUT urothelial tumour in patients with haematuria, by comparison with RUP, using histopathology and clinical follow-up as the reference standard.

PATIENTS AND METHODS

MDCTU and RUP were used to diagnose and stage UUT urothelial tumours in a selected series of patients presenting with haematuria. Initial investigations included IVU and flexible cystoscopy in all. Patients with equivocal or positive IVU findings, and those with persistent haematuria, negative IVU and flexible cystoscopy, were investigated for UUT

TABLE 1 The scanning parameters for MDCTU

	Protocol ID (8), MDCTU			
Variable	Before contrast	+Contrast*	2nd R†	3rd R‡
Start	Top of kidney	Top of liver	Top of liver	Top of liver or kidney
End	Bottom of symphysis	Bottom of symphysis	Bottom of symphysis	Bottom of symphysis
n	1.25 × 8	1.25 × 8	1.25 × 8	1.25 × 8
SC, mm	1.25	1.25	1.25	1.25
BC, mm	10	10	10	10
TS, mm/rot	16.75	16.75	16.75	16.75
Pitch	1.675	1.675	1.675	1.675
SFOV, mm	500	500	500	500
Matrix	512	512	512	512
DFOV, mm	320	320	320	320
SW, mm	2.5	5	2.5	1.25
RI, mm	1.25	5	1.25	0.63
kV	120	120	120	120
Auto mA	190–220	100–300	100–300	100–300

*SC, slice collimation; BC, beam collimation; TS, table feed; SFOV, scanned field of view; DFOV, display field of view; SW, section width; RI, reconstruction interval; n, detector configuration. *First reconstruction for early review; †2nd reconstruction for axial review; ‡3rd reconstruction for reporting and three-dimensional display.*

urothelial tumour with MDCTU and RUP. The study was conducted over a 24-month period.

MDCTU and RUP studies of the UUT were reviewed retrospectively and independently by two radiologists with no knowledge of the demographic details or clinical information. A decision relating to the presence or absence of UUT urothelial tumour was reached. The results were analysed using 2 × 2 tables and the sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated for MDCTU and RUP for diagnosing UUT urothelial tumour. The reference standards were histopathology (obtained by biopsy or from resected specimens) and the clinical follow-up, by reviewing the medical and pathological records over a 3–5-year period.

CT was conducted on a multidetector scanner (GE Lightspeed QX/i, GE Medical Systems, Milwaukee, WI, USA) using eight slices. All patients were given 500–750 mL of water to drink in the 20 min before CT; no oral contrast medium was administered. The patient was placed supine on the CT table. Phase 1 was unenhanced from the top of the kidneys to 2 cm below the symphysis pubis on expiration, using 8.0 × 2.5 mm collimation. A double-bolus of i.v. contrast medium was used, which was a variant of the protocol described by Chow and Sommer [13]. Phase 2 was a combined nephrographic-pyelographic phase. A bolus of 100 mL of non-ionic contrast medium (Iopamidol 300) was given i.v. by hand at 2–3 mL/s and the patient was exercised in the CT room by walking and then touching their toes, and finally by rolling on the table 720° in both clockwise and anticlockwise directions, to thoroughly mix the contrast medium with urine in the UUT and bladder. At 10 min after the first injection, a second bolus of 50 mL of the same contrast medium was given via a pump at 3 mL/s, and the abdomen and pelvis scanned in expiration 100 s after the second bolus, producing a combined nephro-pyelographic phase; the scanning parameters are listed in Table 1.

If the UUT opacification was incomplete when the first axial reconstruction was reviewed by the attending radiologist, a second delayed excretory phase scan was taken with the patient prone; this position was selected to encourage complete UUT opacification and further mixing of contrast medium with urine. The unenhanced scans were reconstructed axially using 2.5-mm sections and 1.25-mm increments. The nephro-pyelographic phase images were reconstructed axially, initially using 5-mm sections at 5-mm intervals, and then using 2.5-mm sections and 1.25-mm increments, and at 1.25-mm sections and 0.625 mm increments in selected cases where multiplanar reformatted images were viewed to achieve isotropic voxels.

For the RUP, informed consent was obtained from all patients and antibiotic prophylaxis (ciprofloxacin 500 mg orally) given. Lidocaine gel was used as a local anaesthetic and lubricant. Sedoanalgesia (diazemuls, 2.5–10 mg i.v., and pethidine 50–100 mg i.v.) was administered as required. The patient's pulse, blood pressure and oxygen saturation were continuously monitored during the procedure.

A flexible cystoscope was passed into the bladder and rotated through 180° to allow greater deviation of the end of the cystoscope and facilitate identification of the ureteric orifices. A 0.09 mm straight hydrophilic guidewire (Terumo Corporation, Tokyo, Japan) was passed into the ureteric orifice under direct vision. The guidewire was manipulated into the renal pelvis using C-arm digital fluoroscopy for guidance (Siemens Polystar, Erlangen, Germany). The flexible cystoscope was removed and a 4 F general-purpose vascular catheter (Cordis, Miami, FL, USA) placed over the wire into the renal pelvis. RUP was then performed using C-arm rotation and the table-tilting facility [14]. Low osmolar non-ionic contrast medium was used (Iopamidol 300) and diluted if appropriate with normal saline.

TABLE 2 UUT urothelial tumour site and frequency

Site	Number
TCC kidney	8
TCC renal pelvis	9
TCC ureter – multifocal	2
TCC ureter – unifocal	13
Total	32

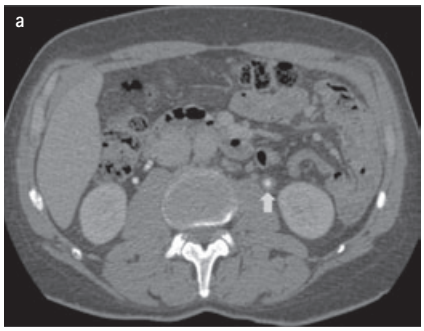
There were three other UUT tumour types, i.e. two RCC and one metastases to kidney from adenocarcinoma of the lung.

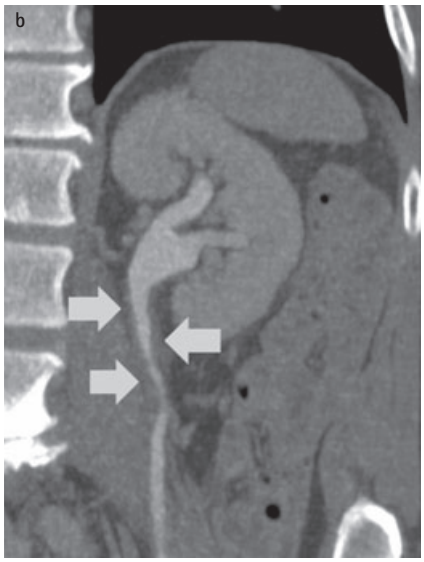
TABLE 3 The evaluation of MDCTU and RUP for diagnosing UUT urothelial tumour

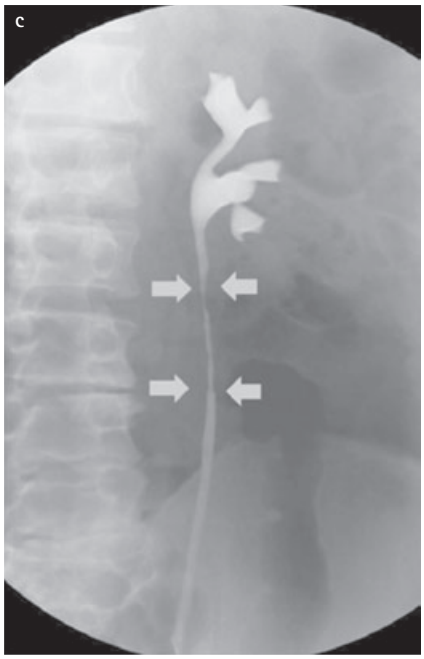
Method	Tumour positive	Tumour negative	Total
MDCTU			
positive	31	8	39
negative	1	111	112
total	32	119	151
RUP			
positive	26	4	30
negative	1	112	113
total	27	116	143

Technical failures and technically successful but not diagnostic studies were excluded from the analysis. For MDCTU, sensitivity 0.97, specificity 0.93, PPV 0.79, NPV 0.99; for RUP, sensitivity 0.96, specificity 0.97, PPV 0.87, NPV 0.97.

FIG. 1. (a) Circumferential urothelial thickening of the ureter seen on an excretory phase CTU caused by TCC; (b) Coronal MPR image of an excretory phase CTU showing circumferential urothelial thickening of the ureter; (c) RUP showing narrowing and minor but definite irregularity of the epithelium of the upper ureter from TCC.







Examinations were reviewed and scored by two radiologists, with no clinical information or knowledge of the patients' demographics. MDCTU, axial, multiplanar reformatted (MPR) images were constructed and reviewed at a workstation, running Voxar3D version 4.2 (Voxar, Edinburgh, UK) on 'abdominal' and 'bone' window settings. Using axial review of phase 1 and then phase 2, a diagnosis could be made in most cases. MPR analysis was used in specific cases only for clarification. The RUP images were also reviewed on a workstation; individual UUTs were reviewed retrospectively and independently by two radiologists and a consensus score obtained. MDCTU and RUP examinations were reviewed 3 months apart.

RESULTS

MDCTU and RUP were compared in 151 UUT in 106 patients (mean age 64.9 years, range 25.1–90.5; 71 men and 35 women) with haematuria (77 macroscopic and 29 microscopic) over a 24-month period. MDCTU was technically successful, providing images of diagnostic quality, in all 151 UUTs. RUP was technically successful in 96% (145/151) of the UUTs attempted.

The aim of RUP is to provide diagnostic information about the entire UUT so that an appropriate clinical management plan can be made. Tumour present in the bladder might prevent an adequate RUP study but does not necessarily indicate UUT involvement. In the present study, six (4%) attempted RUPs were technically unsuccessful; UUT urothelial tumour was present in four and absent in two.

The reasons for technical failure were bladder tumour obscuring the ureteric orifice in four, blood obscuring the orifice in one and tumour obstructing the lower ureter, preventing passage of the guidewire, in one.

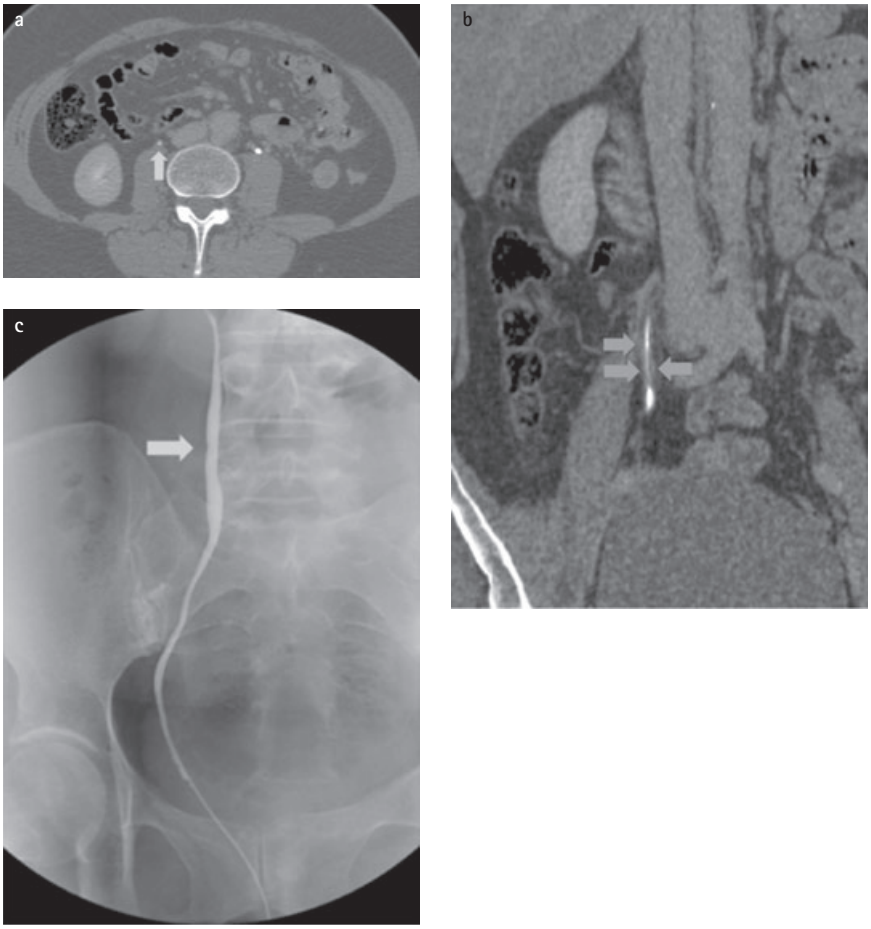
Of all the RUP studies, two were classified as technically successful but not diagnostic; in these two there was complete occlusion of the ureter, making a diagnosis from the RUP images alone impossible. In one of the cases TCC was responsible for the ureteric occlusion, and in the other it was due to PUJ obstruction secondary to chronic pyelonephritis. Thus, of the 151 RUP studies attempted, 143 were technically successful and of sufficient diagnostic quality to be included in the quantitative analysis.

