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Contrast Enhanced Ultrasound as a Radiation-Free Alternative to Fluoroscopic Nephrostogram for Evaluating Ureteral Patency

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Purpose: We compared contrast enhanced ultrasound and fluoroscopic nephrostography in the evaluation of ureteral patency following percutaneous nephrolithotomy.

Materials and Methods: This prospective cohort, noninferiority study was performed after obtaining institutional review board approval. We enrolled eligible patients with kidney and proximal ureteral stones who underwent percutaneous nephrolithotomy at our center. On postoperative day 1 patients received contrast enhanced ultrasound and fluoroscopic nephrostogram within 2 hours of each other to evaluate ureteral patency, which was the primary outcome of this study.

Results: A total of 92 pairs of imaging studies were performed in 82 patients during the study period. Five study pairs were excluded due to technical errors that prevented imaging interpretation. Females slightly predominated over males with a mean $\pm$ SD age of 50.5 ± 15.9 years and a mean body mass index of 29.6 ± 8.6 kg/m^2. Of the remaining 87 sets of studies 69 (79.3%) demonstrated concordant findings regarding ureteral patency for the 2 imaging techniques and 18 (20.7%) were discordant. The nephrostomy tube was removed on the same day in 15 of the 17 patients who demonstrated antegrade urine flow only on contrast enhanced ultrasound and they had no subsequent adverse events. No adverse events were noted related to ultrasound contrast injection. While contrast enhanced ultrasound used no ionizing radiation, fluoroscopic nephrostograms provided a mean radiation exposure dose of 2.8 ± 3.7 mGy.

Conclusions: A contrast enhanced ultrasound nephrostogram can be safely performed to evaluate for ureteral patency following percutaneous nephrolithotomy. This imaging technique was mostly concordant with fluoroscopic findings. Most discordance was likely attributable to the higher sensitivity for patency of contrast enhanced ultrasound compared to fluoroscopy.

Key Words: kidney calculi, ultrasonography, contrast media, fluoroscopy, diagnostic imaging

Abbreviations and Acronyms

BMI = body mass index

CEUS = contrast enhanced ultrasound

CT = computerized tomography

PCNL = percutaneous nephrolithotomy

PNT = percutaneous nephrostomy tube

POD = postoperative day

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Contrast imaging studies are frequently used to evaluate the upper urinary tract for pathological conditions and direct appropriate management. These studies include CT, fluoroscopic nephrostography, excretory urography and retrograde pyelography, of which all require ionizing radiation.[1] The long-term health consequences of ionizing

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radiation exposure in the management of urinary stones is a growing concern for patients and medical personnel,[2,3] magnified by the increasing incidence of urolithiasis with time.[4] With various studies demonstrating an association between ionizing radiation exposure and increased risks of cancer and cataracts,[5–7] there has been growing emphasis on reducing patient exposure to ALARA (as low as reasonably achievable).[8]

PCNL is one of the most commonly performed procedures for kidney stone removal.[9] Fluoroscopic nephrostography, an ionizing radiation imaging modality, is the traditionally accepted standard imaging to confirm ureteral patency when a PNT is placed at procedure completion.[10] Postoperatively it can be performed to delineate the ureter and impact the clinical decision of whether the tube can be safely removed.

Ultrasound is a reliable modality to visualize renal anatomy without ionizing radiation exposure but it is considered inadequate to evaluate the ureter or the functional flow of urine in the upper urinary tract. Microbubble ultrasound contrast agents extend the range of ultrasound imaging. For CEUS intravenous injection is most commonly used for cardiac and liver applications[11,12] but several off label urological applications have been explored.[13–16] One contrast agent was recently FDA (Food and Drug Administration) approved for bladder injection in the evaluation of vesicoureteral reflex in pediatric patients.[17] We reported a pilot feasibility study demonstrating that CEUS may be used to evaluate ureteral patency without ionizing radiation using antegrade injection of ultrasound contrast via PNT[18] but to our knowledge the diagnostic accuracy of this technique is unknown.

To determine the diagnostic accuracy of CEUS for evaluating the collecting system we performed a prospective cohort, noninferiority study comparing CEUS to fluoroscopic nephrostography to evaluate ureteral patency after PCNL for upper urinary tract stone treatment. We hypothesized that CEUS would be equally effective as fluoroscopic nephrostography to evaluate ureteral patency and it would reduce patient radiation exposure.

