Clinical Radiology 74 (2019) 167.e9–167.e16

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Contrast-enhanced ultrasound (CEUS) nephrostogram: utility and accuracy as an alternative to fluoroscopic imaging of the urinary tract

M. Daneshi, G.T. Yusuf*, C. Fang, M.E. Sellars, D.Y. Huang, P.S. Sidhu

Department of Radiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK

ARTICLE INFORMATION

Article history:
Received 20 July 2018
Accepted 10 October 2018

AIM: To establish the feasibility and accuracy of contrast-enhanced ultrasound (CEUS) nephrostogram in comparison to the reference standard, fluoroscopic nephrostogram, in providing alternative imaging of the urinary tract post-nephrostomy insertion.

MATERIALS AND METHODS: This prospective study was approved by the institutional and national ethics committee. All patients for whom a fluoroscopic nephrostogram was requested were included. Fluoroscopic and CEUS nephrostograms were performed within 24 hours. Image analysis (nephrostomy position, opacification of pelvicalyceal system, ureter, and bladder) was performed by two reviewers, and the diagnostic accuracy of the CEUS nephrostograms was compared to fluoroscopic nephrostograms.

RESULTS: Sixty-two nephrostograms were performed in 48 patients from June 2011 to April 2016, (male: 25/48, 52.1%; mean age 65 years, range 28–90 years). Indications for nephrostomy were: malignancy (29/62; 46.8%), benign ureteric stricture (14/62; 22.6%), urinary diversion (8/62; 12.9%), renal calculus (5/62; 8.1%), haematoma (3/62; 4.8%) or pelvi-ureteric junction obstruction (3/62; 4.8%). Two nephrostomies were identified as displaced by both techniques. The pelvicalyceal system was visualised in 60/60 (100%) examinations in both fluoroscopic and CEUS nephrostograms. The entire ureter was visualised in 30/60 (50%) with CEUS compared to 32/60 (53.3%) fluoroscopically. The distal ureter was the least well-visualised segment for both techniques with no significant difference (p=0.815). Both CEUS and fluoroscopy could be used to correctly identify complications including entero-ureteric fistula or urine leak. Fluoroscopic nephrostogram demonstrated drainage into the bladder in 33/60 (55%), CEUS confirmed drainage in 34/60 (56.7%) cases (p=0.317).

CONCLUSIONS: CEUS nephrostogram can determine the correct positioning of a nephrostomy and assess drainage into the bladder with statistically comparable results to fluoroscopy.

* Guarantor and correspondent: G. T. Yusuf, Department of Radiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Tel.: +44 203 299 4164; fax: +44 203 299 3157.
E-mail address: Gibran.yusuf@nhs.net (G.T. Yusuf).

https://doi.org/10.1016/j.crad.2018.10.004

Introduction

Percutaneous nephrostomy (PCN) insertion is a commonly performed interventional procedure to decompress an obstructed kidney, for urinary diversion, or to gain access to the urinary tract for subsequent interventional procedures. Fluoroscopic nephrostogram (FN) is usually performed after PCN to confirm the correct position of the nephrostomy tube and demonstrate ureteric patency (including post-ureteric stent insertion), with the possibility for evaluation of the obstructive cause and any potential associated complication (e.g. fistulation). Traditional fluoroscopic examinations, with iodinated contrast medium, remain an important diagnostic technique owing to the ability to image in a dynamic fashion in real time; however, it necessitates the use of ionising radiation and must be performed in a dedicated fluoroscopy suite. Exposure to ionising radiation represents an increasing concern given the estimation as many as 2% of all malignancies may be radiation induced.[1] From a practical perspective, transferring a patient to a fluoroscopy suite is not always feasible or desirable, particularly if frail or requiring intensive care.

The development of microbubbles as ultrasound contrast agents (UCA) has progressed over the last 20 years and is gaining increasing popularity, particularly following Food and Drug Administration (FDA) approval in the USA.[2] Although licensed uses are historically limited to hepatic, cardiac, vascular, and breast applications a wide range of "off-label applications" exist, including paediatric, renal, and in endocavitary procedures.[3–5] Contrast-enhanced ultrasound (CEUS) benefits from the advantages of traditional ultrasound, such as portability and lack of ionising radiation, whilst the UCA provides a safe contrast medium which is truly intravascular or intraluminal[6] with exquisite spatial resolution, and importantly allowing real-time assessment. The most common UCA used in Europe is gas-filled microbubbles of sulphur hexafluoride covered by a stabilising biocompatible shell with an average diameter of 2–6 μm, which are small enough to traverse the pulmonary capillary bed filter. When CEUS is performed at a low mechanical index (MI), microbubbles oscillate in a non-linear fashion, producing harmonic signals that can be selectively detected on ultrasound systems with specific multi-pulse CEUS-specific software.[7] CEUS may be safely deployed in the presence of renal impairment, as metabolism of UCA are not renal dependent; sulphur hexafluoride is exhaled via the lungs and the phospholipid shell is excreted via the liver.[5–7] CEUS has an excellent safety profile, with an incidence of adverse reactions lower than that observed for both iodinated and gadolinium-based contrast agents in adults and children.[6,8–10]