The prevalence of UUT urothelial tumour in the patients assessed was 30.2% (32/106). Such a high prevalence is explained by the inclusion criteria for the study. The sites and frequency of UUT urothelial tumour are shown in Table 2.

Analysing the results for MDCTU compared with the reference standard of histopathology and follow-up showed that MDCTU had a sensitivity of 0.97 and a specificity of 0.93, with a PPV of 0.79 and NPV of 0.99 for the diagnosis of UUT urothelial tumour (Table 3). MDCTU was false-negative for urothelial tumour in one UUT; the lower ureter was incompletely opacified at the site of a small urothelial tumour. Diagnosis from the MDCTU was not possible from the excretory phase images. MDCTU was false-positive for urothelial tumour in eight UUT. Debris in the collecting system was misinterpreted as tumour in three. Circumferential ureteric wall thickening was mistaken for tumour in two. One of these cases was secondary to an iatrogenic injury at ureteroscopy for stone removal, and the other showed slight, circumferential wall thickening at the site of a ureteric kink.

RCC with collecting system invasion was interpreted as TCC in one case. A vessel causing an indentation in an upper pole infundibulum was interpreted incorrectly as TCC in one other, and the final false-positive MDCTU showed a small filling defect on axial sections in the lumen of the lower ureter close to the vesico-ureteric junction. The corresponding RUP showed a tumour-free ureter with 'fish-hooking' as it passed over an exophytic bladder cancer in one case.

FIG. 2. (a) Axial excretory phase CTU showing circumferential wall thickening of the right ureter caused by TCC. (b) Excretory phase CTU; coronal MPR image showing circumferential wall thickening of the right ureter from TCC; (c) RUP showing a smooth epithelium, masking the presence of urothelial tumour.



Analysing the results for RUP compared with histopathology and follow-up, with the technically inadequate studies excluded from the analysis, RUP had a sensitivity of 0.96 and a specificity of 0.97, with a PPV of 0.87 and NPV of 0.97 for the diagnosis of UUT urothelial tumour (Table 3). RUP was false-negative for one UUT urothelial tumour when there was circumferential ureteric wall thickening with no epithelial irregularity, which was detectable only on MDCTU. RUP was false-positive for UUT urothelial tumour in four cases. A vascular impression caused irregularity of the inferior margin of an upper pole infundibulum of the right kidney in one. Subsequently CT arteriography confirmed these signs were due to a serpiginous vessel from as small arteriovenous fistula. Irregularity of the epithelium in the region of the PUJ was shown by MDCTU to be secondary to an impacted calculus dislodged and not identified at RUP in one case. A solid RCC and a renal metastasis from adenocarcinoma of the lung were tumours that mimicked UUT urothelial tumour, both showing invasion of the collecting system.

DISCUSSION

In this study we evaluated quantitatively the use of MDCTU for diagnosing UUT urothelial tumour. Currently there are very few studies comparing the performance of various diagnostic imaging methods for diagnosing TCC in the UUT [15,16]. High detection rates for TCC on contrast-enhanced CT images are suggested [3,17,18], but such reviews have no statistical analysis. The AUA Best Practice Policy Recommendations of 2001 state that

FIG. 3. (a) Excretory phase CTU showing no opacification of the right ureter, with no dilatation; (b) RUP showing a lower ureteric filling defect confirmed as TCC on ureteroscopic biopsy.

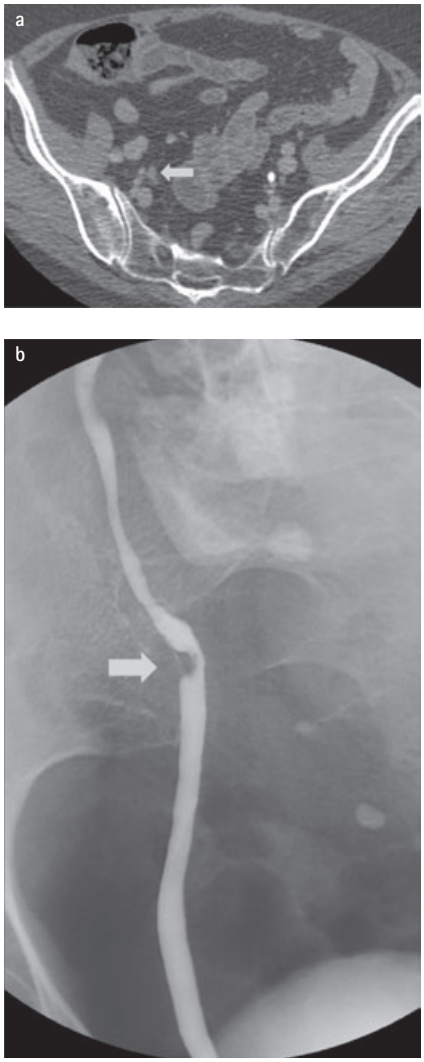
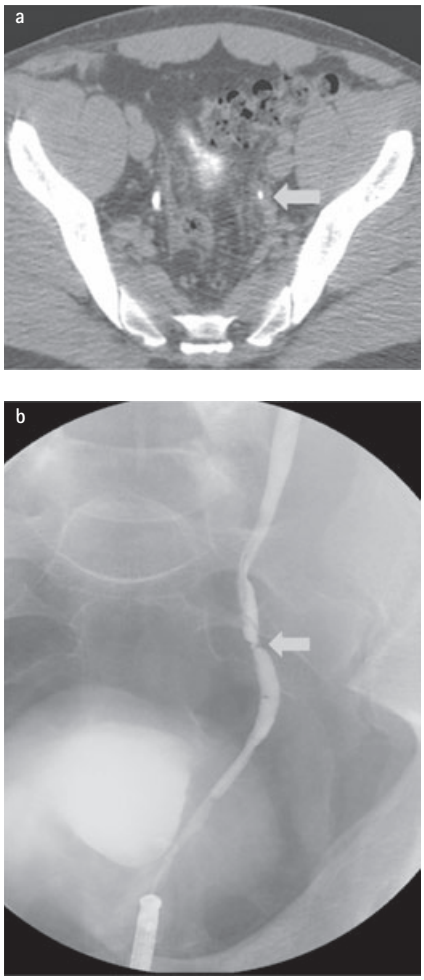


FIG. 4. (a) Axial excretory phase CTU; circumferential wall thickening of the left lower ureter was interpreted as TCC. In this study, a history of a difficult ureteroscopic stone removal was not available when the image was interpreted; (b) RUP showing a raised urothelial flap and a short lower ureteric stricture after ureteroscopy for stone removal, but no evidence of TCC.



RUP is generally considered the best imaging method for detecting and characterizing ureteric abnormalities [5]. In the present study we evaluated MDCTU for diagnosing UUT urothelial tumour and provide a statistical analysis. MDCTU was compared with RUP because RUP is currently assumed to be the best diagnostic test for these tumours.

MDCTU and RUP have similar high sensitivities for diagnosing UUT urothelial tumour; sessile or pedunculated TCC might be detected with similar sensitivity by both MDCTU and RUP. Those urothelial tumours that show circumferential urothelial thickening with epithelial irregularity (Fig. 1) might also be diagnosed by both diagnostic techniques. However, MDCTU can detect urothelial wall thickening with no epithelial irregularity. Such cases of UUT urothelial tumour will be missed by RUP (Fig. 2).

The one case of false-negative MDCTU for UUT urothelial tumour was due to incomplete ureteric opacification by contrast medium. The diagnosis of UUT urothelial tumour depends on the difference in density between the tumour and surrounding contrast medium. In ureteric segments in which there is incomplete opacification the difference in density between the tumour and ureteric wall might be so small as to render small tumours undetectable (Fig. 3). Complete and homogenous opacification of the collecting system and ureter with contrast medium is therefore desirable for optimum sensitivity of MDCTU for diagnosing UUT urothelial tumour.

The most common technical error of MDCTU is incomplete ureteric opacification, most frequently of the distal ureter [19]. Various manoeuvres can promote complete opacification of the ureter, including oral hydration before scanning [20–22], i.v. frusemide (5–10 mg), exercising the patient immediately before scanning the excretory phase [23], test scanning at defined levels before the excretory phase [24], and undertaking further series [18,25].

There is the theoretical risk of missing tumour at CTU due to incomplete mixing of contrast medium with urine within the renal pelvis, ureters and bladder. Rolling the patient on the CT table and exercising the patient just before acquiring the excretory-phase series encourages homogenization of contrast medium and urine, aiming to increasing the sensitivity of MDCTU for the diagnosis of UUT urothelial tumour.

The MDCTU false-positive results for UUT urothelial tumour fall into three groups; those with urothelial abnormalities, those with luminal abnormalities and those with extra-urothelial abnormalities, simulating UUT urothelial tumour. For the first, in the present study an iatrogenic ureteric injury at ureteroscopy led to circumferential urothelial thickening and was misdiagnosed as UUT urothelial tumour (Fig. 4). With no history, denied to the reviewers under the conditions of the study, this might be suspected. In the other case, mild circumferential urothelial thickening was identified at the site of a ureteric kink. A routine MPR review would assist in differentiating UUT tumour thickening from artefactual wall thickening. Other causes of urothelial wall thickening include irritation by calculi or stent, fibroepithelial polyp or rare tumours such as the nephrogenic adenoma.

For luminal abnormalities, in four UUT debris was mistaken for UUT urothelial tumour (Fig. 5). Lack of enhancement would help to differentiate debris from tumour, as might repositioning and re-scanning with the patient prone, and at the specific site of interest, to see if the debris shifted with repositioning. Intraluminal clot could be

differentiated from tumour using these techniques.

For the last group, vascular indentation on an upper pole infundibulum is difficult to distinguish from tumour (Fig. 6). CT arteriography or RUP would help to clarify this situation. Finally, other tumour types sometimes mimic TCC, e.g. RCC when invading the collecting system (Fig. 7). The only method of determining the exact cell type under these conditions is by biopsy and histopathology review.

In principle MDCTU has many advantages over other imaging methods for investigating patients with haematuria who are at risk of urological malignancy. MDCTU might be used as a single noninvasive test for examining the entire urinary tract. It provides information on the presence of stones, urothelial tumours, renal tumours and extra-genitourinary pathology [4]. Recent work suggests that it has a role for diagnosing bladder tumours [26]. Compared with RUP, MDCTU, as it is noninvasive, offers less chance of physical trauma, e.g. rupture of the collecting system, introduction of infection or irritation to the urinary tract.

The principal disadvantage of MDCTU is the increase in radiation dose to the patient when compared with IVU or RUP [27,28]. For patients with possible malignancy the increased radiation risk of MDCTU is justified because it has equivalent sensitivity and specificity for the diagnosis of UUT urothelial tumour when compared with RUP, but offers the additional benefits of being noninvasive, quicker, less labour-intensive, cheaper, with fewer complications, and allows simultaneous diagnosis and staging of UUT tumours.

For young patients in whom malignancy is unlikely and for those with benign disease, MDCTU can be used as a last resort test only if the other imaging tests are negative, and with continuing symptoms or equivocal findings [25].