MATERIALS AND METHODS

This prospective cohort study was performed at a single center (University of California-San Francisco). Institutional review board approval was obtained prior to enrolling patients and initiating the study (CHR15-17478). We obtained FDA exemption (IND 129264) to use Optison™ (Perflutren Protein-Type A Microspheres Suspension), an ultrasound contrast agent, for off label application.

Study inclusion criteria were all consecutive weekday patients older than 18 years who underwent PCNL at our institution and consented to participate in the study. We excluded patients who had contraindications for intravascular administration of Optison. These contraindications included 1) right to left or bidirectional cardiac shunts, 2) hypersensitivity to perflutren, blood products or albumin and 3) pregnancy.[19]

The primary end point measured for CEUS and fluoroscopic nephrostogram was ureteral patency on imaging as determined by visualization of contrast material instilled through the PNT in the bladder. Sample size power calculation was based on results from our pilot study comparing CEUS and fluoroscopic nephrostogram, which demonstrated a 0% discordance rate between the 2 imaging studies.[18] Based on our clinical experience we estimated that a discrepancy rate of 5% or less between our index test and the reference standard would be considered clinically insignificant. Assuming no discordance based on our pilot study, a sample of 84 patients was required to yield a 95% CI on discordance with an upper bound of 5%.

Demographic data, basic laboratory results and stone characteristics determined by noncontrast CT were obtained in all patients preoperatively. All PCNL procedures were performed by 2 endourologists under fluoroscopic (MS) or ultrasound (TC) guidance with PNT routinely placed at the completion of each procedure. The nephrostomy tube consisted of a 10Fr Cope loop catheter or a 16Fr Foley catheter according to surgeon preference. In clinically stable patients on POD 1 CEUS and fluoroscopic nephrostogram were performed within 2 hours of each other.

Details of our CEUS imaging protocol have been previously published.[18] Briefly, we began with gray scale ultrasound with the patient supine to identify the targeted kidney and evaluate for residual stone fragments. Subsequently 1.5 ml Optison were injected via the PNT followed by 5 ml normal saline. A GE LOGIQ™ E9 ultrasound scanner with contrast compatible software was used to confirm the presence of contrast material in the upper collecting system and bladder.

Immediately after Optison injection the bladder was examined to identify the presence of contrast medium that would indicate a patent ureter with an unobstructed antegrade urine flow from kidney to bladder (fig. 1, *a*). We evaluated the bladder for the presence of contrast material at 1-minute intervals for 3 minutes. If contrast medium was not seen in the bladder after 3 minutes, another 1.5 ml ultrasound contrast agent were injected in the PNT, followed by a normal saline flush. The bladder was again examined at 1-minute intervals for another 7 minutes. Absent contrast material in the bladder 10 minutes after the first injection was interpreted as an obstructed ureter with absent antegrade urine flow (fig. 2, *a*).

Fluoroscopic nephrostogram was also performed by experienced interventional radiologists on the same day within 2 hours of CEUS. The patient was placed supine on a fluoroscopy table. An initial plain film was performed to evaluate for residual stone fragments. Then 10 to 30 ml Omnipaque™ iohexol contrast solution were injected via the PNT. Multiple fluoroscopic screening shots were obtained to outline the collecting system and evaluate ureteral patency. Demonstration of contrast agent passing from ureter to bladder was categorized as a patent ureter with unobstructed antegrade urine flow from kidney to bladder (fig. 1, *b*). Failure to demonstrate any contrast