CEUS lends itself well to endocavitary use,[11–13] with currently the leading use in assessing vesicoureteric reflux after intra-vesical instillation in paediatric practice.[13,14] A further established application is in assessment of fallopian tube patency as an alternative to fluoroscopic hysterosalpingogram with 100% concordance between the two methods reported.[3,15,16] Case series and case reports have described CEUS cholangiography demonstrating location of the draining bile duct and ductal stenosis following intraductal UCA injection, and also depicting complications such as biliary-arterial fistulae.[17,18] The technique of CEUS nephrostograms have been described previously as a radiation-free alternative to fluoroscopic nephrostogram to evaluate ureteral patency, and this has been confirmed by other groups.[19–22] The purpose of the present study was to establish the feasibility and accuracy of nephrostogram using CEUS when compared to the reference standard of fluoroscopic nephrostogram with blinded independent review of the two techniques.

Materials and methods

Patient population

The prospective study was approved by institutional and national ethics committees. Written consent was obtained from all patients. Patients were recruited consecutively, between June 2011 and April 2016. The inclusion criteria included age ≥18 years old, patient who required a fluoroscopic nephrostogram following PCN insertion, with or without ureteric stent placement. The exclusion criteria included patients who were unable to give consent or if CEUS nephrostogram and the fluoroscopic nephrostogram could not be performed within 24 hours of each other.

Nephrostomy and fluoroscopic nephrostogram technique

The nephrostomy tubes inserted were non-locking 6 and 8 F pigtail catheters (Cook Medical, Bloomington, IN, USA), with the procedure performed in the conventional manner by trained interventional radiologists. The procedure was performed based on clinical need for the procedure, and the reason was recorded for each patient. Nephrostomy tubes were capped or left on free drainage prior to examination depending on the clinical need; obstructed kidneys were allowed to drain freely. Any covering nephrostomy inserted at the same time as an antegrade ureteric stent were clamped. Any indwelling urinary bladder catheters were clamped approximately an hour prior to both the fluoroscopy and CEUS examinations. All study participants had their fluoroscopy and CEUS nephrostograms performed within 24 hours of each other.

The fluoroscopic nephrostogram was performed in a conventional manner by placing the patient in a supine position, using standard fluoroscopy techniques, by a number of skilled operators experienced in fluoroscopy techniques, following a standard department protocol. Initially a control image was acquired over the area of interest. Following injection of low osmolality iodinated contrast medium (Omnipaque 240, GE Healthcare, Cork, Ireland) into the renal collecting systems via the nephrostomy tube, several fluoroscopic images, video loop, and acquired images were obtained of the renal collecting system, ureters, and bladder, as needed. If no iodinated contrast medium was seen within the bladder on optimised

imaging after 10 minutes, the ureter was deemed obstructed. Images were stored on the local picture archiving and communication system (PACS, GE Healthcare, Barrington IL, USA) system as per standard department practice and used for retrospective image review.

CEUS nephrostogram technique

All studies were performed by experienced operators (P.S.S., M.E.S., D.H., G.T.Y., M.D.; 20, 15, 15, 7, and 5 years of experience, respectively) in CEUS technique using an Acuson S2000/3000, a Sequoia (Siemens Healthcare, Mountain View, CA, USA), or Samsung RS80 Prestige (Samsung Medison, Seoul, Korea). Optimised greyscale targeted ultrasound of the affected kidney was performed to assess the calyces, renal pelvis, and residual hydronephrosis using 4–6 MHz (Siemens) or 1–7 MHz probe (Samsung) curvilinear transducers. The presence of a ureteric stent was identified on greyscale by parallel hyperechoic lines within the renal pelvis or proximal ureter as well as within the bladder. Both machines had software for CEUS imaging using low mechanical index techniques, with side-by-side imaging comparison with the B-mode image. Imaging was set to obtain optimal representative static CEUS images, with cine loops obtained as needed.