The most effective method to reduce the radiation dose is to use fewer acquisitions or series. If MDCTU could be limited to one series through the abdomen and pelvis, or unenhanced through the kidneys followed by one series after i.v. contrast medium including the abdomen and pelvis, then the effective dose of MDCTU would fall within the range of conventional urography [28], making MDCTU an even more attractive method.

FIG. 5. (a) Axial excretory phase CTU showing hydronephrosis of the right kidney and many small filling defects caused by debris, misinterpreted as multifocal TCC; (b) RUP showing tight PUJ obstruction and hydronephrosis of the right kidney. The filling defects seen on CTU within the collecting system were not identified at RUP.

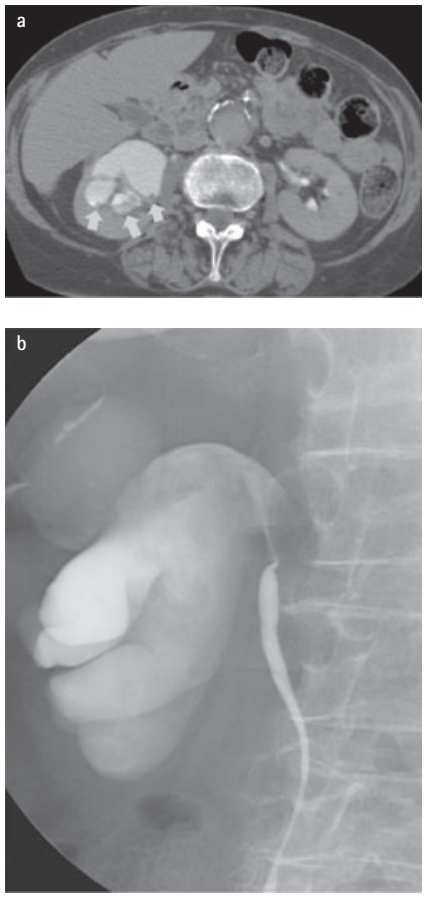
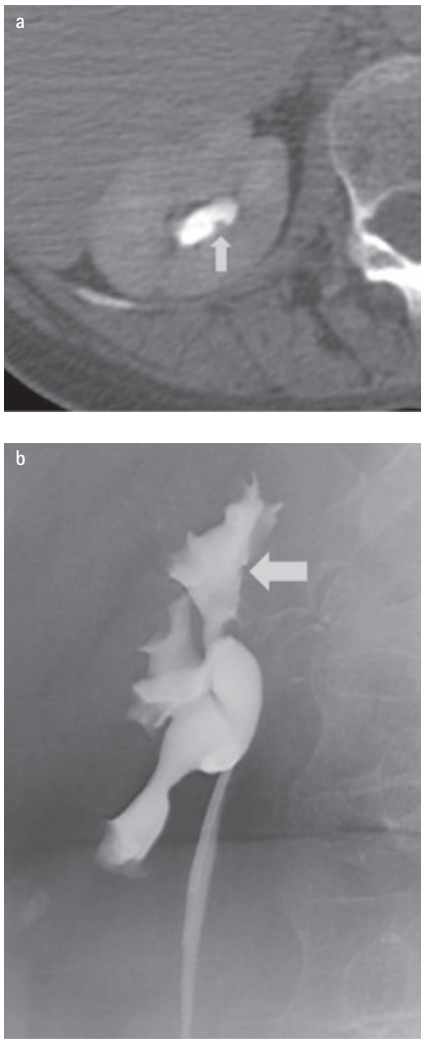
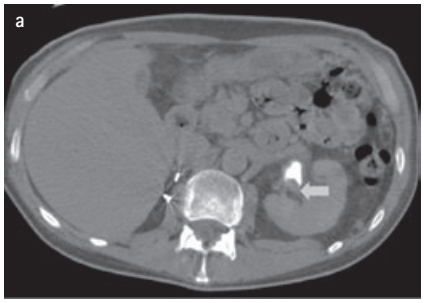


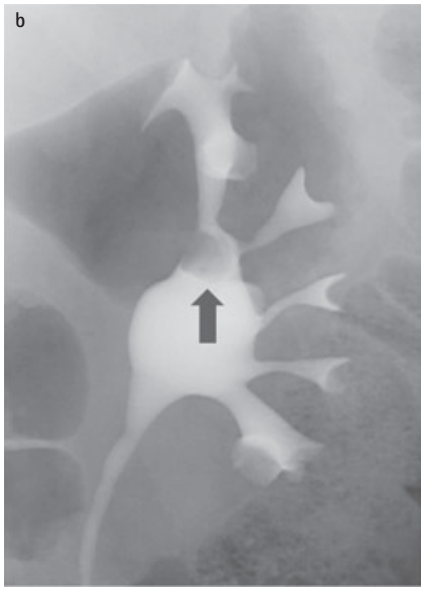
FIG. 6. (a) Axial excretory phase CTU; the small impression on the upper pole infundibulum (arrow) was recorded as urothelial tumour; (b) RUP showing the upper pole infundibulum with smooth indentation (arrow) characteristic of a vascular impression.



The present study provides a quantitative evaluation of MDCTU for detecting UUT urothelial tumour in adults presenting with haematuria. The results are significant because the increased sensitivity and similar specificity of MDCTU for detecting UUT urothelial tumour compared with RUP means that CTU is now used before RUP in our institution. RUP is no longer used to clarify equivocal IVU or ultrasonography results, but instead we use MDCTU, a change in practice brought about by the present work. In those centres with MDCTU, it is often used as a problem-solving technique when the other imaging methods provide equivocal or normal results in the presence of continuing haematuria [25]. The present study adds to the evidence that MDCTU could be used as a first-line investigation in those patients where the risk of disease outweighs the risk of radiation exposure. The most appropriate patients are those at high risk of urological cancer. If MDCTU is used as a first-line test, ultrasonography and IVU can be avoided and RUP used only if the MDCTU findings are equivocal or not diagnostic, e.g. in the unusual case of incomplete ureteric opacification. The overall result of making this readjustment is an acceleration of the diagnostic imaging pathway for diagnosing UUT urothelial tumour.

FIG. 7. (a) Axial excretory phase CTU showing a soft-tissue density mass indenting the infundibulum. The patient had had a right nephrectomy for RCC. This was reported as a TCC without the benefit of the clinical history; (b) RUP showing a filling defect with a smooth margin indenting the superior part of the renal pelvis. The lesion was reported as a TCC.





The method of RUP used was unusual, as it was done with the patient under sedoanalgesia in the radiology department, using high-quality digital C-arm fluoroscopy [14]. The RUP images are of higher quality than those obtained using a mobile unit. As this method is not widely used, it makes the present study difficult to replicate. RUP was followed by ureteroscopy and biopsy when RUP was positive for urothelial tumour. A few reports suggest that ureteroscopy and biopsy are more sensitive than RUP for diagnosing urothelial lesions [10]. It is assumed that a 3–5-year clinical follow-up, as used here, will be sufficient to allow the diagnosis of all UUT urothelial tumours in the population.

In conclusion, MDCTU and RUP have similar diagnostic sensitivity and specificity for diagnosing UUT urothelial tumour, which validates quantitatively the use of MDCTU. MDCTU should therefore be used before RUP, as it is a single noninvasive comprehensive test that allows simultaneous diagnosis and/or staging. RUP should be restricted to patients with a non-diagnostic MDCTU (usually due to incomplete ureteric opacification) or with impaired renal function, and hence a predisposition to contrast-induced nephropathy [29].

If MDCTU potentially replaces ultrasonography, IVU and RUP for investigating haematuria in specific groups of patients in whom the increased radiation dose is justified, the imaging pathway for diagnosing UUT urothelial tumour might be accelerated by reducing the number of diagnostic episodes with no reduction in diagnostic accuracy [27].

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Israel GM, Bosniak MA.** How I do it: evaluating renal masses. *Radiology* 2005; **236**: 441–50
2 **Memarsadeghi M, Heinz-Peer G, Helbich TH *et al.*** Unenhanced multi-detector row CT in patients suspected of having urinary stone disease: effect of section width on diagnosis. *Radiology* 2005; **235**: 530–6
3 **Caoili EM, Cohan RH, Korobkin M *et al.*** Urinary tract abnormalities: initial experience with multi-detector row CT urography. *Radiology* 2002; **222**: 353–60
4 **Liu W, Mortele KJ, Silverman SG.** Incidental extraurinary findings at MDCT urography in patients with haematuria: prevalence and impact on imaging costs. *AJR Am J Roentgenol* 2005; **185**: 1051–6
5 **Grossfeld GD, Litwin MS, Wolf JS Jr *et al.*** Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy –parts I & II. *Urology* 2001; **57**: 599–610
6 **Buckley JA, Urban BA, Soyer P, Scherrer A, Fisherman EK.** Transitional cell carcinoma of the renal pelvis: a retrospective look at CT staging with pathologic correlation. *Radiology* 1996; **201**: 194–8
7 **Igarashi T, Muakami S, Shichijo Y, Matsuzaki O, Isaka S, Shimazaki J.** Clinical and radiological aspects of infiltrating transitional cell carcinoma of the kidney. *Urol Int* 1994; **52**: 181–4
8 **Oosterlinck W, Solsona E, van der Meijden AP *et al.*** EAU guidelines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. *Eur Urol* 2004; **46**: 147–54
9 **Babaian RJ, Johnson DE.** Primary carcinoma of the ureter. *J Urol* 1980; **123**: 357–9
10 **Chen GL, El-Gabry EA, Bagley DH.** Surveillance of upper urinary tract transitional cell carcinoma: the role of ureteroscopy, retrograde pyelography, cytology and urinalysis. *J Urol* 2000; **164**: 1901–4
11 **Scolieri MJ, Paik ML, Brown SL, Resnick MI.** Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. *Urology* 2000; **56**: 930–4
12 **Badalament RA, Bennett WF, Bova JG *et al.*** Computed tomography of primary transitional cell carcinoma of upper urinary tracts. *Urology* 1992; **40**: 71–5
13 **Chow LC, Sommer FG.** Multidetector CT urography with abdominal compression and three-dimensional reconstruction. *AJR Am J Roentgenol* 2001; **177**: 849–55
14 **McFarlane JP, Cowan C, Holt SJ, Cowan MJ.** Outpatient ureteric procedures: a new method for retrograde ureteropyelography and ureteric stent placement. *BJU Int* 2001; **87**: 172–6
15 **Lang EK, Macchia RJ, Thomas R *et al.*** Computerized tomography tailored for the assessment of microscopic hematuria. *J Urol* 2002; **167**: 547–54
16 **Gray Sears CL, Ward JF, Sears ST, Puckett MF, Kane CJ, Amling CL.** Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic

microhematuria. *J Urol* 2002; **168**: 2457–60
17 **Caoili EM, Cohan RH, Inampudi P *et al.*** MDCT urography of upper tract urothelial neoplasms. *AJR Am J Roentgenol* 2005; **184**: 1873–81
18 **Noroozian M, Cohan RH, Caoili EM, Cowan NC, Ellis JH.** Multislice CT urography: state of the art. *Br J Radiol* 2004; **77** (Spec no. 1): S74–86
19 **Meindl T, Coppenrath E, Kahlil R, Muller-Lisse UL, Reiser MF, Muller-Lisse UG.** MDCT urography: retrospective determination of optimal delay time after intravenous contrast administration. *Eur Radiol* 2006; **16**: 1667–74
20 **Kawamoto S, Horton KM, Fishman EK.** Opacification of the collecting system and ureters on excretory-phase CT using oral water as contrast medium. *AJR Am J Roentgenol* 2006; **186**: 136–40
21 **McTavish JD, Jinzaki M, Zou KH, Nawfel RD, Silverman SG.** Multi-detector row CT urography: comparison of strategies for depicting the normal urinary collecting system. *Radiology* 2002; **225**: 783–90
22 **Caoili EM, Inampudi P, Cohan RH, Ellis JH.** Optimization of multi-detector row CT urography: effect of compression, saline administration, and prolongation of acquisition delay. *Radiology* 2005; **235**: 116–23
23 **Anderson KE, Cowan NC.** Multidetector CT urography (MDCTU) for investigation of haematuria. *Radiology* 2003; (Suppl.): 532
24 **Kemper J, Regier M, Stork A, Adam G, Nolte-Ernsting C.** Multislice CT urography (MSCTU): evaluation of a modified scan protocol for optimized opacification of the collecting system. *Rofo* 2006; **178**: 531–7
25 **Nolte-Ernsting C, Cowan N.** Understanding multislice CT urography techniques: many roads lead to Rome. *Eur Radiol* 2006; **16**: 2670–86
26 **Turney BW, Willatt JM, Nixon D, Crew JP, Cowan NC.** Computed tomography urography for diagnosing bladder cancer. *BJU Int* 2006; **98**: 345–8
27 **Hellawell GO, Cowan NC, Holt SJ, Mutch SJ.** A radiation perspective for treating loin pain in pregnancy by double-pigtail stents. *BJU Int* 2002; **90**: 801–8
28 **Nawfel RD, Judy PF, Schleipman AR, Silverman SG.** Patient radiation dose at CT urography and conventional urography. *Radiology* 2004; **232**: 126–32
29 **Thomsen HS, Morcos SK.** Radiographic contrast media. *BJU Int* 2000; **86** (Suppl. 1): 1–10

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Abbreviations: **MDCT(U)**, multidetector CT (urography); **UUT**, upper urinary tract; **RUP**, retrograde ureteropyelography; **EAU**, European Association of Urology; **P(N)PV**, positive (negative) predictive value; **MPR**, multiplanar reformatted.