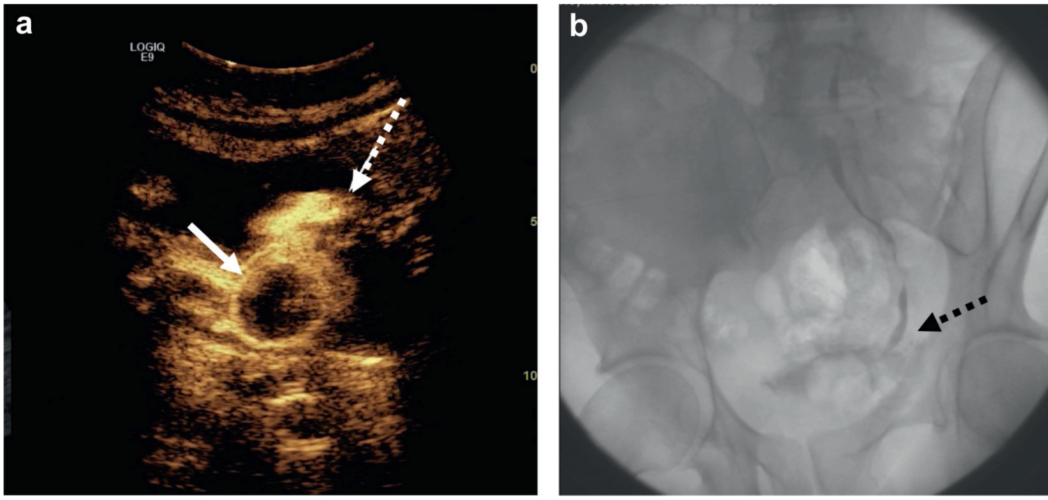

Figure 1. CEUS and fluoroscopic nephrostogram images of 60-year-old male with patent collecting system 1 day after PCNL. *a*, 1 minute after injecting ultrasound contrast agent via preplaced nephrostomy tube CEUS of bladder identified contrast agent in bladder (dashed arrow). Note Foley balloon (solid arrow). *b*, fluoroscopic nephrostogram confirmed ureteral patency and contrast agent entering bladder (dashed arrow).

material in the bladder was interpreted as an obstructed ureter with absent antegrade urine flow (fig. 2, *b*). Fluoroscopic screening time in minutes and estimated radiation exposure dose from the fluoroscopy machine were also recorded and calculated as effective doses in mGy.[20]

In patients in whom the PNT was not removed after imaging on POD 1 CEUS and fluoroscopic nephrostograms were repeated on POD 2.

CEUS images were independently evaluated for ureteral patency by 2 blinded radiologists (SW and JM) with more than 10 and 3 years of experience in interpreting ultrasound, respectively. Discrepancies were resolved by consensus. Study reporting followed QUADAS (Quality Assessment of Diagnostic Accuracy Studies) guidelines (supplementary Appendix, http://jurology.com/).[21] Data are expressed as the mean ± SD or the percentage. Diagnostic accuracy comparing the 2 imaging studies was calculated as well. Statistical analyses were performed with Stata/SE™, version 14.1.

RESULTS

Of the 111 patients eligible for study participation 82 consented to participate from September 2015 to October 2016. A total of 29 eligible patients were excluded from analysis due to staff unavailability. Ten of the 82 study participants underwent repeat

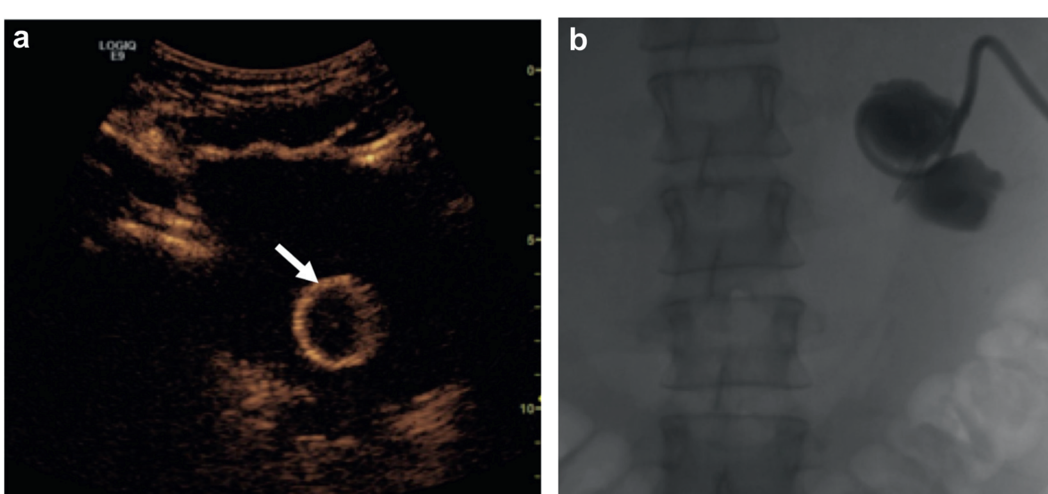

Figure 2. CEUS and fluoroscopic nephrostogram images of 64-year-old female with obstructed collecting system. *a*, 10 minutes after injecting ultrasound contrast agent via preplaced nephrostomy tube CEUS of bladder failed to identify any contrast agent in bladder lumen. Note Foley balloon (arrow). *b*, fluoroscopic nephrostogram confirmed persistent obstruction of left collecting system with no spontaneous flow of contrast material into ureter or bladder.

imaging on POD 2 for a total of 92 CEUS and fluoroscopic nephrostogram imaging studies. Five of these 92 studies in a total of 5 patients were subsequently excluded from analysis because of PNT dislodgement from the collecting system in 3, as confirmed on CEUS and fluoroscopic nephrostogram, and significant extravasation after contrast injection in the other 2 studies.