CEUS of the kidney was performed using SonoVue (Bracco SpA, Milan, Italy). UCA (0.2 ml) was mixed in 50 ml of 0.9% saline contained in a 50 ml Luer lock type syringe (Becton Dickinson, Franklin, NJ, USA) and introduced gently in small volumes (5–10 ml) into the renal collecting system directly via the indwelling nephrostomy catheter using an aseptic technique. A repeat UCA injection (50 ml) was performed if no UCA was seen in the ureter or bladder during the slow injection. Again, as with the fluoroscopic technique, if no UCA was seen in the bladder after 10 minutes, the ureter was deemed obstructed. If bilateral examinations were performed, bladder emptying was achieved by means of voiding or using the existing bladder catheter to ensure no residual bladder UCA prior to performing the contralateral nephrostogram. If voiding was not possible, microbubbles were destroyed using several short-interval high mechanical index pulses ("Flash" technique[23]). Digital cine-clips and still images were recorded during CEUS examinations and transferred to the PACS system, as for retrospective evaluation.[23] Any adverse reactions related to the conventional nephrostograms and the intracavitary CEUS nephrostograms were recorded from review of the patients' notes.

Imaging review

All fluoroscopic examinations were performed prior to the CEUS study with the CEUS operators blinded to the results and patients not informed of the findings of the fluoroscopy. Images and videos from fluoroscopic and CEUS nephrostograms were reviewed by two interventional uroradiologists (DH and GY) with 15 and 7 years of experience, respectively in CEUS techniques, and with experience in assessing conventional iodinated nephrostograms. The review was performed 6 months following closure of recruitment, in a blinded fashion and in random order of investigations. The presence of iodinated contrast medium and UCA within 1) the renal calyceal, 2) upper, 3) mid, 4) lower ureter, and 5) bladder were recorded for each of the studies, and reported in consensus, any conflicts were resolved by a third reviewer (C.F.). In addition, the presence of urothelial lesions and filling defects were also documented, with the site detailed according to the site as described above. Visualisation of a ureteric stent (seen as a double hyperechoic linear structure along the course of the ureter, a pigtail curl could also be seen within the renal pelvis and bladder) was documented. The results were documented according to a proforma and recorded in a standardised data table. Consensus between the two reviews was achieved in all cases.

Statistical analysis

The statistical software used was IBM SPSS Statistics version 24 (IBM, Chicago, IL, USA). A sample size of 60 was required to allow 80% power to reject the null hypothesis of no significant difference between CEUS nephrostogram and fluoroscopic nephrostogram. The null hypothesis was evaluated using McNemar's test with $p<0.05$ considered significant.

Results

Sixty-two paired CEUS and fluoroscopic nephrostograms were performed in 48 patients, 25 males and 23 female patients with a mean age of 65 (range 28–90 years). Bilateral nephrostograms examinations were performed in 14 patients. Three patients had a renal transplant, with the transplant kidney situated in right iliac fossa. Indications for nephrostomy placement were: malignancy (29/62; 46.8%), benign ureteric stricture (14/62; 22.6%), establishing urinary diversion following trauma, fistulation or iatrogenic injury (8/62; 12.9%), renal calculus (5/62; 8.1%), haematoma (3/62; 4.8%), or pelvi-ureteric junction obstruction (PUJ; 3/62; 4.8%). In the malignancy group, bladder tumours were the most common ($n=14$). The indications of obstruction in the transplant kidneys were haematoma ($n=1$) and anastomotic stricture ($n=2$). An in dwelling ureteric stent was present in 35/62 (56.4%), CEUS visualised 25/35 (71.4%) ureteric stents and incorrectly identified a stent when there none was present in 2/35 (5.7%), thought to be misinterpretation of a low-lying nephrostomy tube.

Both CEUS and conventional fluoroscopic imaging correctly demonstrated two (2/62; 3.2%) misplaced nephrostomy tubes lying outside the kidney with contrast medium extravasation (Fig 1). In the remaining 60 cases, the renal pelvicalyceal system was visualised in 60/60 (100%) of examinations at both CEUS nephrostogram and fluoroscopy (Fig 2). The proximal, mid, and distal ureter were visualised in 51, 44, and 35 (85%, 73%, and 58%) cases on fluoroscopic nephrostogram and 58, 47, and 35 (97%, 78%, and 58%) cases, respectively, on CEUS nephrostograms (Table 1). Although a higher percentage of upper and mid ureters were visualised on CEUS than fluoroscopy, there was no