BJUI
BJU INTERNATIONAL

Evaluation of diagnostic strategies for bladder cancer using computed tomography (CT) urography, flexible cystoscopy and voided urine cytology: results for 778 patients from a hospital haematuria clinic

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Study Type – Diagnostic (exploratory cohort)
Level of Evidence 2b

OBJECTIVES

- To evaluate and compare the diagnostic accuracy of computed tomography (CT) urography with flexible cystoscopy and voided urine cytology for diagnosing bladder cancer.
- To evaluate diagnostic strategies using CT urography as: (i) an additional test or (ii) a replacement test or (iii) a triage test for diagnosing bladder cancer in patients referred to a hospital haematuria rapid diagnosis clinic.

PATIENTS AND METHODS

- The clinical cohort consisted of a consecutive series of 778 patients referred to a hospital haematuria rapid diagnosis clinic from 1 March 2004 to 17 December 2007. Criteria for referral were at least one episode of macroscopic haematuria, age >40 years and urinary tract infection excluded. Of the 778 patients, there were 747 with technically adequate CT urography and flexible cystoscopy examinations for analysis.
- On the same day, patients underwent examination by a clinical nurse specialist followed by voided urine cytology, CT urography and flexible cystoscopy. Voided urine cytology was scored using a 5-point system. CT urography was reported immediately by a uroradiologist and flexible cystoscopy performed by a urologist. Both examinations were scored using a 3-point system: 1, normal; 2, equivocal; and 3, positive for bladder cancer.
- The reference standard consisted of review of the hospital imaging and histopathology databases in December 2009 for all patients and reports from the medical notes for those referred for rigid cystoscopy. Follow-up was for 21–66 months.

RESULTS

- The prevalence of bladder cancer in the clinical cohort was 20% (156/778). For the diagnostic strategy using CT urography as an additional test for diagnosing bladder cancer, when scores of 1 were classified as negative and scores of 2 and 3 as positive, sensitivity was 1.0 (95% confidence interval [CI] 0.98–1.00), specificity was 0.94 (95% CI 0.91–0.95), the positive predictive value (PPV) was 0.80 (95% CI 0.73–0.85) and the negative predictive value (NPV) was 1.0 (95% CI 0.99–1.00).

What's known on the subject? and What does the study add?
Haematuria clinics with same day imaging and flexible cystoscopy are an efficient way for investigating patients with haematuria. The principal role of haematuria clinics with reference to bladder cancer is to determine which patients are 'normal' and may be discharged, and which patients are abnormal and should undergo rigid cystoscopy. It is well recognised that CT urography offers a thorough evaluation of the upper urinary tract for stones, renal masses and urothelial neoplasms but the role of CT urography for diagnosing bladder cancer is less certain. The aim of the present study was to evaluate the diagnostic accuracy of CT urography in patients with visible haematuria aged >40 years and to determine if CT urography has a role for diagnosing bladder cancer.

This study shows that the optimum diagnostic strategy for investigating patients with visible haematuria aged >40 years with infection excluded is a combined strategy using CT urography and flexible cystoscopy. Patients positive for bladder cancer on CT urography should be referred directly for rigid cystoscopy and so avoid flexible cystoscopy. The number of flexible cystoscopies required therefore may be reduced by 17%. The present study also shows that the diagnostic accuracy of voided urine cytology is too low to justify its continuing use in a haematuria clinic using CT urography and flexible cystoscopy.

- For the diagnostic strategy using CT urography as a replacement test for flexible cystoscopy for diagnosing bladder cancer, when scores of 1 were classified as negative and scores of 2 and 3 as positive, sensitivity was 0.95 (95% CI 0.90–0.97), specificity was 0.83 (95% CI 0.80–0.86), the PPV was 0.58 (95% CI 0.52–0.64), and the NPV was 0.98 (95% CI 0.97–0.99). Similarly using flexible cystoscopy for diagnosing bladder cancer, if scores of 1 were classified as negative and scores of 2 and 3 as positive, sensitivity was 0.98 (95% CI 0.94– 0.99), specificity was 0.94 (95% CI 0.92–0.96), the PPV was 0.80 (95% CI 0.73–0.85) and the NPV was 0.99 (95% CI 0.99–1.0).
- For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), patients with a positive CT urography score are referred directly for rigid cystoscopy, and patients with an equivocal or normal score were referred for flexible cystoscopy. Sensitivity was 1.0 (95% CI 0.98–1.0), specificity was 0.94 (95% CI 0.91–0.95), the PPV was 0.80 (95% CI 0.73–0.85), and the NPV was 1.0 (95% CI 0.99–1.0).
- For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 2), patients with a positive CT urography score are referred directly for rigid cystoscopy, patients with an equivocal score are referred for flexible cystoscopy and patients with a normal score undergo clinical follow-up. Sensitivity was 0.95 (95% CI 0.90–0.97), specificity was 0.98 (95% CI 0.97–0.99), the PPV was 0.93 (95% CI 0.87–0.96), and the NPV was 0.99 (95% CI 0.97–0.99).
- For voided urine cytology, if scores of 0–3 were classified as negative and 4–5 as positive for bladder cancer, sensitivity was 0.38 (95% CI 0.31–0.45), specificity was 0.98 (95% CI 0.97–0.99), the PPV was 0.82 (95% CI 0.72–0.88) and the NPV was 0.84 (95% CI 0.81–0.87).

CONCLUSIONS

- There is a clear advantage for the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), in which patients with a positive CT urography score for bladder cancer are directly referred for rigid cystoscopy, but all other patients undergo flexible cystoscopy.
- Diagnostic accuracy is the same as for the additional test strategy with the advantage of a 17% reduction of the number of flexible cystoscopies performed.
- The sensitivity of voided urine cytology is too low to justify its continuing use in a hospital haematuria rapid diagnosis clinic using CT urography and flexible cystoscopy.

KEYWORDS

sensitivity and specificity, haematuria, urinary bladder neoplasms, computed tomography X-ray, urography, cystoscopy, cytology

INTRODUCTION

Haematuria, either macroscopic or microscopic, may indicate significant underlying disease such as urinary bladder cancer, upper urinary tract urothelial cell cancer (UUT-UCC), RCC or urinary tract stones [1–3]. Early and accurate diagnosis helps optimise prognosis but conventional diagnostic pathways are complicated and long, incorporating multiple imaging tests and many diagnostic algorithms exist that have not been rigorously evaluated [4]. The concept of an integrated haematuria clinic, referred to as rapid diagnosis clinic in the present paper, dates from as early as 1990 [5] and usually incorporates clinical examination, voided urine cytology, flexible cystoscopy, ultrasonography and excretory urography [1,6]. When designing a diagnostic pathway, first-line diagnostic imaging tests should have high sensitivity to ensure disease positives are included in the test population for further investigation. Second-line investigations should be highly specific, to ensure false positives are minimised. As each diagnostic test incurs cost, increases time from presentation to diagnosis, and has inevitably some associated risk, the quest is to replace a series of tests with a single diagnostic test providing information about both the UUT and lower urinary tract (LUT). The chosen first-line test should not only be able to accurately diagnose UUT disease but also be able to determine accurately which patients should be referred for rigid cystoscopy and which should be simply discharged or followed-up, as the diagnosis of bladder cancer ultimately depends on rigid cystoscopy of the bladder and histological evaluation of the resected tissue [7]. It has been proposed that the diagnostic accuracy of the investigative pathway and the time to diagnosis may be improved by substituting CT urography for ultrasonography and excretory urography for examination of the UUTs [8]. CT urography is emerging as a 'one-stop' diagnostic imaging technique that offers a thorough evaluation of the urinary tract for stones, renal masses, and urothelial neoplasms in a single examination [9].

The precise role of CT urography for diagnosing bladder cancer is more controversial [10–12].

An estimated 104 400 incident cases of bladder cancer were diagnosed in Europe in 2006, of which 82 800 were found in men and 21 600 in women. This represents 6.6% of the total cancers in men and 2.1% in women, with an estimated male : female ratio of 3.8:1.0. For men, bladder cancer is the fourth most common cancer resulting in 4.1% of total male cancer deaths and 1.8% of total female cancer deaths. At diagnosis, 70% of bladder cancers are non-muscle-invasive and ≈30% are muscle-invasive [13].

The prevalence of bladder cancer increases with age, the highest incidence occurring in those aged 70–80 years, with a peak age of 71 years [14]. Early diagnosis is important as disease progression may be rapid. A delay of >12 weeks is a negative prognostic indicator for muscle-invasive bladder cancer [15,16]. The most common presentation is macroscopic haematuria and the prevalence of bladder cancer in patients with macroscopic haematuria is 12–20% [1–3].

Cytological evaluation of exfoliated cells in the voided urine can be used to detect urothelial cancers. The value of voided urine

cytology in evaluating patients with haematuria remains controversial [4,17,18].

The accepted reference standard for examining the bladder in patients with haematuria is flexible or rigid cystoscopy [4,7], although there are few studies evaluating the diagnostic accuracy of flexible cystoscopy. Flexible cystoscopy is reported to be at least equivalent in diagnostic accuracy to rigid cystoscopy and for some lesions, e.g. those at the anterior bladder neck, superior [19,20]. Flexible cystoscopy is a very commonly performed minimally invasive procedure with low morbidity [21], but is associated with an infection risk of ≈3% [22] and some patients find it painful [23]. In a study evaluating patients experience after flexible cystoscopy, macroscopic haematuria (19%), urinary frequency (37%), and dysuria (50%) were found more frequently than expected [21].

CT urography is defined as multidetector CT examination of the kidneys, ureters and bladder with at least one imaging series acquired during the excretory phase after i.v. contrast administration [8]. CT urography offers a single imaging test of high diagnostic accuracy with the potential to replace multiple alternative imaging tests in the diagnostic pathway, improve patient experience, improve diagnostic performance and accelerate diagnosis [24]. CT urography is rapidly becoming accepted as the preferred test for diagnosing UUT disease responsible for haematuria, such as calculi, UUT-UCC and RCC [8,9,24]. CT urography has been assessed for the evaluation of urinary tract calculi [25,26], renal masses [27,28] and UUT-UCC [29,30] and is in general clinical use.

CT urography has high diagnostic accuracy for urothelial cancers compared with excretory urography [29,31–33] but has the disadvantage of a higher radiation exposure of 20.1 mSv compared with 11.9 mSv for excretory urography [34]. The improvement in diagnostic capabilities outweighs the use of increased radiation dose for CT urography in this population group with a prevalence of UUT and LUT cancer of 25% [34].

Excretory phase CT urography opacifies the collecting system, ureter and bladder with excreted contrast medium for assessment of the urothelium. Thin collimation, fast table speed and single breath hold acquisition are important factors that help provide multiplanar reformatted images of high spatial resolution. Review of multiplanar reformatted images further improves specificity [8,35].