Females predominated in the remaining 77 patients available for analysis. There was an even distribution between right and left PCNL procedures while staghorn stones were present on preoperative imaging in a third of the cases. No significant intraoperative complications were experienced in any PCNL procedure. Compared to the 29 eligible patients who were excluded from study participation for staff availability reasons, demographic parameters were comparable to those included in analysis with regard to age, gender, BMI and procedure laterality (see table).

Of the 87 pairs of imaging studies 69 (79.3%) that were available for the analysis comparing CEUS to fluoroscopic nephrostograms demonstrated concordance between the 2 imaging techniques in identifying ureteral patency and 18 (20.7%) demonstrated discordance. These discordant studies included 17 sets of studies with positive antegrade urine flow on CEUS but not on fluoroscopic nephrostogram and 1 with positive flow on fluoroscopic nephrostogram but not on CEUS (fig. 3). Three of these 17 studies were from patients in whom imaging was repeated on POD 2.

The chi-square test and logistic regression analysis revealed that patient gender ($p = 0.52$) and age ($p = 0.80$) were not strongly predictive of discordant imaging results. BMI ($p = 0.11$) appeared associated with discordant imaging, although this did not achieve statistical significance.

Using fluoroscopic nephrostogram as the reference standard to evaluate ureteral patency we calculated that CEUS had 98.0% sensitivity, 52.8% specificity, 74.6% positive predictive value and 95.0% negative predictive value to predict the presence of ureteral patency. The specificity and positive predictive values should be interpreted in the context of evidence of limited sensitivity of the fluoroscopic reference test, as described.

PNT management was based on the results of CEUS and fluoroscopic nephrostogram, and the clinical judgment of the treating surgeon. Of the 18

Characteristics and perioperative variables of patients included in and excluded from analysis

	Included	Excluded	p Value
Preop			
No. pts	77	29	—
Mean ± SD age	50.5 ± 15.9	54.9 ± 18.7	0.23
No. female (%)	44 (57.1)	20 (69.0)	0.27
No. male (%)	33 (42.9)	9 (31.0)	
Mean ± SD BMI (kg/m^2)	29.6 ± 8.6	26.8 ± 4.4	0.10
No. PCNL laterality (%):			
Lt	39 (50.7)	14 (48.3)	0.83
Rt	38 (49.3)	15 (51.7)	
Mean ± SD stone size (mm)	35.2 ± 20.9	44.5 ± 20.4	<0.05
No. stone type (%):			
Caliceal	20 (25.9)	3 (10.3)	0.16
Pelvic	16 (20.8)	6 (20.7)	
Staghorn	26 (33.8)	13 (44.8)	
Proximal ureteral	5 (6.5)	0	
Multiple	10 (13.0)	7 (24.2)	
No. hydronephrosis degree (%):			
None	51 (66.2)	16 (55.2)	0.31
Mild	15 (19.5)	9 (31.0)	
Moderate	7 (9.1)	4 (13.8)	
Severe	4 (5.2)	0	
Intraop			
Mean ± SD operative time (min)	120.7 ± 49.3	108.3 ± 32.8	0.21
Mean ± SD estimated blood loss (ml)	72.1 ± 64.2	86.4 ± 43.7	0.27
No. nephrostomy tube type (%):			
Cope tube	58 (75.3)	9 (31.0)	<0.05
Foley catheter	19 (24.7)	20 (69.0)	
Postop			
No. imaging time sequence (%):		Not applicable	—
CEUS before fluoroscopic nephrostogram	35 (40.2)		
Fluoroscopic nephrostogram before CEUS	52 (59.8)		
Mean ± SD fluoroscopic nephrostogram:		Not applicable	—
Screening time (mins)	2.0 ± 2.6		
Radiation exposure dose (mGy)	2.8 ± 3.7		