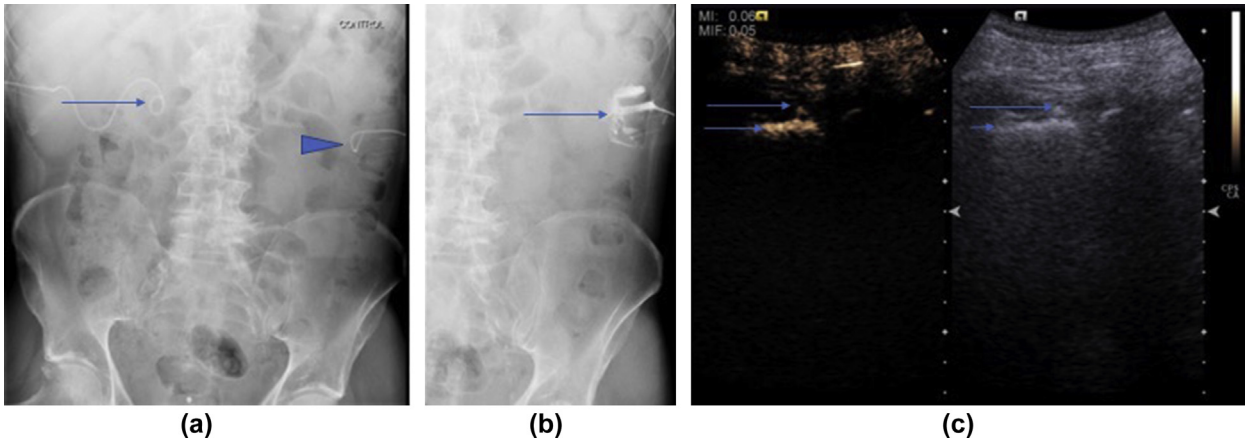

Figure 1 Flouroscopic and CEUS nephrostogram on a patient with a misplaced left nephrostomy. (a) Control film of a fluoroscopic nephrostogram shows an appropriately placed right nephrostomy (thin arrow); however, the left nephrostomy has an abnormal position and shape suggestive of lying outside the left kidney. (b) Single image from a nephrostogram through the left nephrostomy showing amorphous pooling indicating it is misplaced. (c) CEUS nephrostogram with simultaneous contrast-specific mode and b-mode image. Following UCA administration through the left nephrostomy, superficial pooling of contrast medium is seen on both the b-mode and CEUS-specific mode (arrow).