The principal purpose of CT urography is assessment of the UUT, and CT protocols are designed to optimise UUT opacification and hence maximise diagnostic accuracy for UUT disease. In addition to diagnosing UUT-UCC [36], CT urography can also be used to diagnose bladder cancer [10,11,37]. A secondary additional role is provision of a non-invasive method of assessing bladder abnormalities [10–12].

If CT urography is performed before flexible cystoscopy, identification of a bladder mass may direct the cystoscopist to the tumour enhancing the sensitivity of cystoscopy. CT urography may also be of value in cases where flexible cystoscopy is a technical failure.

The role of CT urography and flexible cystoscopy for diagnosing bladder cancer is to determine which patients undergo rigid cystoscopy to make the final diagnosis of bladder cancer by histological evaluation of biopsied or resected tissue and determine which patients are classified as normal. In the present study, we consider CT urography and flexible cystoscopy within the patient pathway as additional, replacement or triage tests [38].

The primary aim of the present study was to evaluate and compare the diagnostic accuracy of CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer. The second aim was to evaluate diagnostic strategies using CT urography as: (i) an additional test, (ii) a replacement test, or (iii) a triage test for diagnosing bladder cancer in patients referred to a hospital haematuria rapid diagnosis clinic.

PATIENTS AND METHODS

The study was performed according to the standard hospital haematuria rapid diagnosis clinic protocol with approval from the Chairman of the Hospital Institutional Review Board.

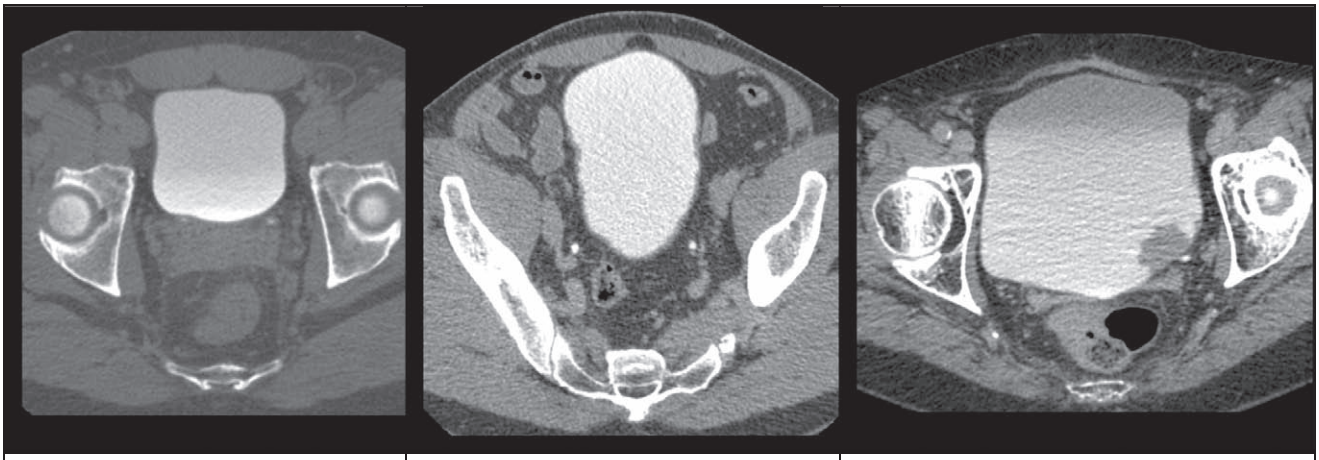
The clinical cohort consisted of a consecutive series of 778 patients attending a hospital haematuria rapid diagnosis clinic between 1 March 2004 and 17 December 2007. There were 619 (79.6%) men and 159 (20.4%) women with a mean (range) age of 67.4 (36.7–97.5) years. Criteria for referral were at least one episode of macroscopic haematuria, age ≥40 years, and UTI excluded.

Five patients of 778 patients were excluded because of technically inadequate CT urography due to lack of contrast administration because of patient refusal (one patient) and needle phobia (one), inadequate opacification of the bladder secondary to chronic urinary retention (two) and artefact from bilateral metallic hip prostheses obscuring the bladder (one). In all, 26 patients were excluded because of technically inadequate flexible cystoscopy and all subsequently underwent rigid cystoscopy under general anaesthetic. The reasons for the technically inadequate flexible cystoscopy were inability to pass the flexible cystoscope (15 patients), unable to tolerate the procedure (two), poor visibility (five), flexible cystoscopy not performed due to an administrative error (one), UTI (one), consent refused (two).

The final study population consisted of 747 patients with CT urography and flexible cystoscopy correlation.

A Lightspeed QXi, eight-slice CT machine (General Electric, Milwaukee, USA) was used. Patients were given 750–1000 mL tap water to drink in the waiting room during the 30 min before the study and asked to void immediately before the CT examination. The first acquisition series was from the top of the kidneys to 2 cm below the symphysis pubis on expiration. Via an i.v. cannula in the antecubital fossa, using a split-bolus protocol, 100 mL non-ionic contrast medium (Iopamidol 300) was given (300 mgI/mL). Between the nephrographic and excretory phase acquisitions the patient was exercised by walking around the CT gantry. At 6–8 min the patient was replaced on the CT table and rolled twice in an anticlockwise direction and then clockwise. New scout views were obtained and at 10 min a further 50 mL of i.v. contrast medium was injected via a pump (3 mL/s) and 100 s after the second bolus, a series was acquired from the top of the liver to 2 cm below the pubic symphysis. If there was full opacification of

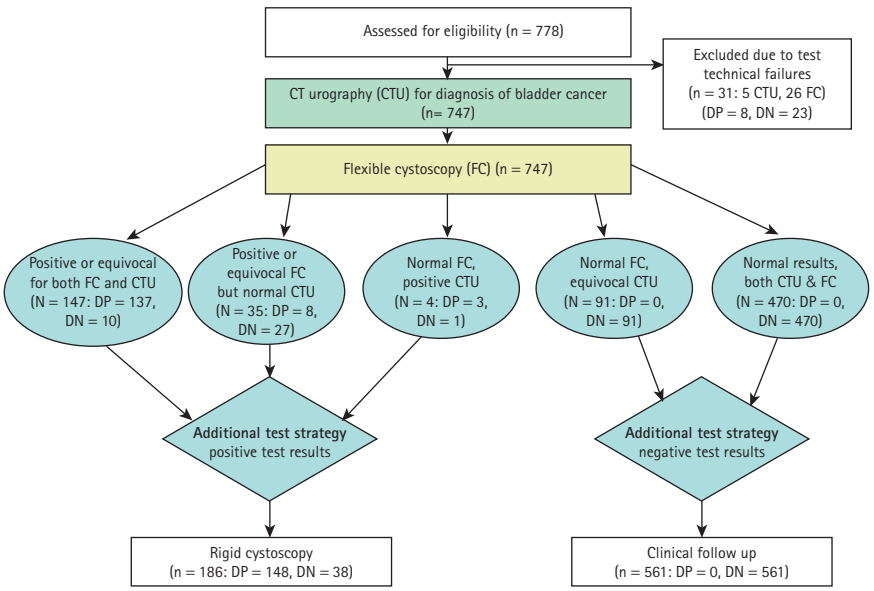
FIG. 1. CT urography scoring of the bladder.



a	b	c
Score 1 = Normal	Score 2 = Equivocal (minor focal wall thickening).	Score 3 = Bladder cancer

the ureters on the first axial reconstruction, the examination was considered completed. Images were viewed on a workstation as axial and multiplanar reformatted images running Advantage Windows (G.E. Healthcare, U.K.) or Voxar3D software version 6.3, (Toshiba Medical Visualization Systems, U.K.). The examinations were reported as soon as they were available on the local workstation by a consultant uroradiologist initially with 4 years experience of reading CT urograms and 11 years uroradiology experience. The CT urography report was available before the patient underwent flexible cystoscopy. The uroradiologist was 'blinded' to the flexible cystoscopy results as CT urograms were reported before the flexible cystoscopy tests were completed. For the last 18 months of the study, the CT urography images were available to the cystoscopist for review on the hospital web picture archiving and communication system (PACS) before the flexible cystoscopy.

FIG. 2. Flow diagram showing the diagnostic strategy using CT urography as an additional test for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic. DN, disease negative; DP, disease positive.



Both CT urography and flexible cystoscopy examinations were scored using a 3-point system: 1, 'normal'; 2, 'equivocal'; and 3, 'positive for bladder cancer'. Examples of the CT urography scoring system are provided in Fig. 1.

On the same day, flexible cystoscopy was performed after the CT urogram, by a urologist with experience ranging from over 10 years as a consultant to 2 years specialist urological training. Patients with a flexible cystoscopy score of 1 and a negative CT urography of the UUTs were discharged. Those patients with cystoscopy scores of 2 and 3 were referred for rigid cystoscopy and biopsy, or transurethral resection of the bladder tumour (Fig. 2).

For both tests clinical information consisting of age, sex and referral symptoms were available to those reporting index tests, as is standard during clinical practice.

Voided urine cytology was scored using a 5-point system: 0, inadequate or no specimen; 1, normal; 2, atypical probably benign; 3, atypia of uncertain significance;

TABLE 1 Results of CT urography and flexible cystoscopy scores compared for diagnosing bladder cancer

	CT urography			
Score	3	2	1	Total
For disease (bladder cancer) positive patients				
Flexible cystoscopy				
3	126	7	5	138
2	1	3	3	7
1	3	0	0	3
Total	130	10	8	148
For disease (bladder cancer) negative patients				
Flexible cystoscopy				
3	0	2	6	8
2	0	8	21	29
1	1	91	470	562
Total	1	101	497	599

Score 3, tumour; score 2, equivocal; and score 1, normal.

4, atypia suspicious of malignancy; and 5, malignant.

The sensitivity and specificity, the positive predictive value (PPV) and the negative predictive value (NPV) of CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer were calculated.

The reference standard consisted of review of the hospital imaging and histopathology databases in December 2009 for all patients and reports from the medical notes for those referred for rigid cystoscopy. Follow-up ranged from 21 to 66 months. The reference standard for bladder cancer consisted of rigid cystoscopy and histopathological evaluation of tissue from cystoscopic biopsy or transurethral resection.

Standard paired measures of diagnostic accuracy: sensitivity and specificity, the PPV and the NPV were calculated per patient. The 95% CIs were calculated using CIA software [39] using the Newcombe method [40] for paired proportions and the Wilson method for single proportions [41].

Uninterpretable results, for technically inadequate CT urography or flexible cystoscopy were carefully examined for each patient to determine whether the cause of the technical inadequacy could have been potentially related to presence of disease. This was not found in any patient, so these patients were excluded from the analysis without risk of introducing bias into the study results.

Indeterminate test results, where test result were equivocal (score 2 for CT urography and flexible cystoscopy) are included in each analysis as specified.

RESULTS

The present study evaluated and compared CT urography, flexible cystoscopy and voided urine cytology for diagnosing bladder cancer in a clinical cohort of 778 patients from a hospital haematuria rapid access clinic.

Of the 778 patients referred for all three tests on the same day, there were five technical failures for CT urography (Table S1), 26 technical failures for flexible cystoscopy (Table S2) and 747 patients with technically adequate CT urography and flexible cystoscopy examinations for comparison. The test results for CT urography and flexible cystoscopy scores for patients with and without bladder cancer are given in detail in Table 1. The prevalence of bladder cancer was 20% (156/778). Of the 131 patients with a definite positive CT urography (score 3), 99% (130/131) were histologically confirmed to have bladder cancer. The patient with a false-positive CT urography result was found to have an adherent blood clot at cystoscopy (Fig. 6).

In three patients bladder cancer was missed at flexible cystoscopy (3/788, 0.04%) but detected on CT urography (Figs 7 and 8).