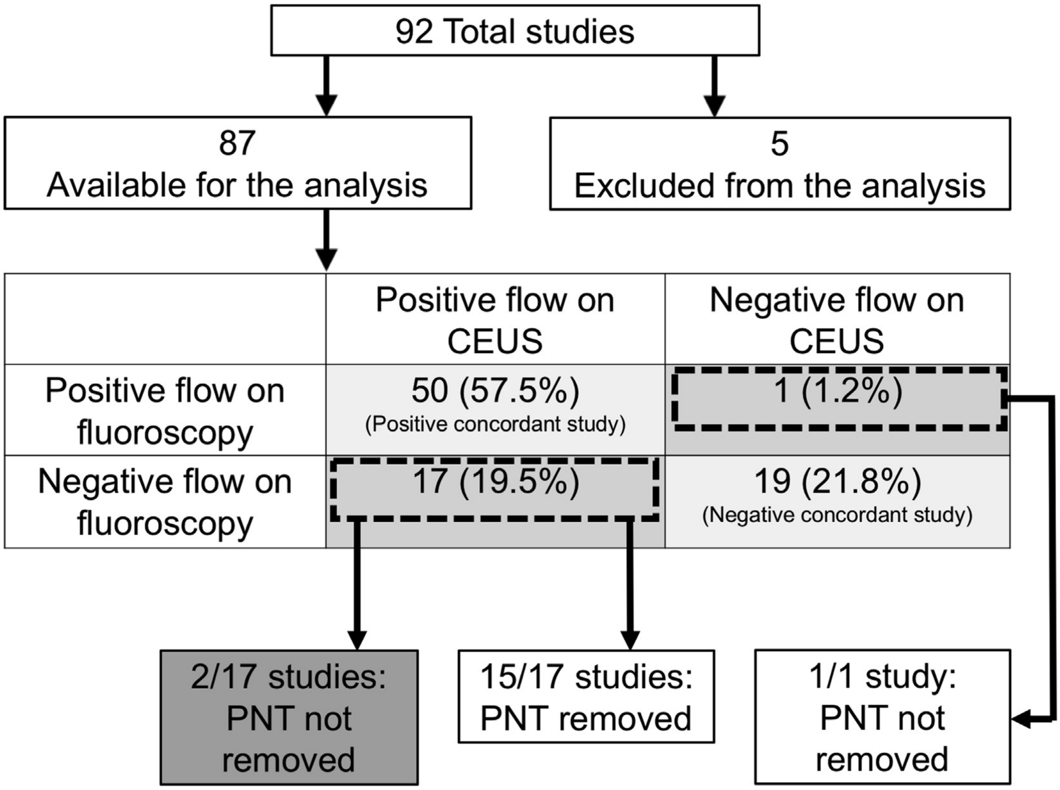

Figure 3. Study design flow diagram and comparison of imaging confirmed ureteral patency between CEUS and fluoroscopic nephrostogram.

patients in whom paired studies demonstrated imaging discordance the PNT was managed in a fashion concordant with CEUS results in 16 (89%) while in 2 (11%) the tubes were managed in alignment with fluoroscopic nephrostogram results (fig. 3).

No adverse events were associated with ultrasound contrast or iodinated contrast PNT injection in this study. Additionally, during a 4-week observation period after PNT removal no patients experienced any signs or symptoms of ureteral obstruction, including severe flank pain, persistent urine leakage, fever or any adverse event requiring hospital readmission.

For fluoroscopic nephrostogram the mean fluoroscopic screening time was 2.0 $\pm$ 2.6 minutes (range 0.1 to 18.3) and the mean radiation exposure dose was 2.8 $\pm$ 3.7 mGy (range 0.6 to 18.1). However, these data were only available on 49 and 21 studies, representing 56.3% and 24.1% of the total (see table).

DISCUSSION

To our knowledge no established imaging techniques exist to evaluate ureteral patency without ionizing radiation. The aim of our study was to demonstrate that CEUS is noninferior to fluoroscopic nephrostography to identify the presence of ureteral patency after PCNL. Approximately 80% of studies demonstrated concordance between the 2 imaging modalities. Among the discordant studies 94% of the time there was positive antegrade urine flow on CEUS but not on fluoroscopic nephrostogram while 6% of the time this discordance was reversed.

Although CEUS showed substantial discordance with fluoroscopic results, we believe that the cases in which only CEUS demonstrated positive antegrade flow represent false-negative findings on fluoroscopy rather than false-positive findings on CEUS. In these cases study results seen with CEUS were thought to represent true ureteral patency for 4 reasons.