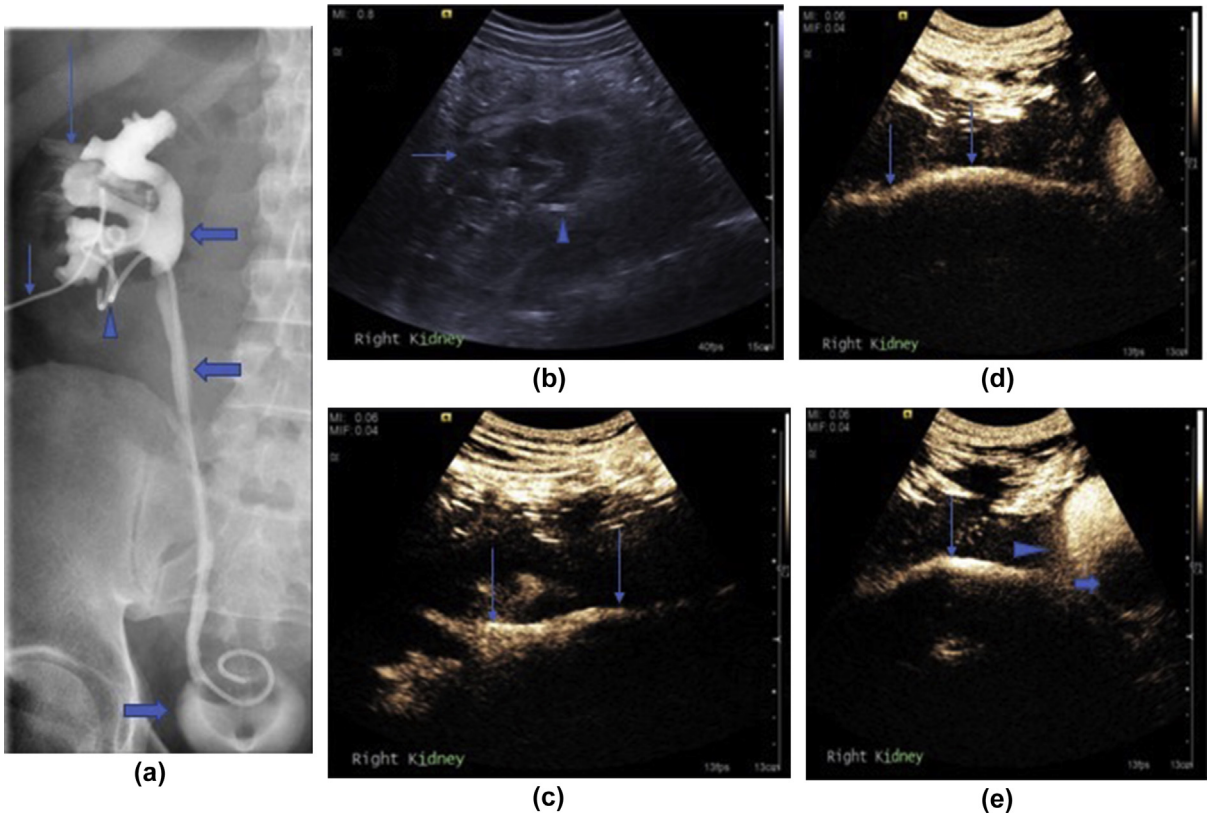

Figure 2 Conventional fluoroscopic of the right kidney, B-mode image of the right kidney CEUS nephrostogram through the right nephrostomy. (a) Fluoroscopic nephrostogram with an indwelling nephrostomy (thin arrow) and ureteric stent with the proximal end lying in an unopacified calyx (arrowhead) (b) B-mode image of the right kidney (arrow) with the proximal aspect of a ureteric stent seen (arrowhead). (c–e) CEUS nephrostogram images showing filling of the renal pelvis and proximal ureter (c), mid/distal ureter and bladder (d,e). A filling defect seen within the bladder (thick arrow) represents a urinary catheter.

significant statistical difference between the two techniques in visualising either upper (p=0.053) or mid (p=0.670) segments. The entire ureter was visualised in 30/60 (50%) cases with CEUS nephrostogram compared to 32/60 (53.3%) on fluoroscopic nephrostogram with no statistical significant difference between the two (p=0.815).

There was also no statistical significant difference in demonstrating drainage of iodinated contrast medium or

Table 1
Table comparing visualisation of segments of the urinary tract on contrast-enhanced ultrasound (CEUS) nephrostogram and conventional fluoroscopic nephrostogram including whether a uretric stent is present.

$n=62$[a]	CEUS nephrostogram						Fluoroscopic nephrostogram					
	Stent present	Renal pelvis	Proximal ureter	Mid ureter	Distal ureter	Bladder	Stent present	Renal pelvis	Proximal ureter	Mid ureter	Distal ureter	Bladder
Seen	40.3% (25/62)	96.8% (60/62)	93.5% (58/62)	75.8% (47/62)	56.5% (35/62)	54.8% (34/62)	56.5% (35/62)	96.8% (60/62)	82.3% (51/62)	71% (44/62)	56.5% (35/62)	53.2% (33/62)
Not seen	60.7% (37/62)	3.2% (2/62)	6.5% (4/62)	24.2% (15/62)	43.5% (27/62)	45.2% (28/62)	43.5% (27/62)	3.2% (2/62)	17.7% (11/62)	29% (18/62)	43.5% (27/62)	46.8% (27/62)

[a] Two patients who had misplaced nephrostomy tubes not in the kidneys are included in the analysis.

UCA into the bladder between fluoroscopic nephrostogram (33/60, 55%) and CEUS nephrostogram (34/60, 57%; $p>0.999$). When bladder drainage was confirmed on conventional fluoroscopic nephrostogram, the referring clinical team removed the nephrostomy within 24 hours. In one case where CEUS nephrostogram demonstrated drainage and conventional fluoroscopic nephrostogram failed to, the nephrostomy was clamped for 24 hours and following normal urine output the nephrostomy was removed. No kidney calculi were identified in any patients on either type of examination. CEUS nephrostogram did not identify any ureteric calculi, while fluoroscopic nephrostogram identified one case with a ureteric calculus.

Several additional findings were present within the study. CEUS demonstrated a urine leak from the mid ureter in one patient post-iatrogenic ureteric injury, not evident on fluoroscopy, but previously demonstrated on computed tomography (CT) imaging (Fig 3). An entero-ureteric fistula in a post-radiotherapy patient, was demonstrated with both techniques, with contrast medium presence in the small bowel loops. CEUS was able to define the point of fistulation, conventional nephrostogram could not. In a case where there were multiple pelvicalyceal filling defects on a CEUS nephrostogram, the endocavitary contrast medium was removed and intravenous UCA (1.2 ml SonoVue) was injected, confirmed absence of enhancement within the calyceal lesion in keeping with haematoma rather than a vascularised tumour. There were no adverse reactions related to endocavitary application of UCA in this study.