DIAGNOSTIC STRATEGY USING CT UROGRAPHY AS AN ADDITIONAL TEST TO FLEXIBLE CYSTOSCOPY

For the diagnostic strategy using CT urography as an additional test for diagnosing bladder cancer (Fig. 2), when scores of 1 were classified as negative and scores of 2 and 3 as positive, the sensitivity was 1.0 (95% CI 0.98–1.00), the specificity was 0.94 (95% CI 0.91–0.95), the PPV was 0.80 (95% CI 0.73–0.85) and the NPV was 1.0 (95% CI 0.99–1.00). This diagnostic strategy was the original strategy used when the rapid diagnosis clinic began. It has the advantage of high diagnostic accuracy but as both CT urography and flexible cystoscopy are performed this strategy is the most expensive of those analysed.

DIAGNOSTIC STRATEGY USING CT UROGRAPHY AS A REPLACEMENT TEST FOR FLEXIBLE CYSTOSCOPY

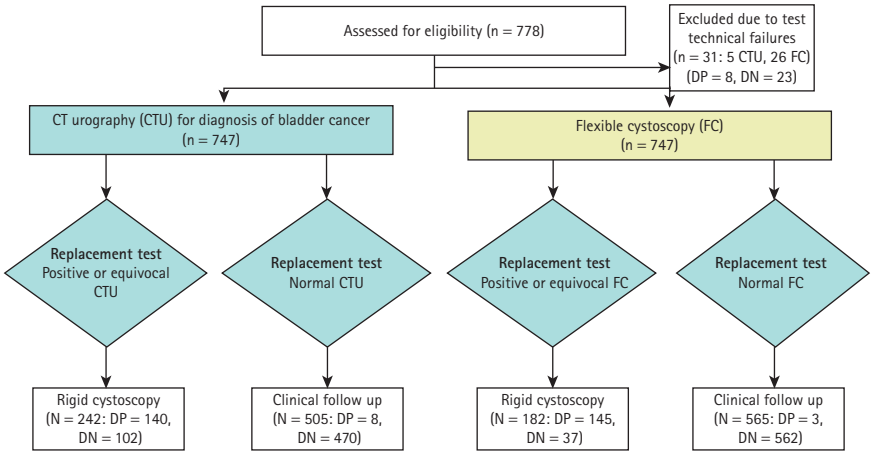
This diagnostic strategy considers CT urography as a potential replacement test for flexible cystoscopy before referral for rigid cystoscopy or follow-up (Fig. 3). A positive CT urography test result was defined as patients with either an equivocal or positive score (scores 2 and 3), so all patients with a potentially positive diagnosis are referred for rigid cystoscopy. Similarly, a positive flexible cystoscopy test result was defined as either an equivocal or positive score (scores 2 and 3).

The sensitivity of CT urography was 0.95 (95% CI 0.90–0.97) and the sensitivity of flexible cystoscopy was 0.98 (95% CI 0.94–0.99). Comparing the sensitivity of the two tests, flexible cystoscopy had a higher sensitivity by 0.03 (95% CI –0.013 to 0.085), but this was not significantly different from CT urography. Of the 505 patients scored as normal (score 1) on CT urography, eight patients (1.6%) were subsequently diagnosed with bladder cancer of which seven were small non-muscle-invasive

tumours and one was a flat carcinoma *in situ*. Of these, three were related to the bladder base, which is a particularly difficult site for visualisation (Table S3). Three patients with subsequently confirmed bladder cancer were missed, by flexible cystoscopy (score 1, Table S4).

The specificity of flexible cystoscopy was 0.94 (95% CI 0.92–0.96) and CT urography was 0.83 (95% CI 0.80–0.86). The specificity of flexible cystoscopy was significantly higher 0.11 (95% CI 0.074–0.144). The higher specificity of flexible cystoscopy is important, as using this diagnostic strategy referral of CT urography positive patients results in an extra 9% (65/747) of patients being incorrectly referred for rigid cystoscopy (Table 1 and Fig. 3).

FIG. 3. Flow chart showing the diagnostic strategy using CT urography as a replacement test for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic. DN, disease negative; DP, disease positive.



DIAGNOSTIC STRATEGY USING CT UROGRAPHY AS A TRIAGE TEST BEFORE RIGID CYSTOSCOPY, FLEXIBLE CYSTOSCOPY OR FOLLOW-UP

If CT urography is used as a triage test for diagnosing bladder cancer in the rapid access clinic, two options are presented.

For option 1, where CT urography is used as a triage test to 'rule in' bladder cancer (Fig. 4), patients identified as positive by CT urography are referred directly for rigid cystoscopy and patients with equivocal and normal results by CT urography are referred for flexible cystoscopy. The flow chart for this diagnostic strategy is shown in Fig. 4 and the results for diagnostic accuracy in Tables 2 and 3.

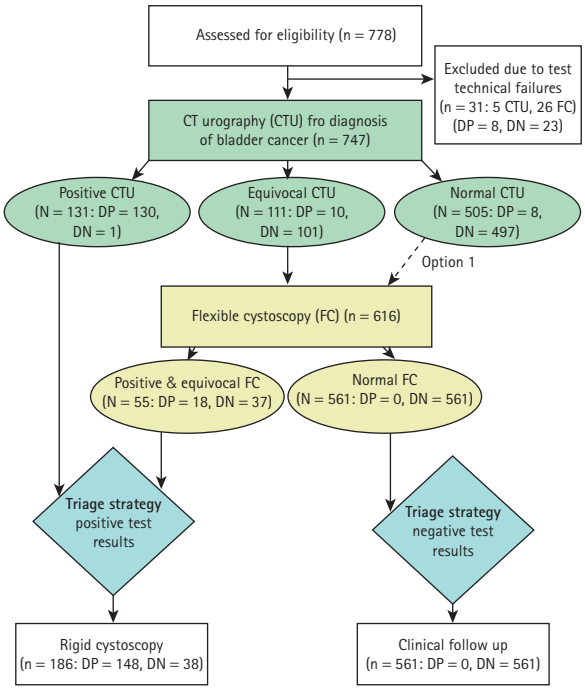


FIG. 4. Flow digram illustrating the diagnostic strategy using CT urography as a triage test, option 1, for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic. DN, disease negative; DP, disease positive.

For the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1), the sensitivity was 1.0 (95% CI 0.98–1.0), the specificity was 0.94 (95% CI 0.91–0.95), the PPV was 0.80 (95% CI 0.73–0.85), and the NPV was 1.00 (95% CI 0.99–1.00).

Using this strategy, both sensitivity and specificity are exactly the same as the additional test strategy (Table 3) but the number of flexible cystoscopies is reduced by 17% with considerable cost savings.

In option 2, CT urography is used as a triage test both to 'rule in' and 'rule out' bladder cancer. In option 2, patients with positive CT urography scores for bladder cancer are referred directly for rigid cystoscopy, patients with equivocal CT urography scores are referred for flexible cystoscopy, and patients with negative CT urography results are referred for clinical follow-up (Fig. 5). The test results of this alternative strategy are shown in Fig. 5 and in Table 3. For the diagnostic strategy triage test option 2, the sensitivity was 0.95 (95% CI 0.90–0.97), the specificity was 0.98 (95% CI 0.97–0.99), the PPV was 0.93 (95% CI 0.87–0.96), and the NPV was 0.99 (95% CI 0.97–0.99). Compared with both the additional test strategy and triage option 1, the triage option 2 strategy has a significantly lower sensitivity by 0.054 (95% CI 0.017–0.103), excluding it from clinical use (Table 3). However, triage option 2 had a significantly higher specificity (0.045: 95% CI 0.029–0.065) compared with the additional test and triage option 1 (Table 3).

ROLE OF VOIDED URINE

Urine cytology had an unacceptably low sensitivity for diagnosis of any urothelial

FIG. 5.
Flow diagram illustrating the diagnostic strategy using CT urography as a triage test, option 2, for diagnosing bladder cancer in patients attending a hospital haematuria rapid diagnosis clinic.

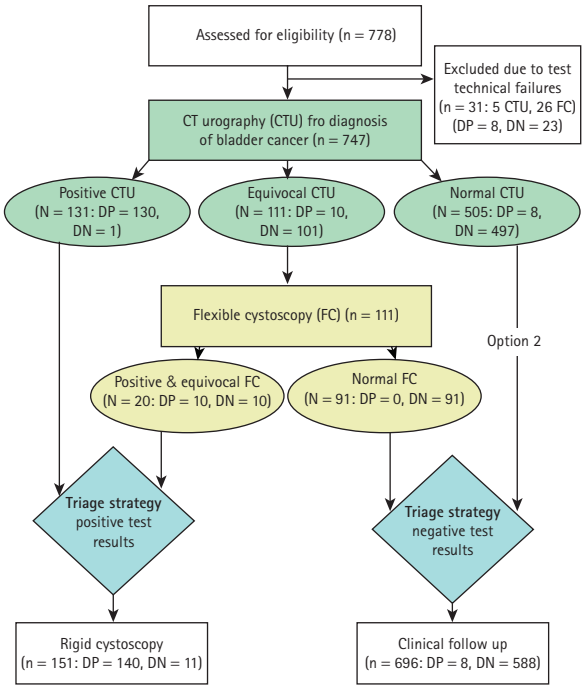
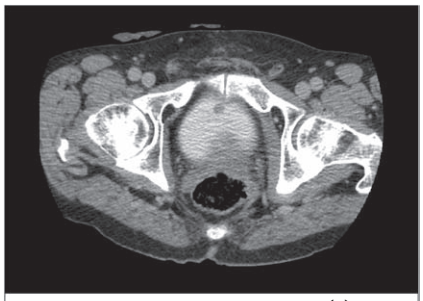
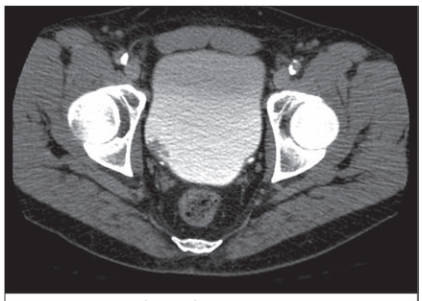


FIG. 6. The single case for which CT urography was false positive for bladder cancer.



CT urography score of bladder cancer (3) but the mass lesion in the bladder was adherent blood clot.

FIG. 7. Bladder cancer (G1 Ta) missed on flexible cystoscopy.



Bladder cancer (G1 Ta) missed on flexible cystoscopy

TABLE 2 Tables for triage strategy Option 1. All CT urography negatives referred for flexible cystoscopy

	Additional test strategy		
	Positive	Negative	Total
Patients with bladder cancer (disease positive)			
Triage test (all CT urography negative to flexible cystoscopy)			
Positive	148	0	148
Negative	0	0	0
Total	148	0	148
Patients without bladder cancer (disease negative)			
Triage test (all CT urography negative to flexible cystoscopy)			
Positive	38	0	38
Negative	0	561	561
Total	38	561	599

cancer of 0.38 (95% CI 0.31–0.45), even though the specificity was 0.98 (95% CI 0.96–0.99), using the clinically relevant threshold where scores of 4 and 5 were classified as positive results (Tables S5 and 6). In this clinical cohort, there were no cases of histologically confirmed bladder cancer in whom voided urine cytology was positive and CT urography and flexible cystoscopy were negative; however, there were two patients with bladder cancer, a negative CT urography score and a positive cytology result (Table S3).

DISCUSSION

The role of CT urography and flexible cystoscopy for diagnosing bladder cancer is to determine which patients undergo rigid cystoscopy to make the final diagnosis of bladder cancer by histological evaluation of biopsied or resected tissue and determine which patients are classified as 'normal'.

Exercising the patient before the excretory series by walking around the CT machine and rolling on the CT table to improve bladder opacification [10,42] is an important manoeuvre, which may improve the diagnostic accuracy of CT urography for diagnosing bladder cancer (Fig. 9).

The present study examined the role of CT urography for diagnosing bladder cancer with reference to various diagnostic strategies in which CT urography is (i) an additional test, (ii) as a replacement test and (iii) as a triage test (options 1 and 2).

The strategy currently in use is the additional test strategy, which shows high diagnostic accuracy but is the most expensive option as both CT urography and flexible cystoscopy are attempted on every patient. It is the standard by which other strategies are compared.