1) The ultrasound contrast agent used in this study is associated with a low threshold for visualization based on and in vitro study[22] and the contrast dose used with our protocol is more than sufficient for detection in the bladder. We used a small volume or injection, which was unlikely to disrupt the normal physiology of ureteral peristalsis. 2) In each of these patients there was an unambiguous contrast signal in the bladder identical to that in concordantly patent patients. 3) The

bladder of each patient was scanned in contrast mode prior to instilling contrast medium through the PNT. In no case, including concordant cases, was signal ever seen in the bladder that resembled contrast signal prior to instillation. Based on this it was deemed extremely unlikely that the signal came from something other than ultrasound contrast material. 4) To our knowledge there is no physiologically plausible mechanism by which ultrasound contrast microbubbles can transit from the renal collecting system to the bladder other than via a patent ureter.

In light of these observations we believe that these discordant study results support the notion that CEUS has greater sensitivity to detect ureteral patency than fluoroscopic nephrostography. Supporting this is the finding that 15 of the 17 patients in whom antegrade urine flow was noted only on CEUS had the PNT removed on the same day and none of these 15 patients experienced any subsequent adverse events.

There are several possible explanations for the increased sensitivity of CEUS. Ultrasound contrast produces a signal as much as 5 to 6 orders of magnitude higher than an equal volume of iodinated contrast medium.[23] Additionally, ultrasound is a cross-sectional modality and, thus, the contrast signal is set against virtually no background signal in the fluid filled bladder. In comparison, fluoroscopy is a projection imaging modality in which the contrast signal must be distinguished against the background signal of overlying and underlying anatomical structures in the pelvis, including bowel and blood vessels.[23]

This study should be considered in the context of some limitations. Contrast injection could alter anatomy or physiology in the upper urinary tract and impact the outcome of subsequent studies. Ureteral patency could also change during the interval between 2 imaging studies. This appears to have occurred in the 1 discordant imaging case, in which fluoroscopic nephrostogram showed the presence of antegrade flow whereas CEUS demonstrated none. Furthermore, although it was not rigorously randomized, ordering of the 2 studies was determined by equipment availability and resulted in comparable numbers of pairs of studies with each ordering (35 study pairs with CEUS first compared to 52 pairs with fluoroscopy first). Additionally, to quality control adherence to the imaging protocol we included consecutive weekday patients. Patients excluded for this reason (eg POD 1 fell on a weekend or holiday) were comparable to included patients in all aspects except stone size and tube type, which are unlikely to have influenced results.

Our study results suggest that CEUS is sufficiently accurate to predict ureteral patency and guide clinical management. However, this study was neither designed nor powered to measure safe nephrostomy tube removal as an outcome of interest. Considering the 67 CEUS examinations that revealed antegrade ureteral patency, 65 nephrostomy tubes were removed and no patient experienced an adverse outcome after tube removal.

We anticipate future studies to center on the clinical impact of using CEUS to evaluate the collecting system. In the current study each fluoroscopic nephrostogram contributed around 3 mGy of ionizing radiation exposure to patients. This is equivalent to approximately 3 plain x-rays of the kidneys, ureters and bladder, and comprises a little more than 5% of the annual limit of radiation exposure recommended by OSHA (Occupational Safety and Health Administration).[8] The radiation exposure from each study ranged widely with 1 patient receiving 18 minutes of exposure due to bowel gas pattern interference. Radiation exposure effects are cumulative. Understanding the impact of using CEUS to eliminate fluoroscopic exposures will certainly be a focus for future studies.

Another area of interest is how CEUS can best be incorporated into clinical practice. Currently nephrostomy tube management after PCNL is dictated by a range of strategies. We have previously compared capping trials with clinical monitoring and methylene blue injection to fluoroscopic nephrostogram and found that there are advantages to a management strategy that includes anatomical imaging.[10] We plan to investigate the clinical outcomes and economic costs of CEUS vs other common strategies such as a capping trial, methylene blue injection and CT.

CONCLUSIONS

Contrast enhanced ultrasound enables the evaluation of ureteral patency without exposing patients to ionizing radiation. Although some discordance was observed between CEUS and traditional fluoroscopy, we believe that nearly all of these discordances can be explained by the limited sensitivity of fluoroscopy relative to CEUS. Future randomized studies are planned to determine whether the high specificity and potentially higher sensitivity of CEUS relative to fluoroscopic nephrostography may lead to improved clinical outcomes.

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