Discussion

The present study demonstrated that CEUS nephrostogram is equivalent to the current reference standard fluoroscopic nephrostogram in terms of visualisation of the renal pelvicalyceal system and the entire ureter. CEUS nephrostogram can determine the correct positioning of the nephrostomy tube and assess adequate drainage of UCA into the bladder as effectively as conventional fluoroscopic nephrostograms using iodinated contrast medium. Complicating features, such as urine leak and entero-ureteric fistulas, can also be appreciated on CEUS, which may improve on fluoroscopy depiction, with the better spatial and temporal resolution of ultrasound. Pelvicalyceal “filling defects” were readily identifiable in both techniques. The ability to administer intravenous UCA at the time of the examination, allowed for the vascularisation of the “filling defect” to be interrogated to exclude a potential vascularised malignancy as opposed to a non-vascularised area of haematoma, adding to the utility of the CEUS examination. Strictures and changes in calibre were also identified with the fluoroscopy and CEUS studies, with concordance between the techniques. The excellent spatial and temporal resolution of CEUS nephrostogram depicting incomplete obstruction, with bladder UCA identified readily, may be an ideal solution to monitor the resolution of a ureteric obstruction.

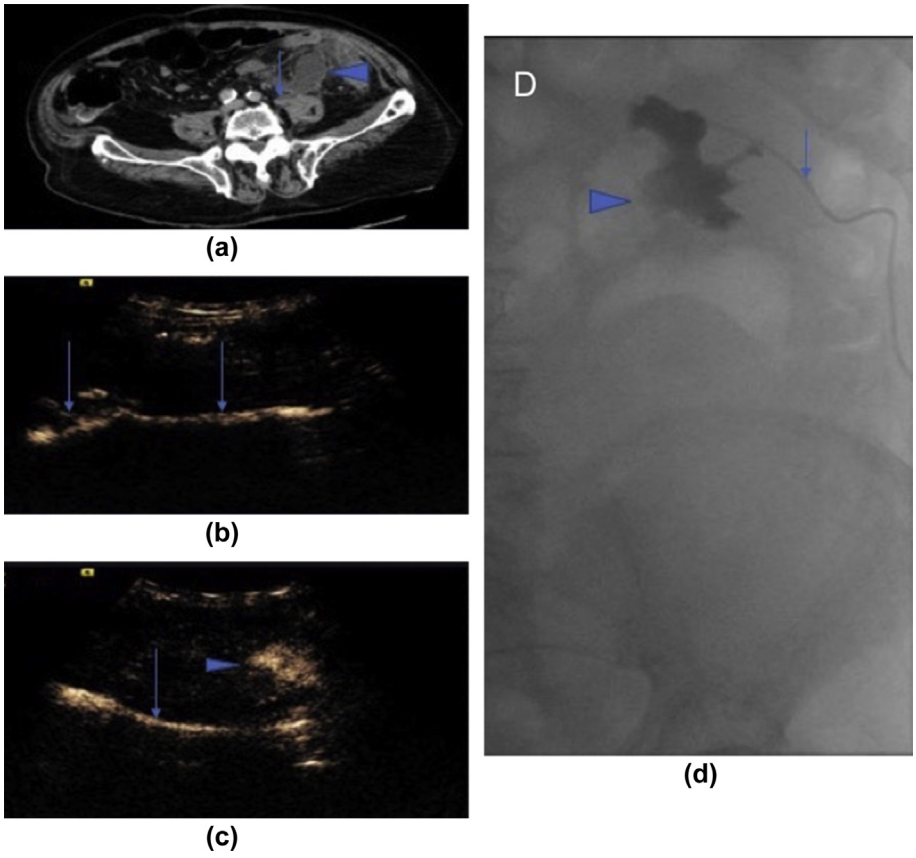

Figure 3 CT, CEUS nephrostogram, and fluoroscopic nephrostogram all performed within a 24-hour period with interval nephrostomy insertion post-CT for a ureteric leak. (a) Venous CT demonstrates a fluid collection (arrowhead) associated with the distal left ureter (arrow). After insertion of a nephrostomy CEUS nephrostogram was performed (b,c), which showed filling of the renal pelvis, proximal and mid ureter (arrows), but also showed pooling of contrast medium within a collection (arrowhead). (d) Flouroscopic nephrostogram via the nephrostomy (arrow) showed filling of the renal pelvis (arrowhead), but no drainage into the ureter, bladder, or known urinoma.

With these findings, CEUS has the potential to develop into the standard technique for imaging the urinary tract following PCN insertion, replacing fluoroscopic nephrostograms or could be deployed as the "bedside" assessment of the patient on the intensive care unit. Furthermore, with efforts to reduce any co-morbidity of imaging procedures, the lack of ionising radiation and low risk of adverse events makes the CEUS nephrostogram an attractive procedure, particularly in young patients.[4,6,8–10] This is of importance as the subset of patients requiring PCN often require serial CT examinations of the underlying cause of the renal obstruction, thus increasing the lifetime radiation dose as well as cancer risk.[1] Ultrasound is readily available and performed easily at the bedside, making it more tolerable for patients and convenient for staff. Fluoroscopy requires a dedicated suite often positioned within the Radiology Department. There are no concerns over nephrotoxicity or thyroid gland reactivity; therefore, it is not necessary to perform laboratory tests before administration of UCA. They are ideal contrast agents in patients with severe renal failure in whom iodinated contrast medium is contraindicated; a frequent finding in a patient undergoing nephrostomy insertion, although thought not to be an issue with endocavitary use.