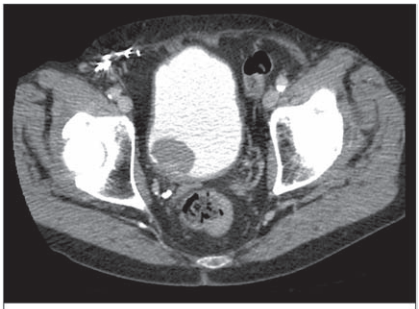
In the replacement strategy, CT urography and flexible cystoscopy have similar sensitivities for diagnosing bladder cancer, but CT urography is not a suitable replacement test for flexible cystoscopy as the specificity is significantly lower, which would mean too many patients being referred unnecessarily for rigid cystoscopy.

Two diagnostic strategies using CT urography as a triage test are presented.

TABLE 3 Results for the diagnostic accuracy of CT urography (CTU), flexible cystoscopy (FC) and voided urine cytology for diagnosing bladder cancer

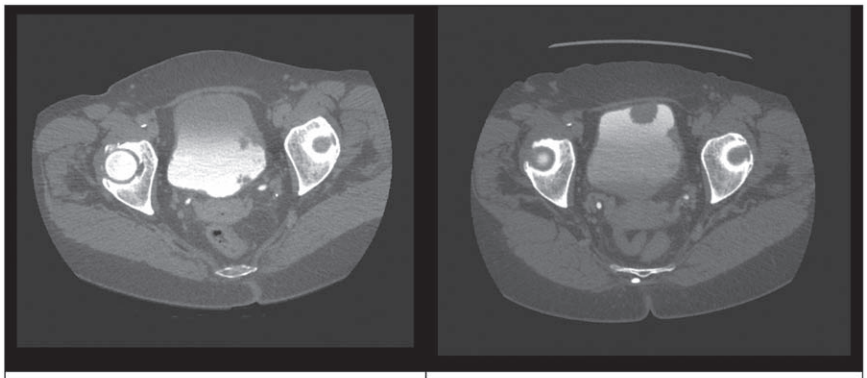
	Additional test	Replacement test		Triage test option 1	Triage test Option 2	Voided urine cytology
	CTU and FC	CTU	FC	CTU and/or FC	CTU and/or FC	
Strategy using CT urography as:	Scores 3 and 2, positive; Score 1, negative	Scores 3 and 2, positive; Score 1, negative	Scores 3 and 2, positive; Score 1, negative	CTU score 3, positive; scores 2 and 1, equivocal; FC scores 3 and 2, positive; Score 1, negative	CTU score 3, positive; score 2, equivocal; score 1, negative; FC scores 3 and 2, positive; Score 1, negative	Scores 1–3, negative; Scores 4 and 5, positive
Sensitivity (95% CI)	1.00 (0.98–1.00)	0.95 (0.90–0.97)	0.98 (0.94–0.99)	1.0 (0.98–1.00)	0.95 (0.90–0.97)	0.38 (0.31–0.45)
Specificity (95% CI)	0.94 (0.91–0.95)	0.83 (0.80–0.86)	0.94 (0.92–0.96)	0.94 (0.91–0.95)	0.98 (0.97–0.99)	0.98 (0.97–0.99)
PPV (95% CI)	0.80 (0.73–0.85)	0.58 (0.52–0.64)	0.80 (0.73–0.85)	0.80 (0.73–0.85)	0.93 (0.87–0.96)	0.82 (0.72–0.88)
NPV (95% CI)	1.00 (0.99–1.00)	0.98 (0.97–0.99)	0.99 (0.99–1.0)	1.0 (0.99–1.0)	0.99 (0.97–0.99)	0.84 (0.81–0.87)
Average number of tests per patient	2.0	1.0	1.0	1.8	1.15	1.0

FIG. 8. Bladder cancer (G3 T1) missed on flexible cystoscopy.



Bladder cancer (G3 T1) missed on flexible cystoscopy

FIG. 9. Exercising the patient by rolling on the CT table may improve bladder opacification and diagnostic accuracy of CT urography for bladder cancer.



a CT urogram showing an excretory-phase image of the bladder acquired supine at 12.5 min post-contrast administration.

b Following rolling the patient on the CT table, a large anterior wall bladder cancer is now demonstrated.

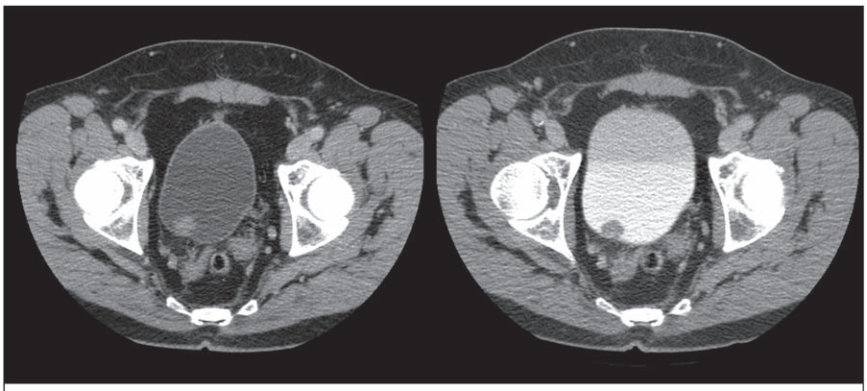
Option 1 has equal sensitivity to the additional test strategy and allows reduction in the number of flexible cystoscopies by 17%. Option 2, has slightly less sensitivity compared with the additional test strategy, although not statistically significant, but would have missed eight patients with bladder cancer. The advantage of option 2 is that it that it allows a reduction in the number of flexible cystoscopies by 43%.

The sensitivity of voided urine cytology is too low to justify its continuing use in a hospital haematuria rapid diagnosis clinic using CT urography and flexible cystoscopy. It is a redundant test that could be eliminated from the diagnostic pathway without adversely affecting diagnostic accuracy.

From the results of the present study comparing different strategies using CT urography (Table 3), the preferred strategy is triage test option 1 (Fig. 4). This has identical diagnostic performance to the current strategy, which uses CT urography as an additional test, but reduces the number of tests for patients identified with bladder cancer by CT urography. These patients are referred directly to rigid cystoscopy without an additional flexible cystoscopy, with a cost saving at no diagnostic penalty. If the costs of the four strategies at standard private patient charges are calculated and the difference between the additional strategy calculated, there is an overall saving of £142 350 across 747 patients, equivalent to £190 per patient for triage strategy option 1, (Table S7).

The reference standard, although the best achievable with the study design, is still imperfect as there is the potential for incomplete follow-up. Some patients may move out of the hospital catchment area and be lost to follow-up or patient follow-up details on the hospital databases

FIG. 10. To fully optimize CT urography for diagnosing bladder cancer, images are acquired during multiple phases of contrast enhancement.



Both the 60 s and 12.5 min post-contrast images clearly demonstrate a small bladder cancer close to the right ureteric orifice.

might be incomplete. The risk of this happening is small but it is noted as a limitation to the study.

The results of the present study are from a specially designed clinic in a single centre. Research on a wider scale in multiple centres would be useful before recommendations for the NHS are made.

Training programmes to teach radiologists how to read CT urography are required on a national basis. Teaching courses similar to those for CT colonography have many advantages for the future [43].

The CT technique described in the present paper is optimised for UUT evaluation rather than for evaluation of the bladder requiring multiple image series acquired at different phases after the administration of i.v. contrast in the presence of a full bladder [11,44,45] (Fig. 10).

To help optimise opacification of the UUTs by encouraging urine flow, patients void immediately before the CT examination. This manoeuvre inevitably compromises the diagnostic accuracy of CT urography for diagnosing bladder cancer, as the bladder may be partially distended at the time of imaging making identification of small bladder wall lesions more difficult as they may be confused with folds.

In conclusion, we recommend the diagnostic strategy using CT urography and flexible cystoscopy as a triage test for rigid cystoscopy and follow-up (option 1) for use in a hospital haematuria rapid diagnosis clinic. Patients with a positive CT urography score for bladder cancer are directly referred to rigid cystoscopy, but all other patients undergo flexible cystoscopy. Diagnostic accuracy is the same as for the additional test strategy with the cost saving advantage of a reduction in the number of flexible cystoscopies performed by 17%.

The sensitivity of voided urine cytology is too low to justify its continued use in a hospital haematuria rapid diagnosis clinic using CT urography and flexible cystoscopy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS.** A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU Int* 2006; **97**: 301–5

2 **Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE.** A prospective analysis of 1,939 patients with hematuria to evaluate current diagnostic practice. *J Urol* 1999; **163**: 524–7

3 **Sutton JM.** Evaluation of haematuria in adults. *JAMA* 1990; **263**: 2475–80

4 **Rodgers M, Nixon J, Hempel S *et al*.** Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technol Assess* 2006; **10**: iii–iv, xi–259

5 **Plail R.** Detecting bladder cancer. *Br Med J* 1990; **301**: 567–8

6 **Yip SK, Peh WC, Tam PC, Li JH, Lam CH.** Day case hematuria diagnostic service: use of ultrasonography and flexible cystoscopy. *Urology* 1998; **52**: 762–6

7 **Stenzl A, Cowan NC, De Santis M *et al*.** The Updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2009; **55**: 815–9

8 **Van Der Molen A, Cowan N, Mueller-Lisse U *et al*.** CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol* 2008; **18**: 4–17

9 **O'Connor OJ, Fitzgerald E, Maher MM.** Imaging of Hematuria. *AJR Am J Roentgenol* 2010; **195**: W263–7

10 **Turney BW, Willatt JMC, Nixon D, Crew JP, Cowan NC.** Computed tomography urography for diagnosing bladder cancer. *BJU Int* 2006; **98**: 345–8

11 **Cohan RH, Caoili EM, Cowan NC, Weizer AZ, Ellis JH.** MDCT Urography: exploring a new paradigm for imaging of bladder cancer. *AJR Am J Roentgenol* 2009; **192**: 1501–8

12 **Sadow CA, Silverman SG, O'Leary MP, Signorovitch JE.** Bladder cancer detection with CT urography in an academic medical center. *Radiology* 2008; **249**: 195–202

13 **Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P.** Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007; **18**: 581–92

14 **Cancer Research UK.** Bladder cancer – UK incidence statistics. 2008. Available at: http://info.cancerresearchuk.org/cancerstats/types/bladder/incidence/. Accessed November 2011

15 **Hollenbeck BK, Dunn RL, Ye Z *et al*.** Delays in diagnosis and bladder cancer mortality. *Cancer* 2010; **116**: 5235–42

16 **Sánchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB.** An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003; **169**: 110–5