UCA are inherently safe and their components are inert with a low incidence of side effects.[4–6,10,24] A study of UCA after intravesical injection for diagnosis of vesicoureteral reflux in a paediatric population did not demonstrate any serious adverse events with a small number of minor events that were self-limiting and thought due to urinary catheter insertion.[24] UCA are truly intravascular and stable through the pulmonary circulation and are at undetectable levels within minutes, and appear to have a longer "imaging" window with intracavitary use, where they remain within the cavity unless there is a "breech" of the cavity.[7] Endocavitary use of UCA is a relatively new technique[13] and recent European federation of societies for ultrasound in medicine and biology (EFSUMB) guidelines on non-hepatic applications of CEUS have incorporated clinical indications for intracavitary use of UCA, but this technique remains "off-label".[5] Dilute UCA should be used to allow a greater volume of injection, so as to freely diffuse within a cavity. The vascular system drives the UCA around the circulation and dilutes to the volume of the entire blood pool. With intracavitary use, the volume of the cavity is small in comparison, a very small volume of UCA is required, but needs a larger volume to facilitate motion and tracking through a cavity. There is no entry into the vascular space

from an endocavitary injection, making the complications associated with intravascular administration minimal. In the present population, there were no immediate or delayed adverse effects recorded.

There have been recent studies into usefulness of endocavitary CEUS in imaging the urinary tract post-nephrostomy and PCNL patients. These preliminary studies performed in small patient numbers have suggested that CEUS has the potential to become a new diagnostic method in urology patients with potential advantages over fluoroscopy.[19–22] This study confirms these findings with statistically comparable results to the reference technique and supports the more widespread application of the technique.

The present study has several limitations. There was inherently a time gap between the two examinations, in some cases up to 24 hours, which may have affected ureteric patency in the second study; although this is thought not to be substantial. CEUS has its own limitations similar to those of conventional ultrasound. These include patient body habitus and obstructing superimposed structures, such as bone or air, resulting in poor image quality. Imaging the ureter, a retroperitoneal structure, presents a challenge on ultrasound and may not always be adequate; however in the present study, there was no significant difference between CEUS and fluoroscopic nephrostograms in visualising various parts of ureter, an area never previously imaged with any form of ultrasound. There are multiple factors that make imaging the lower ureter more challenging in both techniques and these include anatomy, presence of overlying bowel gas and patient body habitus. The effect of other factors, such as patient body mass index (BMI), on the diagnostic accuracy of both techniques was not compared. Although ultrasound can determine ureteric obstruction due to absence of UCA within the bladder, the level and cause of obstruction is inherently more difficult to identify, particularly in obese patients. In addition, the authors acknowledge that the CEUS nephrostogram is a diagnostic investigation, and should antegrade stenting be required, fluoroscopic imaging is needed for guidance.

In conclusion, the present study indicates that CEUS is a feasible alternative technique for imaging the urinary tract following PCN insertion with comparable results for evaluation of ureteric patency and several advantages over fluoroscopy. CEUS can become the diagnostic standard imaging technique for assessment of urinary drainage in patients allowing reduction of patient exposure to radiation, with any contraindication to iodinated contrast media and those in an intensive care setting. This potentially includes the most vulnerable patients, both young and elderly.

Conflict of interest

On behalf of all the named authors, I certify that I understand the policy of Clinical Radiology. In accordance with the policy, I wish to declare the following real or apparent conflicts which concern this article. MD – None, GTY – Speaker for Siemens, Bracco, CF – None, MES – Speaker for Bracco, DYH – Speaker for Bracco, PSS – Speaker for Bracco, Hitachi, Siemens healthcare, GE healthcare and Philips healthcare.

References

1. Brenner DJ, Hall EJ. Computed tomography — an increasing source of radiation exposure. *N Engl J Med* 2007;**357**(22):2277–84.
2. US Food and Drug Administration. *Drugs@FDA: FDA approved Drug products*. 2016. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203684. [Accessed 14 February 2018].
3. Heinzmann A, Müller T, Leitlein J, *et al*. Endocavitary contrast enhanced ultrasound (CEUS)—work in progress. *Ultraschall Med* 2012;**33**(1):76–84.
4. Sidhu PS, Cantisani V, Deganello A, *et al*. Role of contrast-enhanced ultrasound (CEUS) in paediatric practice: an EFSUMB position statement. *Ultraschall Med* 2017;**38**(1):33–43.
5. Sidhu PS, Cantisani V, Dietrich CF, *et al*. The EFSUMB guidelines and recommendations for the clinical practice of contrast enhanced ultrasound (CEUS) in non -hepatic applications. Update 2017 (Long version). *Ultraschall Med* 2018;**39**:e2–44.
6. Piscaglia F, Bolondi L. Italian society for ultrasound in medicine and biology (SIUMB) study group on ultrasound contrast agents. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;**32**(9):1369–75.
7. Cosgrove D. Ultrasound contrast agents: an overview. *Eur J Radiol* 2006;**60**(3):324–30.
8. Kusnetzky LL, Khalid A, Khumri TM, *et al*. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol* 2008;**51**(17):1704–6.
9. Katayama H, Yamaguchi K, Kozuka T, *et al*. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;**175**(3):621–8.
10. Yusuf GT, Sellars ME, Deganello A, *et al*. Retrospective analysis of the safety and cost implications of pediatric contrast-enhanced ultrasound at a single center. *AJR Am J Roentgenol* 2017;**208**(2):446–52.
11. Ascenti G, Zimbaro G, Mazziotti S, *et al*. Harmonic US imaging of vesicoureteric reflux in children: usefulness of a second generation US contrast agent. *Pediatr Radiol* 2004;**34**(6):481–7.
12. Greis C. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol* 2004;(suppl. 8):P11–5.
13. Yusuf GT, Fang C, Huang DY, *et al*. Endocavitary contrast enhanced ultrasound (CEUS): a novel problem solving technique. *Insights Imaging* 2018;**9**(3):303–11.
14. Zimbaro G, Ascenti G, Visalli C, *et al*. Contrast-enhanced ultrasonography (voiding urosonography) of vesicoureteral reflux: state of the art. *Radiol Med (Torino)* 2007;**112**(8):1211–24.
15. Abramowicz JS. Ultrasonographic contrast media: has the time come in obstetrics and gynecology? *J Ultrasound Med Off J Am Inst Ultrasound Med* 2005;**24**(4):517–31.
16. Exacoustos C, Zupi E, Szabolcs B, *et al*. Contrast-tuned imaging and second-generation contrast agent SonoVue: a new ultrasound approach to evaluation of tubal patency. *J Minim Invasive Gynecol* 2009;**16**(4):437–44.
17. Ignee A, Baum U, Schuessler G, *et al*. Contrast-enhanced ultrasound-guided percutaneous cholangiography and cholangiodrainage (CEUS-PTCD). *Endoscopy* 2009;**41**(8):725–6.
18. Daneshi M, Rajayogeswaran B, Peddu P, *et al*. Demonstration of an occult biliary-arterial fistula using percutaneous contrast-enhanced ultrasound cholangiography in a transplanted liver. *J Clin Ultrasound JCU* 2014;**42**(2):108–11.
19. Chi T, Usawachintachit M, Mongan J, *et al*. Feasibility of antegrade contrast-enhanced US nephrostograms to evaluate ureteral patency. *Radiology* 2017;**283**(1):273–9.
20. Chi T, Usawachintachit M, Weinstein S, *et al*. Contrast enhanced ultrasound as a radiation-free alternative to fluoroscopic nephrostogram for evaluating ureteral patency. *J Urol* 2017;**198**(6):1367–73.
21. Cui X-W, Ignee A, Maros T, *et al*. Feasibility and usefulness of intracavitary contrast-enhanced ultrasound in percutaneous nephrostomy. *Ultrasound Med Biol* 2016;**42**(9):2180–8.

22. Daneshi M, Patel K, Sellars ME, Huang DY, Sidhu PS. Contrast enhanced ultrasound nephrostogram vs. fluoroscopic nephrostogram: initial results. *RSNA Sci Assem Annu Meet Programme* 2013:S372.
23. Harvey CJ, Alsafi A, Kuzmich S, *et al*. Role of US contrast agents in the assessment of indeterminate solid and cystic lesions in native and transplant kidneys. *RadioGraphics* 2015;**35**(5):1419–30.
24. Papadopoulou F, Ntoulia A, Siomou E, *et al*. Contrast-enhanced voiding urosonography with intravesical administration of a second-generation ultrasound contrast agent for diagnosis of vesicoureteral reflux: prospective evaluation of contrast safety in 1,010 children. *Pediatr Radiol* 2014;**44**(6):719–28.