17 **Viswanath S, Zelhof B, Ho E, Sethia K, Mills R.** Is routine urine cytology useful in the haematuria clinic? *Ann R Coll Surg Engl* 2008; **90**: 153–5
18 **Hofland CA, Mariani AJ.** Is cytology required for a hematuria evaluation? *J Urol* 2004; **171**: 324–6
19 **Clayman RV, Reddy P, Lange PH.** Flexible fiberoptic and rigid-rod lens endoscopy of the lower urinary tract: a prospective controlled comparison. *J Urol* 1984; **131**: 715–6
20 **Pavone-Macaluso M, Lamartina M, Pavone C, Vella M.** The flexible cystoscope. *Int Urol Nephrol* 1992; **24**: 239–42
21 **Burke DM, Shackley DC, O'Reilly PH.** The community-based morbidity of flexible cystoscopy. *BJU Int* 2002; **89**: 347–9
22 **Johnson MI, Merrilees D, Robson WA *et al*.** Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. *BJU Int* 2007; **100**: 826–9
23 **Taghizadeh AK, El Madani A, Gard PR, Li CY, Thomas PJ, Denyer SP.** When does it hurt? Pain during flexible cystoscopy in men. *Urol Int* 2006; **76**: 301–3
24 **Nolte-Ernsting C, Cowan N.** Understanding multi-slice CT urography techniques: many roads lead to Rome. *Eur Radiol* 2006; **16**: 2670–86
25 **Smith RC, Verga M, McCarthy S, Rosenfield AT.** Diagnosis of acute flank pain: value of unenhanced helical CT. *AJR Am J Roentgenol* 1996; **166**: 97–101
26 **Smith RC, Rosenfield AT, Choe KA *et al*.** Acute flank pain: comparison of noncontrast enhanced CT and intravenous urography. *Radiology* 1995; **194**: 789–94
27 **Silverman SG, Lee BY, Seltzer SE, Bloom DA, Corless CL, Adams DF.** Small (< or = 3 cm) renal masses: correlation of spiral CT features and pathologic findings. *AJR Am J Roentgenol* 1994; **163**: 597–605
28 **Silverman SG, Gan YU, Mortele KJ, Tuncali K, Cibas ES.** Renal masses in the adult patient: the role of percutaneous biopsy. *Radiology* 2006; **240**: 6–22
29 **Cowan NC, Turney BW, Taylor NJ, McCarthy CL, Crew JP.** Multidetector computed tomography urography (MDCTU) for diagnosing upper urinary tract tumour. *BJU Int* 2007; **99**: 1363–70
30 **Jinzaki M, Matsumoto K, Kikuchi E *et al*.** Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am J Roentgenol* 2011; **196**: 1102–9
31 **Albani JM, Ciaschini MW, Streem SB, Herts BR, Angermeier KW.** The role of computerized tomographic urography in the initial evaluation of hematuria. *J Urol* 2007; **177**: 644–8
32 **Fritz GA, Schoellnast H, Deutschmann HA, Quehenberger F, Tillich M.** Multiphasic multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. *Eur Radiol* 2006; **16**: 1244–52
33 **Gray Sears C, Ward JF, Sears ST, Puckett MF, Kane CJ, Amling CL.** Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. *J Urol* 2003; **168**: 2457–60
34 **Vrtiska TJ, Hartman RP, Kofler JM, Bruesewitz MR, King BF, McCollough CH.** Spatial resolution and radiation dose of a 64-MDCT scanner compared with published CT urography protocols. *AJR Am J Roentgenol* 2009; **192**: 941–8
35 **Dillman JR, Caoili EM, Cohan RH, Ellis JH, Francis IR, Schipper MJ.** Detection of upper tract urothelial neoplasms: sensitivity of axial, coronal reformatted, and curved-planar reformatted image-types utilizing 16-row multi-detector CT urography. *Abdom Imaging* 2008; **33**: 707–16
36 **Caoili EM, Cohan RH, Inampudi P *et al*.** MDCT Urography of Upper Tract Urothelial Neoplasms. *AJR Am J Roentgenol* 2005; **184**: 1873–81
37 **Cowan NC, Crew JP.** Imaging bladder cancer. *Curr Opin Urol* 2010; **20**: 409–13
38 **Bossuyt PM, Irwig L, Craig J, Glasziou P.** Comparative accuracy: assessing new tests against existing diagnostic pathways. *Br Med J* 2006; **332**: 1089–92
39 **Altman DG, Machin D, Bryant TN, Gardener MJ.** *Statistics with Confidence*, 2nd edn. London: BMJ Books, 2000
40 **Newcombe RG.** Improved confidence intervals for the difference between binomial proportions based on paired data. *Stat Med* 1998; **17**: 2635–50
41 **Wilson EB.** Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927; **22**: 209–12
42 **Kim S, Wang LL, Heiken JP, Siegel CL, Hildebolt CF, Bae KT.** Opacification of urinary bladder and ureter at CT urography: effect of a log-rolling procedure and postvoiding residual bladder urine volume. *Radiology* 2008; **247**: 747–53
43 **Dachman AH, Kelly KB, Zintsmaster MP *et al*.** Formative evaluation of standardized training for CT colonographic image interpretation by novice readers. *Radiology* 2008; **249**: 167–77
44 **Jinzaki M, Tanimoto A, Shinmoto H *et al*.** Detection of bladder tumors with dynamic contrast-enhanced MDCT. *AJR Am J Roentgenol* 2007; **188**: 913–8
45 **Kim JK, Park SY, Ahn HJ *et al*.** Bladder cancer: analysis of multidetector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. *Radiology* 2004; **231**: 725–31

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Abbreviations: **UCC**, urothelial cell cancer; **UUT**, upper urinary tract; **LUT**, lower urinary tract; **PPV**, positive predictive value; **NPV**, and negative predictive value.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Results for patients in whom CT urography was a technical failure and with a diagnosis of bladder cancer (three of five patients).

Table S2 Results for patients in whom flexible cystoscopy was a technical failure and with a diagnosis of bladder cancer (five of 26 patients).

Table S3 Information about the eight patients with normal CT urography (score 1) and histopathological confirmed bladder cancer (CT urography false negatives).

Table S4 Information about the three patients with flexible cystoscopy score 1 and histopathological confirmed bladder cancer (flexible cystoscopy false negatives).

Table S5 Results for voided urine cytology for diagnosing bladder cancer.

Table S6 Results for the diagnostic accuracy of voided urine cytology for diagnosing bladder cancer.

Table S7 Standard 2011 private patient costs and savings for the diagnostic strategies when compared with the additional strategy.

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EXAMPLE OF A CT UROGRAPHY SINGLE BOLUS PROTOCOL FOR HAEMATURIA INCLUDING ACQUISITION AND RECONSTRUCTION PARAMETERS

BEFORE THE EXAMINATION
Please remember to use the terms **fine tube** instead of **needle** and **give contrast** instead of **injection** as these terms are much less "scary" for the patient.

1. Give the patient 750-1000 ml of tap water to drink during 30 min prior to examination to encourage urine flow.

2. Remove bras, belts, necklaces to avoid artifacts on reconstructions.

3. Remove patients shoes (to help patient rolling on the CT table). This is very important to promote mixing of contrast with urine for complete opacification.

4. Ask the patient to empty their bladder immediately before entering the room so they are comfortable during the CT examination and do not have to void during the examination.

DURING THE EXAMINATION
5. Position the patient on CT table in supine position.

6. All series to be acquired on **expiration** to extend the ureter and avoid ureteric kinks which may simulate small tumours.

7. Say to the patients "Small breath in, breath out and hold".

8. **Unenhanced series** from top of kidneys to below pubic symphysis.
ST=1.25 -1.5 mm, RST=0.625 - 0.7, TF=18 mm/rot, n=16. RFOV=358 mm. Supine position.

9. Give 150 ml non-ionic contrast I.V. (Iohexol or Iopamidol) (300 mg I /ml) via pump at 3 ml/s and start the digital timer.

10. Scan from the top of liver to bottom of kidneys at 100 s post-contrast administration in the supine position for **nephrographic phase**.

11. Move the patient off table and walk them around CT machine. This exercise is to encourage urine flow and mixing of contrast and urine.

12. At t = 8 min reposition the patient on CT table and roll them twice anticlockwise and twice clockwise. Please do not rock the patient on the table if they are unable to roll, simply place them supine and write the request form "unable to roll".

13. At t=12.5 min post-contrast injection, scan from top of diaphragm to below symphysis in the supine position for the **excretory phase** images.

14. If the pelvic ureters are not fully opacified turn patient prone immediately and rescan from top of iliac crests to below symphysis. Make sure all of the bladder is included in the scan.

AFTER THE EXAMINATION
15. Reconstruct images for reporting: SW=1.5mm, RI=0.7mm, RFOV=358 mm, reconstruction kernel B31F. (RFOV = PS x matrix).

16. Send images to PACS for reporting.

DR NIGEL COWAN 08-10-2013

CT UROGRAPHY SINGLE BOLUS PROTOCOL FOR HAEMATURIA

GE LIGHTSPEED VCT 64

Se	PH	T	C	PO	BW	TF	PI	SF	kV	mAs	SW	RI	MX	DF
1	UE	0	K / P	Supine	1.25x32	39.38	0.98	500	120	170-220	1.25	0.625	512	320
2	NG	100	L / K	Supine	1.25x32	39.38	0.98	500	120	170-220	1.25	0.625	512	320
3	EX-1	750	K / P	Supine	1.25x32	39.38	0.98	500	120	170-220	1.25	0.625	512	320
4	EX-2	900	P	Prone	1.25x32	39.38	0.98	500	120	170-220	1.25	0.625	512	320

Oral water 600-900 ml 30-45 min before examination.
I.V. contrast Iopamidol or Iohexol 300 mg I / ml.
Rate of injection 3 ml / s.

CT UROGRAPHY SINGLE BOLUS PROTOCOL FOR HAEMATURIA

SIEMENS SOMOTOM SENSATION 16

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Se	**PH**	**T**	**C**	**PO**	**BW**	**TF**	**PI**	**SF**	**kV**	**mAs**	**SW**	**RI**	**MX**	**DF**
1	**UE**	**0**	**K / P**	**Sup**	**0.75x16**	**18**	**1.5**	**500**	**120**	**170-220**	**1.5**	**0.75**	**512**	**500**
2	**NG**	**100**	**L / K**	**Sup**	**0.75x16**	**18**	**1.5**	**500**	**120**	**170-220**	**1.5**	**0.75**	**512**	**500**
3	**EX-1**	**750**	**K / P**	**Sup**	**0.75x16**	**18**	**1.5**	**500**	**120**	**170-220**	**1.5**	**0.75**	**512**	**384**
4	**EX-2**	**900**	**P**	**Pro**	**0.75x16**	**18**	**1.5**	**500**	**120**	**170-220**	**1.5**	**0.75**	**512**	**384**

Abbreviations: UE, unenhanced; NG, nephrographic; EX, excretory; T, time after injection in seconds; C, coverage; P, patient position; BW, beam collimation (n x slice collimation [SC] mm); TF, table feed (mm) / rotation; SF, scanned field of view; DF, display field of view (mm); SW, section width; RI, reconstruction interval (mm); MX, matrtic; K, above adrenals to below kidneys; P, pelvis, top of iliac crests to below symphysis pubis; L, liver; A, abdomen, top of diaphragm to below kidneys.

CT urography acquisition and reconstruction parameters for GE x4, x8 and x16 CT machines

GE LIGHTSPEED x16

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Se	PH	T	C	PO	BW	TF	PI	SF	kV	mAs	SW	RI	MX	DF
1	UE	0	K / P	Sup	1.25x16	27.5	1.375	500	120	variable	2.5	1.25	512	500
2	NG	100	A	Sup	1.25x16	27.5	1.375	500	120	variable	2.5	1.25	512	500
3	EX-1	750	K / P	Sup	1.25x16	27.5	1.375	500	120	variable	1.25	0.625	512	320
4	EX-2	900	P	Pro	1.25x16	27.5	1.375	500	120	variable	1.25	0.625	512	320

GE LIGHTSPEED x8 ULTRA

Se	PH	T	C	PO	BW	TF	PI	SF	kV	mAs	SW	RI	MX	DF
1	UE	0	K / P	Sup	1.25x8	16.75	1.675	500	120	170-220	2.5	1.25	512	500
2	NP	100	A	Sup	1.25x8	16.75	1.675	500	120	190-220	2.5	1.25	512	500
3	EX-1	750	K / P	Sup	1.25x8	16.75	1.675	500	120	190-220	1.25	0.625	512	320
4	EX-2	900	P	Pro	1.25x8	16.75	1.675	500	120	190-220	1.25	0.625	512	320

GE LIGHTSPEED x4 QX/i

Se	PH	T	C	PO	BW	TF	PI	SF	kV	mAs	SW	RI	MX	D
1	UE	0	K / P	Sup	2.5x4	15	1.5	500	120	200	2.5	1.25	512	500
2	NG	100	A	Sup	2.5x4	15	1.5	500	120	200	2.5	1.25	512	500
3	EX-1	750	K / P	Sup	2.5x4	15	1.5	500	120	200	2.5	1.25	512	500
4	EX-2	900	P	Pro	2.5x4	15	1.5	500	120	200	2.5	1.25	512	500

Abbreviations: Se, series; PH, phase; T, time after injection (s); C, coverage; PO, position; BW, beam width = detector configuration n x SC; SC, slice collimation (mm); TF, table feed (mm) / rotation; PI, pitch; SF, scanned field of view (mm); SW, section width (mm); RI, reconstruction interval (mm); MX, matrix; DF, display field of view (mm). kV, 120; Auto mA, UE 190-220, R 1-3, 100-300.